When citing an abstract from the 2015 annual meeting please use the format below.

[Authors]. [Abstract Title]. Program No. XXX.XX. 2015 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience, 2015. Online.

Nanosymposium

010. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.01

Topic: A.02. Postnatal Neurogenesis

Title: TLR9 signaling in microglia attenuates seizure-induced aberrant neurogenesis in the adult hippocampus

Authors: *T. MATSUDA[1], N. MURAO[1], Y. KATANO[1], B. JULIANDI[1], J. KOHYAMA[2], S. AKIRA[3], T. KAWAI[4], K. NAKASHIMA[1];
[1]Grad. Sch. of Med. Sciences, Kyushu Univ., Fukuoka, Japan; [2]Dept. of Physiol., Sch. of Medicine, Keio Univ., Tokyo, Japan; [3]Lab. of Host Def., World Premier Intl. Immunol. Frontier Res. Center, Osaka Univ., Osaka, Japan; [4]Lab. of Mol. Immunobiology, Grad. Sch. of Biol. Sciences, NAIST, Nara, Japan

Abstract: Adult neural stem/progenitor cells (aNS/PCs) in the subgranular zone of the adult hippocampal dentate gyrus (DG) proliferate and give rise to new neurons continuously throughout life to maintain proper brain functions. Although this homeostatic neurogenesis is strictly controlled under normal physiological conditions, misregulation of aNS/PCs leads to aberrant neurogenesis and impairment of hippocampal-dependent learning and memory under pathological conditions such as stress, depression, ischemia and epilepsy. The aNS/PC niche, a microenvironment comprising various components including blood vessels, neurons, astrocytes and microglia, is known to contribute to different aspects of neurogenesis under both normal and pathological conditions. However, how it responds to pathological conditions to rectify any aberrant behavior of aNS/PCs has yet to be elucidated. Here, we show that microglia in the mouse hippocampus attenuate convulsive seizure-mediated aberrant neurogenesis through the activation of Toll-like receptor 9 (TLR9), an innate immune sensor known to recognize microbial DNA and trigger inflammatory responses. We found that microglia sense self-DNA from degenerating neurons following seizure, and secrete tumor necrosis factor-α, resulting in attenuation of aberrant neurogenesis. Furthermore, TLR9 deficiency exacerbated seizure-induced cognitive decline and recurrent seizure severity. Our findings thus suggest the existence of bidirectional communication between the innate immune and nervous systems for the maintenance of adult brain integrity.

Disclosures: **T. Matsuda:** None. **N. Murao:** None. **Y. Katano:** None. **B. Juliandi:** None. **J. Kohyama:** None. **S. Akira:** None. **T. Kawai:** None. **K. Nakashima:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.02

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant AG045034

CIRM Grant TB1-01190

NIH NINDS F32 NS083508

Title: Adult neural progenitor cells regulate hippocampal seizure response via secreted VEGF

Authors: *E. D. KIRBY, T. WYSS-CORAY;
Stanford Univ., Palo Alto, CA

Abstract: The adult hippocampus demonstrates remarkable sensitivity to the environment, supporting both the beneficial plasticity inherent in memory function and an often-detrimental vulnerability to a variety of insults. Seizures strongly impact the hippocampus in both humans and rodent models, often leading to cognitive impairment and development of recurrent epileptic activity. The acute response to a seizure strongly shapes the long-term consequences for hippocampal function and has therefore generated much interest as a potential window during which recovery could be supported. During this acute response, a reliably observed increase in hippocampal neurogenesis has generated much debate, with some studies indicating a positive role for new neurons in neuroprotection while others suggest a detrimental role of the many aberrantly integrated new neurons. To date, this debate has focused almost exclusively on new neurons, with little discussion of the neural stem and progenitor cells (NPCs) from which the neurons derive. However, we recently showed that NPCs in the adult hippocampus secrete surprisingly large amounts of vascular endothelial growth factor (VEGF), revealing the possibility that these undifferentiated cells could have functional relevance as sources of secreted growth factors. We therefore investigated the functional relevance of NPC-derived VEGF in seizure response using a murine NPC-specific, inducible VEGF knockdown model. NPC-VEGF iKD mice and littermate controls were exposed to kainic acid (KA) to induce seizures. We then investigated several markers of seizure response and damage. We found that KA-induced seizures stimulated NPC proliferation and vascular reorganization in both NPC-VEGF iKD and control mice to a similar degree. However, KA-induced astrogliosis, microgliosis and heat shock protein response were exaggerated in NPC-VEGF iKD mice compared to controls, suggesting a potential for greater seizure-related damage in iKD mice. Importantly, these studies occurred in a

short time-frame, before any manipulated NPCs could give rise to functional new neurons. Our findings therefore suggest that NPC-derived VEGF may be protective against seizure-related hippocampal damage. Future research will use behavioral assays to confirm the detrimental effect of loss of NPC-derived VEGF in seizure response. These studies show that NPCs may have functional relevance to hippocampal injury response as secretory cells, independent of their ability to create new neurons, and suggest a novel source of plasticity in the adult brain.

Disclosures: E.D. Kirby: None. **T. Wyss-Coray:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.03

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant NS084111

Title: Early events in the development of adult-born dentate granule cells - role of STK25/STRAD

Authors: *S. RAO[1,2], S. GE[1], M. SHELLY[1];
[1]Neurobio. and Behavior, Stony Brook Univ., Stony Brook, NY; [2]Program In Neurosci., Stony Brook, NY

Abstract: Adult-born Dentate Granule Cell (DGC) development is a tightly regulated, dynamic process, where immature neurons undergo a series of orchestrated changes to form mature DGCs that integrate into the hippocampal circuitry. We focus on a critical developmental stage between 7 to 14 days, where immature adult-born DGCs undergo an extensive remodeling of the neuritic processes at the basal domain, resulting in the specification of a single hilar axon and a single apical dendrite. This stage is also characterized by the transition of the somata from tangential to the stereotypical radial orientation within the granule cell layer (GCL). Failure of these developmental events can result in pathological conditions such as epilepsy. However, the cellular/molecular mechanisms that dictate these developmental events remain largely unknown. We specifically focus on the role of the protein complex composed of the Ste20-related kinase1 Stk25 (YSK1, Sok1) and the STE20-related pseudokinase (STRAD), in the direct regulation of basal dendrite formation and elimination in adult-born DGCs, via regulation of Golgi positioning. The STRAD-STK25 complex has been shown to regulate polarized Golgi positioning and neuritic process formation in embryonic CA1 hippocampal neurons. We

hypothesize that exclusive localization of the Golgi to the apical pole and its exclusion from the basal pole, are both crucial events in the establishment of a typical adult-born DGC morphology, with a single apical dendrite, a single basal axon and radial orientation of DGCs in the GCL. We show that in adult-born DGCs, downregulation of STK25 or STRAD resulted in persistent basal dendrites, as well as failure of cells to achieve radial orientation in the GCL. These cells exhibited Golgi dispersion that was present at the base of the persistent basal dendrites. Thus, the Stk25-STRAD complex regulates polarized Golgi positioning and its exclusion from the basal processes. This results in the assumption of the bipolar morphology and radial orientation of the DGCs in the GCL. Furthermore, a homozygous deletion in the STRAD gene resulting in C-terminal 180 amino-acid truncation of the STRAD protein (STRAD-Δ180) causes the human Polyhydramnios, Megalencephaly and Symptomatic Epilepsy (PMSE) syndrome, a neurodevelopmental disorder characterized by infantile-onset epilepsy and severe mental and motor disability. We thus propose that the perturbation of the STRAD-Stk25 complex activity produces morphological aberrations in adult-born DGCs, potentially causing pathological development and activity of these neurons.

Disclosures: **S. Rao:** None. **S. Ge:** None. **M. Shelly:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.04

Topic: A.02. Postnatal Neurogenesis

Title: C-myc couples proliferation to differentiation in adult neurogenesis

Authors: ***A. M. DENLI**, G. SENTURK, S. SCHAFER, C. ZHAO, M. N. KAGALWALA, I. S. GALLINA, M. PENA, F. H. GAGE;
LOG-G, Salk Inst. For Biol. Studies, La Jolla, CA

Abstract: Adult neurogenesis is the process through which new neurons are born in the adult brain with links to learning and memory as well as neurological disorders. Neurogenesis takes place in the subgranular zone (SGZ) of the dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricles. In the DG, newborn neurons mature to become excitatory granule cells that integrate into the existing circuitry. Adult neurogenesis is driven by relatively quiescent radial glial cells, which in combination with active signaling pathways give rise to a proliferative cell population, which mostly adopt a neuronal cell fate. While the cell types involved in adult neurogenesis have been characterized, we are far from a full understanding of molecular

mechanisms involved. The highly conserved transcriptional regulatory protein c-myc is an integral part of development and also acts as a proto-oncogene. A large number of studies have focused on c-myc, but only a minority has been carried out in normal adult stem cells. c-myc is a major wnt pathway target and is involved in diverse processes such as cell growth, proliferation, apoptosis and differentiation: phenomena intimately linked to neural stem cell biology. A clear picture of c-myc function remains to emerge, due to context-dependence, overlapping expression patterns with other myc proteins, weak transcriptional activity and low expression levels in adult cells. We have hypothesized that c-myc may have a function in early steps of adult neurogenesis. We confirmed expression of c-myc in the adult DG as well as cultured adult hippocampal progenitor cells (AHPs). c-myc bound to its known target loci and regulated expression in AHPs, suggesting that c-myc was functional in the adult neural progenitor context. Expression of c-myc was downregulated upon differentiation both *in vivo* and *in vitro*. The expression pattern of c-myc and other myc family members were distinct, suggesting an early function for c-myc. Knockdown of c-myc led to enhanced differentiation, whereas overexpression of c-myc inhibited differentiation of AHPs. Retroviral expression of c-myc in the DG led to an early increase in proliferation followed by an inhibition of subsequent differentiation. Interestingly, further analysis suggested that c-myc function was dose-dependent and that c-myc might have a direct role in coupling proliferation to differentiation. In summary, our data point to a novel role for c-myc in regulation of not only cell proliferation but also cell fate in adult neurogenesis. Potential mechanisms of c-myc function and its role in adult stem cell biology will be discussed.

Disclosures: **A.M. Denli:** None. **G. Senturk:** None. **S. Schafer:** None. **C. Zhao:** None. **M.N. Kagalwala:** None. **I.S. Gallina:** None. **M. Pena:** None. **F.H. Gage:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.05

Topic: A.02. Postnatal Neurogenesis

Support: NHMRC Australia 1024201

NHMRC Australia 1010723

Title: The Netrin/RGM receptor, Neogenin, controls adult neurogenesis by promoting neuroblast migration and cell cycle exit in the rostral migratory stream

Authors: *H. M. COOPER, D. BRADFORD, A. WHITE, C. O'LEARY;
Queensland Brain Ins, Brisbane, Australia

Abstract: A comprehensive understanding of adult neurogenesis is essential for the development of effective strategies for the enhancement of endogenous neurogenesis in the damaged brain. Olfactory interneurons arise throughout life from stem cells residing in the subventricular zone of the lateral ventricles. Neural precursors then migrate along the rostral migratory stream (RMS) to the olfactory bulb. To ensure a continuous supply of adult-born interneurons, precursor proliferation, migration and differentiation must be tightly coordinated. Here we show that the netrin/RGM receptor, Neogenin, is a key regulator of adult neurogenesis. Neogenin loss-of-function (Neogt/gt) mice exhibit a specific reduction in adult-born calretinin interneurons in the olfactory granule cell layer. In the absence of Neogenin neuroblasts fail to migrate into the olfactory bulb and instead accumulate in the RMS. *In vitro* migration assays confirmed that Neogenin is required for Netrin-1-mediated neuroblast migration and chemoattraction. Unexpectedly, we also identified a novel role for Neogenin as a regulator of the neuroblast cell cycle. We observed that those neuroblasts able to reach the Neogt/gt olfactory bulb remained in cell cycle and consequently failed to undergo terminal differentiation. Cell cycle analysis revealed an increase in the number of S-phase neuroblasts within the Neogt/gt RMS and a significant reduction in the number of neuroblasts exiting the cell cycle, providing an explanation for their inability to undergo terminal differentiation. Therefore Neogenin acts to synchronize neuroblast migration and terminal differentiation through the regulation of neuroblast cell cycle kinetics within the neurogenic microenvironment of the RMS.

Disclosures: H.M. Cooper: None. **D. Bradford:** None. **A. White:** None. **C. O'Leary:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.06

Topic: A.02. Postnatal Neurogenesis

Support: Catholic University (Linea D3.2 to C.G.)

Catholic University (Linea D1 to G.P.)

Title: Involvement of CREB-Sirt1-Hes1 circuitry in neural stem cell response to glucose availability

Authors: *L. LEONE[1], S. FUSCO[1], S. A. BARBATI[1], D. SAMENGO[2], R. PIACENTINI[1], G. TOIETTA[5], G. MAULUCCI[3], G. PANI[4], C. GRASSI[1];
[1]Inst. of Human Physiol., Univ. Cattolica, Med. Sch., Rome, Italy; [2]Inst. of Gen. Pathology, [3]Inst. of Physics, [4]Univ. Cattolica Med. Sch., Rome, Italy; [5]Regina Elena Natl. Cancer Inst., Rome, Italy

Abstract: Adult neurogenesis plays increasingly recognized roles in brain homeostasis and repair, and is profoundly affected by energy balance and nutrient availability. Thus it is relevant to the emerging connection between metabolic dysfunction and brain diseases. Excess nutrients lead to a depletion of the neural stem cell (NSC) poll and accelerate brain ageing, but the underlying cellular and molecular mechanisms are far from being defined. Here we demonstrate that hippocampal NSCs cultured in glucose concentrations falling in the physiological range (0.9-1.0 g/L) exhibited increased proliferative and self-renewal capacity compared to NSCs exposed to high glucose (4.0-4.5 g/L) conditions. This effect was paralleled by the enhanced expression of the transcription factor Hes1 (Hairy and Enhancer of Split), a master determinant of neural cell stemness, and increased CREB phosphorylation. More importantly, these responses to glucose availability were nearly completely lost in CREB-deleted NSCs, suggesting that CREB may regulate Hes1 expression. Our bio-informatic search and ChIP analyses demonstrated the presence of a CRE region in the regulatory sequence of the Hes1 gene that was bound by both CREB and the histone deacetylase Sirtuin1 (Sirt1). Low glucose availability promoted CREB binding to the CRE surrounding chromatin and increased histone H3 acetylation, while high glucose condition led to Sirt1 interaction with the same DNA region and consequent chromatin deacetylation and Hes1 repression. Interestingly, CREB phosphorylation and activation seem to be critical for proliferation and glucose responsiveness of NSCs. Indeed the overexpression of CREB mutant form lacking a specific serine in the activation domain (CREB S133A) abolished the proliferative effect of low-glucose culture medium, while the transfection of hyper-phosphorylated form of CREB (CREB K136A) increased NSC self-renewal capacity. The same molecular interactions involving CREB, Sirt1 and Hes1 chromatin that we observed in cultured NSCs exposed to low ambient glucose were found in the hippocampus of mice subjected to calorie restriction, that is a dietary regimen associated with increased insulin responsiveness and lower blood glucose levels. In this animal model the increased Hes1 mRNA and the enhanced CREB interaction with the Hes1 promoter were associated with enhanced NSC proliferation. Collectively, our findings suggest that the glucose-sensitive antagonisms between CREB and Sirt1 for Hes1 transcription may play a critical role in the metabolic regulation of hippocampal adult neurogenesis.

Disclosures: L. Leone: None. **S. Fusco:** None. **S.A. Barbati:** None. **D. Samengo:** None. **R. Piacentini:** None. **G. Toietta:** None. **G. Maulucci:** None. **G. Pani:** None. **C. Grassi:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.07

Topic: A.02. Postnatal Neurogenesis

Support: NIMH Grant MH090115

Title: BubR1 insufficiency impairs adult hippocampal neurogenesis and cognitive function

Authors: *C. CHO[1], C.-I. CHOI[1], Y. ZHONGXI[1,3], Y. GU[4], M.-H. JANG[1,2];
[1]Dept. of Neurolog. Surgery, [2]Dept. of Biochem. and Mol. Biol., Mayo Clin., Rochester, MN; [3]Dept. of Neurosurg., First Hosp. of Jilin Univ., Changchun, China; [4]Dept. of Neurobio. and Behavior, SUNY at Stony Brook, Stony Brook, NY

Abstract: While medical advances have succeeded in extending the average human lifespan, the development of effective treatments combatting associated age-related cognitive decline is lagging. Present therapeutic development is impeded by inadequate understanding of the cellular and molecular mechanisms contributing to cognitive aging. Recently, increasing evidence suggests adult hippocampal neurogenesis, the process generating functionally integrated newborn neurons, plays a fundamental role in memory function, emotional regulation, brain repair, and aging. Impairments in neurogenesis are observed with age and age-related disorders and are now believed to underlie associated cognitive deficits. While the molecular mechanisms mediating these impairments remain largely unknown, the mitotic checkpoint protein BubR1 has been shown to be an essential determinant contributing to age-related pathology. Transgenic mice harboring *BubR1* hypomorphic alleles producing low amounts of BubR1 (BubR1 hypomorphic or $BubR1^{H/H}$ mice) develop progeroid features and exhibit a reduced lifespan. Although cognitive deficits are hallmark symptoms of brain aging, the impact of BubR1 in brain function has remained unknown until now. Here, we find BubR1 is expressed within the adult mouse hippocampus and is significantly reduced with chronological aging. We further show that BubR1 insufficiency impairs multiple aspects of adult hippocampal neurogenesis including neural progenitor proliferation, maturation, and dendrite development of newborn cells in the dentate gyrus *in vivo*. In addition, BubR1 insufficiency leads to increased expression of hippocampal sFRP3, a natural inhibitor of Wnt signaling. Indeed, impaired adult hippocampal neurogenesis caused by BubR1 insufficiency is recovered by sFRP3 knockdown. Furthermore, *BubR1 insufficient mice exhibit increased anxiety and impaired memory function. Increasing newborn neuron activation through optogenetic stimulation ameliorates these behavior impairments, indicating the specific functional impact of newborn neuron activity in attenuating the cognitive deficits caused by BubR1 insufficiency.* Combined, our findings reveal BubR1 as a

novel molecular component regulating newborn neuron development and cognitive function. Such knowledge provides new insight into the development of effective therapies treating a wide spectrum of cognitive disorders.

Disclosures: **C. Cho:** None. **C. Choi:** None. **Y. Zhongxi:** None. **Y. Gu:** None. **M. Jang:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.08

Topic: A.02. Postnatal Neurogenesis

Support: CNRS

Université Claude Bernard Lyon 1

China Scholarship Council

Title: Olfactory perceptual learning shapes morphology of adult-born granule cells and their inputs from locus coeruleus

Authors: ***X. YIN**, J. FOREST, M. MIDROIT, J. SACQUET, N. KUCZEWSKI, M. RICHARD, N. MANDAIRON, A. DIDIER;
CNRS, Univ. Claude Bernard Lyon 1, Lyon, France

Abstract: Our previous works showed that top-down control from the noradrenergic system on adult-born granule cells in the olfactory bulb plays a key role in enrichment-induced olfactory discrimination (perceptual learning). However, the mechanism underlying the noradrenergic neuromodulation of perceptual learning remains unknown. We hypothesized that perceptual learning may modify the connective pattern between noradrenergic fibers and adult-born granule cells. Using lentivirus injection in the subventricular zone to label adult-born neurons and norepinephrine transporter (NET) immunohistochemistry to label noradrenergic terminals in the olfactory bulb, we found that perceptual learning enhanced the density of noradrenergic contacts both on basal dendrites and apical dendrites of adult-born neurons without affecting the overall density of noradrenergic fibers in the olfactory bulb. Moreover these effects lasted at least 4 weeks after learning, a finding entirely consistent with long lasting olfactory discriminative improvement induced by odor exposure. Adult-born neurons integrate the olfactory bulb network by developing dendritic arbors and establishing synaptic contacts. We thus also investigated whether perceptual learning alters the morphology of adult-born granule cells, thereby modifying

their level of synaptic integration and involvement in signal processing. Preliminary results suggested that perceptual learning modified adult-born granule cells in olfactory bulb by enhancing their dendritic spine density, and this effect lasted at least 4 weeks, in accordance with noradrenergic pattern and behavior results. On the basis of these findings, we will next ask whether optogenetic manipulation of noradrenergic activity changes learned olfactory discrimination. Based upon current results, we argue that top-down neuromodulation from the noradrenergic system is a key factor facilitating adult-born granule cells' integration into the olfactory bulb network during perceptual learning.

Disclosures: X. Yin: None. **J. Forest:** None. **M. Midroit:** None. **J. Sacquet:** None. **N. Kuczewski:** None. **M. Richard:** None. **N. Mandairon:** None. **A. Didier:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.09

Topic: A.02. Postnatal Neurogenesis

Support: NSFC (31123002, 31321091)

Title: FGF13 deficiency causes impaired neurogenesis in the developing mouse brain

Authors: *Q. YANG, Y. ZHAI, W. LI, J. ZHOU;
Inst. of neuroscience, Shanghai Inst. For Biol. Sci., Shanghai, China

Abstract: FGF13 is known to be a nonsecretory protein of the fibroblast growth factor (FGF) family which is enriched in brain during development and is correlated with two kinds of non-systematically X-linked mental retardation, suggesting its important roles in mental development of human. Previous studies have shown that FGF13B, one of FGF13 isoforms, is a regulator for microtubule assembly during axonal outgrowth and migration of immature neuron. However, the biological function of FGF13 during brain development remains poorly understood. Toward this end, we generated Fgf13 conditional knockout (cKO) mice by crossing FGF13-floxed mice with either nestin-CreERT2 or hGFAP-Cre mice targeting neural stem cells / progenitors. We found progressively decreased neurogenesis in the hippocampal subgranular zone of Fgf13 cKO mice at various stages of development. *In vitro* cultured Fgf13-null neural stem cells also showed dramatic impairment in the ability to proliferate and self-renew. Interestingly, FGF13A, which is known as the only nuclear isoform of FGF13, contributed more to this phenotype. Yeast-two-hybrid screening identified FGF13A as a interacting protein with AT Rich Interactive Domain

1B (ARID1B), a protein that is known to function as a subunit of SWI/SNF chromatin remodeling complex and is also correlated with human mental retardation diseases, and is also associated with human mental retardation diseases. FGF13A was able to maintain the expression of ARID1B, while it has been known that haploinsufficiency of ARID1B alters cell-cycle dynamics. Taken together, our data suggest that FGF13 functions as an important regulator in the maintenance of neurogenesis in the developing brain.FGF13A is an uncharted component of the SWI/SNF chromatin remodeling complex, providing new insights into the molecular mechanisms of brain development.

Disclosures: **Q. Yang:** None. **Y. Zhai:** None. **W. Li:** None. **J. Zhou:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.10

Topic: A.02. Postnatal Neurogenesis

Support: HDRF MPPN8883

Title: Adult hippocampal neurogenesis confers resilience to chronic psychosocial stress

Authors: ***C. ANACKER**, V. M. LUNA, M. A. LEE, R. HEN;
Dept. of Psychiatry, Columbia Univ. Med. Ctr. and Res. Fndn. for Mental Hyg., New York, NY

Abstract: Adult hippocampal neurogenesis is necessary to confer some of the behavioral effects of antidepressants and to prevent the development of depressive-like symptoms following acute stress. Here, we wanted to investigate the role of adult-born neurons in mediating susceptibility and resilience to chronic psychosocial stress. We exposed transgenic mice with either increased neurogenesis or with chemogenetically inhibited adult-born neurons to 10 days of chronic social defeat stress and examined stress susceptibility and resilience in a social interaction test. First, we used mice with adult-inducible deletion of the pro-apoptotic gene Bax from neural stem cells and their progeny to increase the number of 6-week old neurons in the dentate gyrus. We found that socially defeated mice with normal levels of neurogenesis spent ~40% less time interacting with another mouse in the social interaction test compared with non-stressed controls (Ctrl: 105±5 sec, defeated: 62±4 sec; n=14; $p<0.01$). We also measured corticosterone (CORT) levels in response to acute stress and found that, following chronic social defeat, mice with normal levels of neurogenesis were unable to mount a CORT response to acute stress, as indicated by lower levels of stress-induced CORT than non-defeated controls (Ctrl: 267±13 ng/ml, defeated:

176±5 ng/ml; n=14; $p<0.05$). However, defeated mice with increased levels of neurogenesis showed similar levels of stress-induced CORT as controls (253±8 ng/ml, n=14). In addition, we used transgenic mice with inducible expression of the Gi-protein coupled inhibitory designer receptor exclusively activated by designer drugs (DREADD), hM4Di, specifically in 6-week old adult-born neurons. We show that inhibiting the activity of these young neurons with the DREADD-receptor ligand, clozapine-N-oxide (CNO), during social defeat accelerates the development of social avoidance. Moreover, using intracranial cannulations to infuse CNO locally into the ventral dentate gyrus, we demonstrate that inhibiting adult-born neurons particularly in the ventral dentate gyrus enhances stress susceptibility and reduces social interaction time (Ctrl: 140±3 sec, defeated: 102±10 sec, defeated+CNO: 59±5 sec; n=6, $p<0.05$). In summary, our findings demonstrate that the activity of adult-born neurons in the ventral dentate gyrus during exposure to chronic stress is crucial to control susceptibility and resilience to chronic psychosocial stress.

Disclosures: **C. Anacker:** None. **V.M. Luna:** None. **M.A. Lee:** None. **R. Hen:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.11

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant R01AG047820

Title: Systemic factors mediate exercise-induced enhancement of adult hippocampal neurogenesis

Authors: ***M. J. BETLEY**[1], Z. DE MIGUEL[1], A. JARKE[2], B. LEHALLIER[1], D. BERDNIK[1], T. WYSS-CORAY[1];
[1]Stanford Univ., Palo Alto, CA; [2]Heidelberg Univ., Heidelberg, Germany

Abstract: Voluntary exercise is known to increase hippocampal volume in older adults and reduce the risk of developing dementia. Additionally, mice given access to running wheels display increases in hippocampal neurogenesis and enhanced spatial learning and memory. Despite myriad studies showing the neural benefits of exercise on the hippocampus in mice and humans, the mechanisms connecting physical activity and neural improvements are poorly understood. We hypothesized that exercise-induced enhancement of adult hippocampal neurogenesis is due to alterations in circulatory signaling factors of runners. To test this

hypothesis, we intravenously transferred plasma from exercising 4-month-old C57Bl/6 male mice to non-exercised mice. Recipients of exercise-conditioned plasma showed significant increases in the number of immature neurons, long-term cell survival and short-term proliferation in the subgranular zone of the dentate gyrus. In addition, we used antibody-based protein arrays to identify numerous plasma proteins of interest that are differentially regulated by exercise. Our key finding that exercise-conditioned plasma contains factors capable of increasing neurogenesis supports our hypothesis that the enhancing effect of running on the hippocampus is primarily mediated by changes in the systemic environment.

Disclosures: **M.J. Betley:** None. **Z. De Miguel:** None. **A. Jarke:** None. **B. Lehallier:** None. **D. Berdnik:** None. **T. Wyss-Coray:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.12

Topic: A.02. Postnatal Neurogenesis

Support: Marie Curie IIF 628603

Title: ENaC serves as an electrochemical sensor regulating adult neural stem cells

Authors: ***D. PETRIK**, S. GRADE, M. GÖTZ;
Inst. for Stem Cell Res., Helmholtz Centrum Munich, Munich, Germany

Abstract: Adult neurogenesis is regulated by various signaling pathways and paracrine factors. However, almost nothing is known about the role of ionic electrochemical gradients at the interphase between the neurogenic niche and its surrounding environment. We used our transcriptome analysis (1) to search for ion channels selectively enriched in adult neural stem cells (aNSCs). Out of several hundreds of channels, only the Epithelial Sodium Channel (ENaC) was selectively enriched in aNSC with lower expression in parenchymal astrocytes. As ENaC functions in the brain are poorly understood, we set out to examine its role in adult neurogenesis. Immunohistochemistry (IHC) confirmed ENaC in aNSCs, while it did not detect ENaC in parenchymal astrocytes. We also observed ENaC in progenitors and neuroblasts in both the subependymal zone (SEZ) and subgranular zone (SGZ), but not in migrating neuroblasts or doublecortin (DCX)-positive neurons. To test its role in SEZ cells, we blocked or knocked-down (KD) ENaC by specific blockers, such Benzamil, or by esiRNA in neurospheres or primary SEZ cultures. Three days after blocking or KD of ENaC lead to reduction of cell proliferation and

increased cell death. In differentiation conditions, blocking or KD of ENaC virtually ablated the presence of beta-tubulin+ neuroblasts and neurons derived from both neurospheres and primary cultures. Finally, time-lapse microscopy confirmed that blocking or KD of ENaC in primary SEZ cultures reduced cell proliferation. To examine ENaC function *in vivo*, we used transgenic mice, in which floxed ENaC alpha subunit can be knocked-out in GLAST-expressing aNSCs by Tamoxifen (Tam) administration. Following the GFP+ recombined cell population 10 days after Tam revealed reduced adult neurogenesis in both SEZ and SGZ. In the GFP+ pool, there was a reduction in transit-amplifying progenitors and proliferating neuroblasts in SEZ and virtually no Ki67+ cells in SGZ. These results suggest that ENaC is necessary for proliferation in the neurogenic niches, a finding supported by knocking-down of ENaC by retroviral delivery of alpha-ENaC specific miRNA to SEZ. To explore the mechanisms that may control ENaC, we employed the patch-clamp technique on acute brain slices. In hGFAP-GFP+ aNSCs in SEZ, shear-stress increased Benzamil-sensitive currents as well as increased number of proliferating cells suggesting that flow of the cerebrospinal fluid regulates ENaC activity. In summary, our results suggest for the first time that cells in adult neurogenesis may require ENaC to sense changes of electrochemical gradients in the neurogenic niches. Ref.: (1) Beckervordersandforth et al., Cell Stem Cell 2010.

Disclosures: **D. Petrik:** None. **S. Grade:** None. **M. Götz:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.13

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant R01CA150926

NIH Grant R01CA163493

NIH Grant R01HL073394

Title: Elevated p62/SQSTM1 determines the fate of autophagy-deficient neural stem cells through increasing superoxide

Authors: ***C. WANG**[1], S. CHEN[1], S. YEO[1], G. KARSLI-UZUNBAS[2], E. WHITE[2], N. MIZUSHIMA[3], H. W. VIRGIN[4], J.-L. GUAN[1];
[1]Dept. of Cancer Biol., Univ. of Cincinnati, Cincinnati, OH; [2]Rutgers Cancer Inst. of New

Jersey, New Brunswick, NJ; [3]Dept. of Biochem. and Mol. Biology, The Univ. of Tokyo, Tokyo, Japan; [4]Dept. of Pathology and Immunology, Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Autophagy plays important roles in many biological processes, but our understanding of the mechanisms regulating stem cells by autophagy is still very limited. Further, it remains a major challenge to determine whether various autophagy genes control these processes solely through their roles in autophagy, given that many autophagy genes also have functions beyond their roles in canonical autophagy. Here, we present data that unlike ablation of FIP200 required for autophagy induction, inhibition of autophagy by deletion of Atg5, Atg16L1 or Atg7 involved in autophagosome maturation did not impair the maintenance and differentiation of postnatal neural stem cells (NSCs). Comparative analysis of conditional knockout (cKO) mice for these autophagy genes showed that unlike in the neurons, specifically in the NSCs, only FIP200 deletion, but not Atg5, Atg16L1 or Atg7 deletion, caused p62/sequestome1 aggregates to accumulate. Generation and analysis of a FIP200 and p62 double cKO mice demonstrated that the preferential p62 aggregate formationaccumulation triggers aberrant superoxide increase leading to defective NSC maintenance and differentiation primarily by impairing SOD functions. Together, by comparing the inhibition of autophagy by deletion of Atg5, Atg16L1 or Atg7 with the requirement for FIP200 in autophagy induction, our studies reveal a critical role of increased p62 in determining the fate of autophagy deficient NSCs through controlling intracellular superoxide.

Disclosures: C. Wang: None. **S. Chen:** None. **S. Yeo:** None. **G. Karsli-Uzunbas:** None. **E. White:** None. **N. Mizushima:** None. **H.W. Virgin:** None. **J. Guan:** None.

Nanosymposium

10. Postnatal Neurogenesis

Location: N426A

Time: Saturday, October 17, 2015, 1:00 PM - 4:30 PM

Presentation Number: 10.14

Topic: A.02. Postnatal Neurogenesis

Support: CIHR MOP-137082

NSERC 121795

Title: Lineage tracing of neuronal progenitor cells expressing dlx Genes in the zebrafish brain

Authors: *M. EKKER[1], C. M. SOLEK[2], S. FENG[2], E. MAHONEY[2];
[1]Dept Biol., [2]Biol., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: The proper specification and migration of GABAergic interneurons is essential to the establishment of appropriate synaptic connections during development. Transcription factors of the Dlx homeobox family are involved in the proper specification of GABAergic interneurons in vertebrates. In the forebrain, the expression patterns of the dlx1a/dlx2a and of the dlx5a/dlx6a bigene clusters presents extensive overlaps and the functional specificity of the four dlx paralogs still remains elusive The central objective of this study is to trace the lineage of dlx-expressing cells in the zebrafish brain, from early development to adulthood, and to compare the fate of cells expressing genes from the dlx1a/dlx2a and from the dlx5a/dlx6a clusters. To achieve this, we have produced transgenic zebrafish that express the CreERT2 recombinase under the control of dlx1a/2a and dlx5a/6a regulatory sequences and bred them with individuals that express a floxed GFP gene followed by the mCherry gene under the control of an ubiquitin promoter. Thus, we are able to permanently label dlx-expressing cells by introducing tamoxifen in the embryo medium at different developmental time points. We followed the migration and differentiation of these cells throughout the life of the zebrafish. Our findings indicate that, as predicted, the majority of labeled cells give rise to GABAergic neurons, although a small number of cells in the ventral telencephalic area are not immunoreactive for GABA or neuronal markers. The dlx1a/dlx2a-expressing cells labeled at 24 hours post-fertilization (hpf) seem to give rise to a relatively larger number of mCherry-positive cells when examined in older animals, compared to similar labeling of dlx5a/dlx6a fish. Furthermore, the dlx1a/dlx2a-labeled cells give a higher proportion of cells that remain close to the neurogenic zones, compared to dlx5a/dlx6a-labeled cells. Interestingly, a number of dlx5a/6a-expressing cells, labeled at 5 dpf, give rise to a large number of cells that populate the dorsal telencephalon, the periventricular grey zone and the hypothalamus, something that is not seen with dlx1a/2a-labeled cells nor when induction of dx5a/6a-driven Cre is performed earlier. This lineage tracing system can also be used to characterize the development of new GABAergic neurons in adult zebrafish both in conditions of homeostasis and in regeneration following injury.

Disclosures: **M. Ekker:** None. **C.M. Solek:** None. **S. Feng:** None. **E. Mahoney:** None.

Nanosymposium

011. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH 1R41G044890

The Boye Foundation NJ, The Silver Foundation IL

Title: A novel metabolic gene therapy-based strategy for the treatment of Alzheimer's disease

Authors: *P. LEONE[1], S. W. J. MCPHEE[2], J. S. FRANCIS[1];
[1]Dept. of Cell Biol., Rowan-SOM, Stratford, NJ; [2]Asklepios Biopharmaceutical, Chapel Hill, NC

Abstract: Altered amyloid-ß (Aß) metabolism is the most prominent pathogenic hallmark of AD and leads to the formation of Aß plaques. Although the majority of therapeutic strategies target amyloidosis, a number of translational studies have documented the early loss of metabolic integrity in AD suggesting possible clinical potential for targeting mechanisms involved in maintaining a favorable energetic and oxidative status. In this context, manifest abnormalities in the metabolism of the abundant amino acid derivative N-acetyl-L-aspartic acid (NAA) in AD are of particular interest. Reductions in NAA closely parallel neuronal energetic status, and a clinical prominence in AD likely reflects the early stage loss of metabolic homeostasis. NAA synthesis and catabolism are naturally compartmentalized into neurons and oligodendrocytes, respectively, with catabolism known to be integral to uncoupling fatty acid synthesis from the ATP-generating tricarboxylic acid (TCA) cycle in myelinating oligodendrocytes (Francis et al. 2012). The precise role of NAA outside of myelination is currently unclear, but we have performed studies of early stage pathology in the 5xFAD mouse model of AD which reveal a significant down regulation in expression of the gene encoding for NAA synthase (Nat8L) in the hippocampus, thalamus, and cortex prior to cell loss and cognitive deficit concomitant with a reduction in electron transport chain activity and ATP synthesis (Zaroff et al. 2015). We hypothesized that genetic recompartmentalization of ASPA activity to neurons in the 5xFAD mouse brain would result in a heightened resistance to metabolic stress via the promotion of TCA cycle integrity. Preliminary studies have shown that the viral vector-mediated expression of NAA-deacetylating ASPA (AAV-ASPA) in forebrain neurons of 5xFAD mice result in improved energetic status, reduced amyloid burden, and the promotion of cell survival. In addition, the neuronal expression of ASPA promoted a long-term improvement in spatial memory function, indicating a significant degree of phenotypic rescue. The genetic recompartmentalization of NAA catabolism is a novel therapeutic strategy for AD that utilizes a gene therapy technology platform with proven clinical safety and efficacy (Leone et al., 2012), and represents a significant departure from current amyloid-centric approaches by targeting a specific metabolic cycle that has relevance for all neurodegenerative diseases within which compromised oxidative metabolism can be identified.

Disclosures: **P. Leone:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RowanSOM. **S.W.J. McPhee:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Asklepios Biopharmaceutical. **J.S. Francis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RowanSOM.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA 1R01AG042890

Title: Reduced incidence of Alzheimer's Dementia in solid organ transplant recipients treated with calcineurin inhibitors

Authors: *G. TAGLIALATELA[1], C. RASTELLINI[2], L. CICALESE[2];
[1]Neurol., [2]Surgery, Univ. Texas Med. Br., Galveston, TX

Abstract: Alzheimer's Disease (AD) is the most common age-associated dementia for which there is currently no resolving cure. AD affects almost 12% of the US population >65 years of age with a societal and heath care burden that is predicted to become unbearable by the year 2050. The need to develop an effective treatment for AD is therefore pressing. AD neuropathology is characterized by the aggregation and deposition of misfolded amyloid beta (Aβ) and tau proteins. In particular, small oligomeric aggregates of Abeta are believed to be the most toxic species, targeting the synapse and driving initial cognitive decline. Therefore, there is consensus that inhibiting the synaptotoxic action of Aβ oligomers would be an effective treatment strategy. Experimental evidence by our group and others using *in vitro* and *in vivo* models indicates that the protein phosphatase calcineurin mediates the action of Aβ oligomers, thus suggesting that inhibition of calcineurin may be a viable treatment option for AD. However, there is currently no evidence that inhibition of calcineurin could prevent the onset of AD in humans. Here, we report for the first time that individuals chronically treated with calcineurin inhibitors (mainly FK506, Tacrolimus) to prevent solid organ transplant rejection have a significantly lower incidence of AD/dementia as compared to the general population. Specifically, we retrospectively studied a cohort of 2,644 patients that received solid organ transplants at our institution and were maintained under calcineurin inhibitors for immunosuppressive therapy and found that 1.02% (6/587) of such patients at age 65 or older had evidence of clinically relevant dementia. This is significantly lower as compared to the general population where the incidence of AD/dementia in the same age group is 11.7%. The same results were observed for patients >74 years of age (0.6% vs. 15.3%, respectively) and >85 years of age (0% vs. 32%, respectively), suggesting that the beneficial effects of calcineurin inhibitors were not affected by older age. Remarkably, 3 patients who were diagnosed with dementia at the time of transplant had no mention of clinically relevant dementia in follow up visits (up to 7

years after transplant), suggesting reversal of demented status. Collectively, these results indicate that AD/dementia was prevented (and possibly reversed) in subjects chronically treated with calcineurin inhibitors and prompt further clinical development of calcineurin inhibition as a viable treatment for AD. Supported by NIH/NIA grant 1R01AG042890 to GT.

Disclosures: **G. Taglialatela:** None. **C. Rastellini:** None. **L. Cicalese:** None.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association NIRG 12-237751

Human Brain Project HBP Neuroantibodies

Title: Targeting subcellular pools of Amyloid-β oligomers in living cells through intrabodies: a new concept of conformational-selective interference to study the Alzheimer's disease pathogenesis

Authors: G. MELI[1], A. MANCA[1], V. LA MARCA[1], F. RUGGERI[1], C. SCOPA[1], R. SCARDIGLI[1], *A. CATTANEO[2];
[1]European Brain Res. Inst. - Rita Levi-Montalcini, Roma, Italy; [2]Scuola Normale Superiore, Pisa, Italy

Abstract: Amyloid-β oligomers (AβOs) are neurotoxic proteinaceous forms in Alzheimer's Disease (AD) but still unknown in terms of both molecular/structural composition and cellular generation and activity. Amyloid assembly states and dynamics are very difficult to study in living cells, also for the lack of selective tools of study. To this attempt, conformational-sensitive antibodies represent one of the more promising tools. In particular, recombinant antibody fragments can be exploited as intracellular antibodies (intrabodies) for a subcellular-localized interference to block or modulate the function of target molecules. We generated, by an *in vivo* intracellular selection in yeast cells, a panel of conformation-sensitive antibody fragments selectively recognizing AD-relevant AβO conformers (Meli et al., J Mol Biol 2009). Recently, we expressed an anti-AβO single chain antibody fragment (scFv) as an intrabody, with the aim of intercepting AβOs at subcellular sites of their putative formation, and of attempting their functional silencing. In this way, we established a new experimental paradigm of subcellular-

localized and conformational-selective interference (CSI) (Meli et al., Nature Comm 2014). We provided: i. a novel approach to selectively control levels and toxic conformations of biologically-active AβO in living cells; ii. a new dissection of cellular mechanisms of AβO generation, trafficking and actions. Indeed, by exploiting CSI, we demonstrate that intracellular Aβ can oligomerize into pathological forms, through critical conformations formed inside the endoplasmic reticulum (ER). Currently, we are investigating the functional effects mediated by the ER-localized CSI on some subcellular alterations and mitochondrial disfunctions, describing an altered link between ER and mitochondria as a probable subcellular mechanism of AD pathogenesis. We are also targeting the intrabody through different lentiviral systems in primary neuronal stem cells (NSC) derived from neurogenic niches of the adult brain of AD mouse models and in primary human fibroblasts from AD patients. As future perspective, the intrabody-based CSI can be exploitable for *in vivo* therapeutic applications as well as to improve our understanding of the molecular and cellular processes of AD pathogenesis, thereby uncovering new targets for drugs development.

Disclosures: G. Meli: None. **A. Manca:** None. **V. La Marca:** None. **F. Ruggeri:** None. **C. Scopa:** None. **R. Scardigli:** None. **A. Cattaneo:** None.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA RO1 AG040092

Title: Passive vaccination targeting pyroglutamate-3 Aβ reduces Aβ plaque burden without microhemorrhage and partially rescues cognitive deficits in aged APP/PS1dE9 mice

Authors: *H. CREHAN[1,2], M. KLEINSCHMIDT[3,4], E. FITZPATRICK[1], S. CHOWDHURY[1], K. LE[1], J. L. FROST[1], B. O'NUALLAIN[1,2], B. J. CALDARONE[1,2,6], H.-U. DEMUTH[3], J.-U. RAHFELD[3,5], I. LUES[3], S. SCHILLING[3,5], C. A. LEMERE[1];
[1]Ctr. for Neurologic Dis., Brigham & Women's Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Probiodrug AG, Halle (Saale), Germany; [4]Dept. of Drug Design and Target Validation, Fraunhofer Inst. for Cell Therapy and Immunol., Halle (Saale), Germany; [5]Dept. of Drug Design and Target Validation, Fraunhofer Inst. for Cell Therapy and Immunol., Halle (Saale), MA; [6]Harvard NeuroDiscovery NeuroBehaviour Lab., Boston, MA

Abstract: Pyroglutamate-3 Aβ (pGlu-3 Aβ) is an N-terminally truncated, modified Aβ species found in the Alzheimer's disease (AD) brain (Saido et al., 1995; Lemere et al., 1996). Following truncation of the first two Aβ residues, pGlu-3 Aβ is formed by the cyclization of glutamate at the third residue by glutaminyl cyclase. The pGlu-modified N-terminus has been shown to increase aggregation propensity and neurotoxicity by seeding aggregation and speeding oligomerization of Aβ (Russo et al., 2002; Schilling et al., 2006; Nussbaum et al., 2012). To assess the role of pGlu3-antibody Ig isotype and specificity for therapeutic efficacy in immunotherapy, male APP/PS1dE9 Tg mice (~12 mo; C57BL/6) were passively immunized weekly via intraperitoneal injection with 300μg 07/1 IgG1 (k6) anti-pGlu-3 Aβ monoclonal antibody (mAb) (n=15), 300μg 07/1 IgG2a (m6) anti-pGlu-3 Aβ mAb (n=15), 300μg of a pan-Aβ IgG1 mAb that recognizes a non-pyroGlu-3 epitope within the Aβ N-terminus (3A1; n=15), or PBS (n=15) for 16 weeks. Open Field (OF), Water T Maze (WTM) and Contextual Fear Conditioning (CFC) were initiated at ~15 mo of age and included PBS-treated wildtype (WT) controls. Vaccination did not affect general locomotor activity but Tg-PBS mice travelled less distance in the center of the OF compared to Wt-PBS mice suggesting that Tg-PBS mice were more anxious than Wt-PBS mice. Mice treated with the k6 IgG1 mAb showed a trend to travel a greater distance in the OF center suggesting modest normalization of this anxiety-like behavior. Mice treated with the m6 IgG2a pGlu-3 Aβ mAb showed significant improvement in acquisition ($p<0.05$) and reversal learning ($p<0.05$) in the WTM compared to the Tg-PBS mice. No differences were seen between Tg groups in CFC training or testing. Mice were sacrificed at ~16 mo of age. Quantitative image analysis on 6 fixed frozen brain sections per mouse revealed very few hemosiderin-positive microhemorrhages in all groups with no differences between immunized and PBS-control Tg mice. In the hippocampus, pGlu-3 Aβ immunoreactivity (IR), measured by 07/1 IgG2b (k17) mAb, showed a trend for a reduction in k6 IgG1 pGlu-3 Aβ mAb treated mice, however there was a significant reduction in IR in mice given weekly injections of m6 pGlu-3 Aβ IgG2a mAb ($p<0.01$) compared to Tg-PBS controls. Further pathological and biochemical analyses are underway for multiple Aβ species, gliosis, and synapses. Our results suggest that pGlu-3 Aβ mAb Ig isotype strongly affects Aβ clearance, and that selective targeting of pGlu-3 Aβ with an IgG2a mAb is effective in lowering plaque burden in the absence of microhemorrhage, while improving cognitive performance in APP/PS1dE9 Tg mice with pre-existing plaques.

Disclosures: **H. Crehan:** None. **M. Kleinschmidt:** None. **E. Fitzpatrick:** None. **S. Chowdhury:** None. **K. Le:** None. **J.L. Frost:** None. **B. O'Nuallain:** None. **B.J. Caldarone:** None. **H. Demuth:** None. **J. Rahfeld:** None. **I. Lues:** None. **S. Schilling:** None. **C.A. Lemere:** Other; Unpaid position on Probiodrug AG Scientific Advisory Board.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1R01NS079637

Title: Reduced efficacy of anti-Aβ immunotherapy in a mouse model of amyloid deposition and vascular cognitive impairment co-morbidity

Authors: *E. M. WEEKMAN, C. N. CAVERLY, T. J. KOPPER, T. L. SUDDUTH, D. M. WILCOCK;
Physiol., Univ. of Kentucky, Lexington, KY

Abstract: Alzheimer's disease (AD) and vascular contributions to cognitive impairment and dementia (VCID) are the two most common forms of dementia yet they share similar pathologies. Both vasogenic edema and microhemorrhages occur in some cases of AD and some types of VCID and there are also significant adverse vascular events of anti-amyloid beta (Aβ) immunotherapy. Because it is estimated that 40% of AD patients also have VCID, it is imperative to determine the effect of anti-Aβ immunotherapy on cognition and vascular pathology when AD and VCID are co-morbid. To model AD-VCID co-morbidity we use the APP/PS1 mouse model of amyloid deposition and induce hyperhomocysteinemia (HHcy) via diet, which models a form of VCID. We placed 9 month old wildtype or APP/PS1 mice on a control diet or a diet that induces HHcy. After 3 months on diet, when cerebrovascular pathology is induced by the HHcy, the mice received weekly intraperitoneal injections of IgG2a or 3D6 (N-terminal anti-Aβ antibody). Cognition was assessed with the two day radial arm water maze. During treatment, MRI for microhemorrhages and edema was performed. Matrix metalloproteinase (MMP) activation was measured by gelatin zymography and microhemorrhages were assessed by Prussian blue staining. Aβ levels were quantified using immunohistochemistry, Congo red staining and ELISA measurement. Neuroinflammation was assessed by qPCR for gene markers specific for peripheral macrophage phenotypes. In block 10 of the radial arm water maze, APP/PS1 mice made more errors than wildtype mice and APP/PS1 mice with VCID on 3D6 treatment made more errors than APP/PS1 mice with VCID on IgG2a treatment. Imaging for microhemorrhages showed induction of bleeds in mice on the HHcy diet and on 3D6 treatment. Quantification of MMP expression and activation, Aβ levels, and the neuroinflammatory phenotype is in progress. Overall, early assessment of the data indicates that anti-Aβ immunotherapy may not provide a clinical benefit in individuals with VCID co-morbidity.

Disclosures: **E.M. Weekman:** None. **C.N. Caverly:** None. **T.J. Kopper:** None. **T.L. Sudduth:** None. **D.M. Wilcock:** None.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Research Projects of National Interest (PRIN) Grant 2010/2011

Title: Intranasal treatment, a new tool to deliver BDNF into the brain: Effects in a murine model of Alzheimer's disease

Authors: ***C. CRISCUOLO**[1,2], C. FABIANI[1], S. CAPSONI[3], A. CATTANEO[3,4], L. DOMENICI[1,2];
[1]CNR - Neurosci. Inst., Pisa, Italy; [2]Dept. of Biotechnological and Applied Clin. Sci. - DISCAB, Univ. of L'Aquila, L'Aquila, Italy; [3]Bio@SNS, Scuola Normale Superiore, Pisa, Italy; [4]Neurotrophins and Neurodegenerative Dis. Unit, European Brain Res. Inst. - EBRI, Roma, Italy

Abstract: A therapeutic approach based on brain-derived neurotrophic factor (BDNF) to prevent or slow the cognitive decline characteristic of Alzheimer's disease (AD) has a strong rationale, based on the recent findings that BDNF administration or gene delivery to *in vivo* AD models produce beneficial effects including improvements in learning and memory. Despite this, delivering BDNF to the brain in a safe and long lasting manner presents a significant challenge, because BDNF crosses the blood-brain barrier (BBB) with difficulty and low kinetic of accumulation into the brain, when administered systematically. Here we focused on the use of a protocol for BDNF intranasal administration in a familial AD murine model, 5xFAD, characterized by an accelerated development of beta amyloid (Aβ) plaques with high levels of accumulation of intraneuronal Aβ42 already around a month and a half of postnatal life, well as by spatial learning and memory impaired at 4-5 months of age. Through intranasal administration it is possible to bypass the BBB with therapeutic agents that directly reach the central nervous system (CNS). We first evaluated the alteration of synaptic function in 5xFAD entorhinal cortex (EC), focusing on LTP. Notably, EC is the first brain area involved by injury in AD, moreover, BDNF expression is reduced in the EC of AD patients characterized by Aβ accumulation. Synaptic function was studied recording extracellular field potentials (FPs) in cortical layers II-III of EC slices; LTP was elicited by high frequency stimulation (HFS). Next, we evaluated the protective role of BDNF intranasal delivery on synaptic dysfunction identified

in 4 months old 5xFAD mice. We found a rescue of synaptic function in EC after 3 weeks of BDNF intranasal administration. Moreover, preliminary data on the post-synaptic molecular characterization highlighted a synaptoprotective effect of BDNF on 5xFAD. In fact, BDNF intranasal delivery carried out the rescue of spinophilin expression and PSD95 and TrkB activation, altered in 4 months old 5xFAD mice. In ongoing experiments, in order to complete the description of post-synaptic alterations and recovery in 5xFAD, we are evaluating the expression of glutamate receptor (AMPAr and NMDAr) and BDNF-TrkB signalling pathways on cytoplasmatic membrane of different brain areas, besides to evaluate the time progression of BDNF diffusion after intranasal delivery. Our results extended the effectiveness of BDNF in AD murine models, suggesting that intranasal delivery may improve the prospects of using neurotrophins to treat CNS neurodegenerative diseases.

Disclosures: C. Criscuolo: None. **C. Fabiani:** None. **S. Capsoni:** None. **A. Cattaneo:** None. **L. Domenici:** None.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R21AG044714

UW Madison ADRC NIA P50AG033514

UW Madison ICTR NCATS UL1TR000427

Title: Metabotropic glutamate receptor 5 is a potential therapeutic target for Alzheimer’s disease

Authors: *C. J. WESTMARK, M. J. FILON, L. I. STEINBERG, E. P. WALLACE, S. L. WRIGHT, R. K. MAGANTI;
Univ. Wisconsin, Madison, WI

Abstract: The group I metabotropic glutamate receptors (mGluR1 and mGluR5) are glutamate-activated, G-protein-coupled receptors widely expressed in the central nervous system. We have identified amyloid-beta protein precursor mRNA (*App*) as a synaptic target that is translationally regulated through mGluR5 signaling. *App* mRNA codes for amyloid-beta protein precursor (APP), which is cleaved by beta- and gamma-secretases to produce amyloid-beta, the predominant protein found in the senile plaques that are characteristic of Alzheimer’s disease

(AD). Antagonists of mGluR5 are currently under investigation for a range of indications including anxiety, epilepsy, pain, depression, Parkinson's disease, gastroesophageal reflux, fragile X syndrome, autism and addiction. This project explores the hypothesis that mGluR5 antagonists are a viable therapeutic strategy to treat Alzheimer's disease. Findings from our laboratory indicate that mGluR5 antagonists reduce the expression of amyloid-beta in mouse models of AD. Our current studies are designed to determine if mGluR5 antagonists are a viable therapeutic strategy to rescue learning & memory, seizure and sleep deficits in an AD mouse model. Specifically, we are testing the efficacy of the mGluR5 antagonists: (1) fenobam, which is an off-patent, orphan drug that has passed Phase I and Phase II clinical trials and which could be repurposed for the treatment of AD; and (2) 2-chloro-4-((2,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1H-imidazol-4-yl)ethynyl)pyridine (CTEP), an experimental negative allosteric modulator of mGluR5 with a long half-life and high oral bioavailability in AD J20 mice. The J20 mice express a mutant form of human APP bearing both the familial Swedish (K670N/M671L) and Indiana (V717F) mutations. Ongoing studies are testing the efficacy of the aforementioned mGluR5 antagonists in rescuing APP and amyloid-beta expression, passive avoidance, EEG and rest-activity patterns. Our overall goal is to provide *in vivo* proof-of-concept evidence that mGluR5 antagonists are a viable therapeutic strategy to attenuate multiple AD phenotypes. In aggregate, these studies will provide pre-clinical data on the efficacy of fenobam and CTEP in regards to biomarker, cognitive and behavioral phenotypes in wild type and AD littermate mice.

Disclosures: C.J. Westmark: None. **M.J. Filon:** None. **L.I. Steinberg:** None. **E.P. Wallace:** None. **S.L. Wright:** None. **R.K. Maganti:** None.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: GliaCure, Inc.

Alzheimer's Drug Discovery Foundation

Title: P2Y6 receptors as a novel disease modifying strategy for Alzheimer's disease

Authors: *P. G. HAYDON[1], J. LEE[2], R. T. DOYLE[1], J. DONG[1];
[1]Neurosci., Tufts Univ. Sch. of Med., Boston, MA; [2]Sage Partner Intl., Andover, MA

Abstract: The purinergic P2Y6 receptor is preferentially expressed in the CNS by microglia, where it is known to stimulate phagocytosis, and systemically it is expressed by T cells, where it exerts anti-inflammatory roles. The levels of uridine the precursor of UDP, the endogenous ligand for the P2Y6 receptor, are decreased in the CSF of patients with Alzheimer's disease, raising the potential that enhancing the levels of agonists for these receptors would be beneficial in this disorder. To test this possibility we injected UDP i.c.v. in PSAPP mice and demonstrated that it rapidly reduced amyloid deposition using longitudinal two photon microscopy (i.e., in three days), increased amyloid uptake into microglia, reversed deficits in synaptic plasticity and restored contextual fear conditioning. Using P2Y6 receptor-expressing cells we tested rationally designed novel chemical entities for their ability to mobilize intracellular Ca^{2+} and identified compounds with selectivity for P2Y6 over P2Y2 and P2Y4 receptors. With these compounds we performed phenotypic screening and identified GC021109 as a candidate for progression. GC021109, delivered i.p. once daily for seven days, reduced amyloid deposition in 6-month-old mice and, when delivered daily from 3 months to 6 months of age, reduced the accumulation of amyloid, prevented deficits in contextual fear conditioning and reduced the accumulation of cytokines IL-12(p70), IL-10, and IL-4, all of which have been implicated in Alzheimer's disease. IND-enabling toxicology studies together with studies in healthy volunteers demonstrated that GC021109 is safe and well tolerated and exhibits excellent pharmacokinetic parameters. Currently GC021109 is being studied in a Phase 1b multiple ascending dose study in patients with mild to moderate Alzheimer's disease. Together these studies demonstrate that modulation of P2Y6 receptors, acting through parallel anti-inflammatory and phagocytic mechanisms of action, has the potential to treat Alzheimer's disease.

Disclosures: **P.G. Haydon:** A. Employment/Salary (full or part-time); GliaCure, Inc. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; GliaCure, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GliaCure, Inc. **J. Lee:** None. **R.T. Doyle:** None. **J. Dong:** None.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Counteracting impaired lipidation of apoE4 and the associated brain pathology and cognitive deficits by the ABCA1 agonist peptide CogpepB

Authors: A. BOEHM-CAGAN[1], J. O. JOHANSSON[2], J. K. BIELICKI[3], *D. M. MICHAELSON[4];
[1]Neurobio., Tel Aviv Univ., Tel Aviv, Israel; [2]Artery Therapeut., San Francisco, CA; [3]Lawrence Berkeley Lab., Berkeley, CA; [4]Tel-Aviv Univ., Tel-Aviv, Israel

Abstract: The allele ε4 of apolipoprotein E (apoE4) is the most prevalent genetic risk factor for Alzheimer's disease (AD) and is thus a natural therapeutic target. Human and animal model studies suggest that apoE4 is hypolipidated. Furthermore, apoE4 is markedly less efficacious than its AD benign isoform, apoE3, in promoting cholesterol and phospholipid efflux from astrocytes and neurons. The ATP-binding cassette transporters A1 (ABCA1) is a key lipidating protein. The present study addresses the hypothesis that cognitive and brain pathological effects of apoE4 are driven by its hypolipidation and that treatment with specific ABCA1 agonists can correct the lipidation deficiency of apoE4 and the associated cognitive and brain impairments. ABCA1 agonists were screened for efficacy, safety and drugability. *In vitro* studies showed significantly lower ABCA1 mediated and total cholesterol efflux from apoE4 astrocytes compared to apoE3 astrocytes. Co-incubation with CogpepB, a peptide derived from the C-terminal of apoE, increased level of ABCA1 driven lipid efflux from E4 astrocytes by approximately 6 fold and rendered it comparable to that seen with E3 astrocytes. These *in vitro* findings suggest that CogpepB is a potent ABCA1 agonist. We next examined whether the effects of apoE4 *in vivo* can be reversed by i.p. injection of CogpepB (20 mg/kg/48h) for 6 weeks to 12 weeks old apoE3 and apoE4 TR mice (n=6-8/group). This revealed that the apoE4 driven brain pathology (e.g. accumulation of Aβ42 and of phosphorylated tau in hippocampal neurons and corresponding decreased levels of VGluT1 and apoER2) where reversed by the CogpepB treatment. Furthermore, CogpepB counteracted cognition deficits in the apoE4 mice in a novel object recognition test and the Morris water maze. PK studies and brain tissue distribution at therapeutic doses showed that the peptide largely co-localized with hippocampal astrocytes and that its concentration in the brain 24 post-administration was higher than its corresponding *in vitro* EC50. These findings suggest that an ABCA1 agonist, CogpepB corrects the lipidation insufficiency of apoE4 thereby preventing the consequent brain pathology and cognitive deficits. The data support lipidation of apoE4 by CogpepB as a novel therapeutic approach in apoE4 AD.

Disclosures: A. Boehm-Cagan: None. **J.O. Johansson:** None. **J.K. Bielicki:** None. **D.M. Michaelson:** None.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

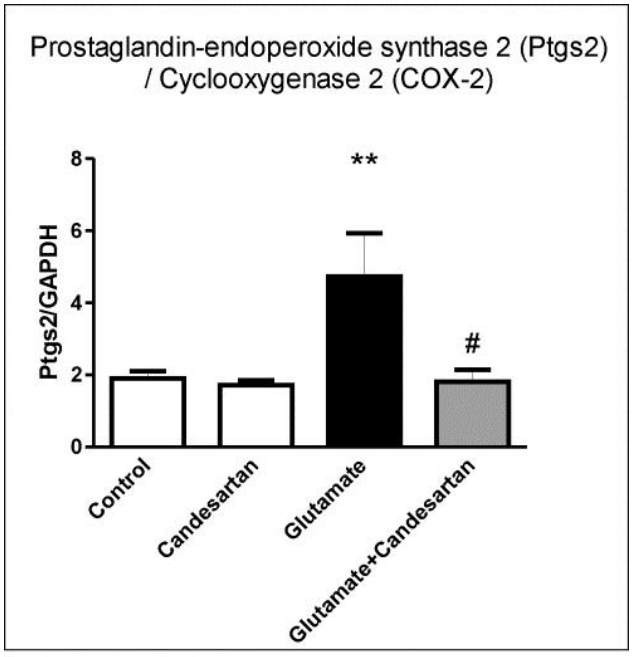
Presentation Number: 11.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Candesartan prevents glutamate-induced inflammation in cultured primary neurons

Authors: *J. M. SAAVEDRA[1], A. G. ELKAHLOUN[2], R. HAFKO[3];
[1]Pharmacol. and Phisiology, Georgetown Univ. Med. Ctr., Washington, DC; [2]Natl. Human Genome Res. Inst., NIH, Bethesda, MD; [3]Section on Pharmacol., NIMH, Bethesda, MD

Abstract: Alzheimer's disease (AD) is the most frequent age-related dementia, currently without treatment. There is increasing interest to clarify initial pathogenic mechanisms, possible targets for early therapeutic intervention. We focused on glutamate excitotoxicity, a major early pathogenic factor, and the effects of candesartan, an Angiotensin Receptor Blocker (ARB) of neuroprotective efficacy in cell culture systems, rodent models of AD, and a group of compounds demonstrated to ameliorate AD risk factors, such as hypertension and diabetes. Primary cerebellar granule cells (CGC), isolated from 8-day old Sprague Dawley rat pups, were exposed to 100 μM glutamate and pre-treated for one hour with the AT1R blocker candesartan at neuroprotective concentrations (10 μM). Gene expression was quantified by qPCR. Candesartan significantly reduced glutamate-induced inflammation. Multiple group comparisons were performed by one-way ANOVA followed by Newman-Keuls post-test. A probability value of ≤0.05 was considered for statistical significance. Exposure to glutamate significantly reduced neuronal viability while up-regulating the expression of multiple genes on pro-inflammatory pathways, including Interleukin 1 alpha (IL-1α), endothelin-1 (ET-1), prostaglandin-endoperoxide synthase 2 (Ptgs2) (COX-2) (Figure, ** <005 vs control; # <005 vs glutamate), Intercellular adhesion molecule (Icam1) and Vascular cell adhesion molecule (Vcam1). In all cases, pretreatment with candesartan completely prevented glutamate-induced neurotoxicity. Our results indicate that Angiotensin II receptor blockade with candesartan is strongly and directly neuroprotective, significantly ameliorating neuronal injury as a result of glutamate excitotoxicity, an early injury factor in AD. These results support the use of candesartan and other ARBs for the treatment of AD in its preclinical, early stages.



Disclosures: **J.M. Saavedra:** None. **A.G. Elkahloun:** None. **R. Hafko:** None.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Grants-in-Aid for Young Scientists (B) from the Japanese Ministry of Education Culture, Sports, Science and Technology, Japan

Novartis Foundation for Gerontological Research

Takeda Foundation for Life Science Research

Title: Effects of AntiParkinsonian Agents on β-amyloid and α-synuclein Oligomer Formation *in vitro*

Authors: *K. ONO[1], J.-I. TAKASAKI[2], R. TAKAHASHI[2], T. IKEDA[2], M. YAMADA[2]; [1]Dept. of Neurol., Sch. of Medicine, Showa Univ., Tokyo, Japan; [2]Dept. of Neurol. and Neurobio. of Aging, Kanazawa Univ., Kanazawa / Ishikawa, Japan

Abstract: The aggregation of β-amyloid protein (Aβ) and α-synuclein (αS) is hypothesized to be the key pathogenic event in Alzheimer's disease (AD) and Lewy body diseases (LBD), with oligomeric assemblies thought to be the most neurotoxic. Inhibitors of oligomer formation, therefore, could be valuable therapeutics for patients with AD and LBD. Here, we examined the effects of antiparkinsonian agents (dopamine, levodopa, trihexyphenidyl, selegiline, zonisamide, bromocriptine, peroxide, ropinirole, pramipexole, and entacapone) on the *in vitro* oligomer formation of Aβ40, Aβ42, and αS using a method of photo-induced cross-linking of unmodified proteins (PICUP), electron microscopy, and atomic force microscopy. The antiparkinsonian agents except for trihexyphenidyl inhibited both Aβ and αS oligomer formations, and, among them, dopamine, levodopa, pramipexole, and entacapone had the stronger *in vitro* activity. Circular dichroism and thioflavin T(S) assays showed that secondary structures of Aβ and αS assemblies inhibited by antiparkinsonian agents were statistical coil state and that their seeding activities had disappeared. The antiparkinsonian agents could be potential therapeutic agents to prevent or delay AD and LBD progression.

Disclosures: K. Ono: None. **J. Takasaki:** None. **R. Takahashi:** None. **T. Ikeda:** None. **M. Yamada:** None.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: HSC SOM RAC grant

NINDS Grant R21NS077089-01A1

NIH Grant R01NS083704

Alzheimer's Association Grant NIRG-11-204995

Bright Focus Foundation Grant A2011372

Title: A novel virus-like particle based vaccine against tau pathology

Authors: *N. M. MAPHIS[1], E. CROSSEY[1], J. PEABODY[1], F. A. J. AHMAD[2], D. PEABODY[1], B. CHACKERIAN[1], K. BHASKAR[1];
[1]Mol. Genet. and Microbiology, [2]Univ. of New Mexico, Albuquerque, NM

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease clinically characterized by cognitive decline leading to dementia. The major pathological hallmark responsible for this decline in cognition is the neuronal accumulation of hyperphosphorylated Microtubule Associated Protein Tau (MAPT or Tau) into aggregated neurofibrillary tangles (NFTs). Thus far, there are no effective therapies to treat or prevent AD. Recently, Virus-Like Particles (VLPs) emerged as a promising vaccination technology. VLPs efficiently harness the immune system to raise antibodies against specific antigens (conjugated to their surface) without inducing a severe inflammatory response. VLP-conjugated antigens are presented to the immune system in a high-density multivalent array format, which leads to a robust and long-lasting immune response generating antibodies against the antigen. In the current study we engineered a novel VLP-immunogen by conjugating a pathologically relevant form of tau peptide (pathological Tau or pTau) onto Qβ VLP particles creating 'Qβ-pTau' immunogen. The Qβ-pTau and the unconjugated Qβ control were administered intramuscularly, bi-weekly, for 6-weeks to rTg4510, a mouse model of tauopathy. First, we observed a five fold increase of antibody titers against the specific pTau protein generated in the sera of Qβ-pTau vs. Qβ control-vaccinated animals. Second, the Qβ-pTau vaccination, but not the Qβ control, resulted in significant improvement in recognition and spatial memory in the rTg4510 mice, as demonstrated by the Novel Object Recognition ($p<0.05$) and the Morris Water Maze tests ($p<0.01$), respectively. In addition, Qβ-pTau-vaccinated rTg4510 mice exhibited decreased levels of phosphorylated tau ($p<0.05$), NFTs ($p<0.05$), and CD45 positive neuroinflammation. In summary, immunization with Qβ-pTau rescues cognition, reduces hyperphosphorylated tau, NFTs, and neuroinflammation in the rTg4510 mouse model of tauopathy. Therefore, VLP-based immunotherapy, targeting pathological tau, provides a potential opportunity for developing future therapies against tau pathology.

Disclosures: **N.M. Maphis:** None. **E. Crossey:** None. **J. Peabody:** None. **F.A.J. Ahmad:** None. **D. Peabody:** None. **B. Chackerian:** None. **K. Bhaskar:** None.

Nanosymposium

11. Alzheimer's Disease: Experimental Therapeutics

Location: S403

Time: Saturday, October 17, 2015, 1:00 PM - 4:15 PM

Presentation Number: 11.13

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Air Force Office of Scientific Research (EOARD, London, UK), and Air Force Material Command, USAF, under grant number FA8655-05-1-3065

Swedish Medical Research Council (Nr 2710-HSS)

Swedish Strategic Research Foundation, Stockholm, Sweden

Ministry of Science & Technology, Govt. of India & Govt. of Sweden (HSS/AS),

Indian Medical Research Council, New Delhi, India (HSS/AS);

India-EU Research Co-operation Program (RP/AS/HSS)

The University Grants Commission, New Delhi, India (HSS/AS),

Title: Histamine H3 Inverse agonist or antagonist with partial H4 agonist activity reduces amyloid-beta peptide induced brain pathology in Alzheimer's disease

Authors: *R. PATNAIK[1], A. SHARMA[2], S. D. SKAPER[3], D. F. MURESANU[4], R. J. CASTELLANI[5], A. NOZARI[6], H. S. SHARMA[2];
[1]Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [2]Anesthesiol. & Intensive Care Med., Uppsala Univ. Hopsital, Uppsala, Sweden; [3]Dept. of Pharmaceut. and Pharmacol. Sci., Univ. of Padova, Padova, Italy; [4]Clin. Neurosciences, Univ. of Med. & Pharm., Cluj-Napoca, Romania; [5]Pathology, Univ. of Maryland Sch. of Med., Baltimore, MD; [6]Anesthesiol. & Intensive Care, Massachusetts Gen. Hospital, Harvard Univ., Boston, MA

Abstract: Increasing evidences suggest that histamine is involved in the pathogenesis of Alzheimer's disease (AD). Decrease of histamine concentration in several brain areas are seen in postmortem studies on human AD cases. Also, increased levels on histamine in plasma and in some areas of the brain are seen in Alzheimer's dementia brain. However, the precise mechanism of histamine induced AD pathology is not well known. Since histamine induces breakdown of the blood-bran barrier (BBB) in several brain areas and activated astrocytes and microglia causing disturbances in brain microenvironment, it is quite likely that the amine could play critical roles in AD pathology. Histamine could modulate brain functions through Histamine H1 to H4 receptors. Few studies indicate an involvement of H3 receptors in reducing amyloid beta protein (AβP) pathology in model experiments. This indicates that H3 receptors that regulate cognitive and memory functions in hippocampus could be involved in AD pathology. Since H4 histamine receptors are present in the brain and stimulation of these receptors regulate neuronal functions, it would be interesting to see whether drugs blocking the H3 receptors and/or stimulating H4 receptors may have some beneficial effects in AD induced brain pathology. In present investigation we examined the influence of one potent histamine H3 receptor inverse agonist BF 2649 hydrochloride and one selective H3 receptors antagonist with partial H4 agonist properties Clobenpropit dihydrobromide in our rats model of AβP induced AD like brain pathology. AD like pathology was produced in rats by administering AβP (1-40) intraventricularly (i.c.v.) in the left lateral ventricle (250 ng/10 µl) once daily for 4 weeks. Control rats received saline. In separate group of rats either BF 2649 (1 mg/kg, i.p.) or

Clobenpropit (1 mg/kg, i.p.) once daily was administered 3 weeks after the 1st AβP administration and continued for 1 week. After 30 days of the 1st AβP infusion, the rats were examined for BBB breakdown, edema, neuronal, glial injuries and AβP deposits in their brain. Our results showed a significant reduction in AβP deposits in the brain along with neuronal damage and glial activation. Interestingly, the breakdown of the BBB to Evans blue albumin and radioiodine in cortex, hippocampus, hypothalamus and cerebellum was significantly reduced in drug treated group as compared to control. Clobenpropit showed superior effects than BF2649 in reducing brain pathology in AD. Taken together our observations are the first to show that blockade of H3 and stimulation of H4 receptors are beneficial for the treatment of AD pathology, not reported earlier.

Disclosures: R. Patnaik: None. **A. Sharma:** None. **S.D. Skaper:** None. **D.F. Muresanu:** None. **R.J. Castellani:** None. **A. Nozari:** None. **H.S. Sharma:** None.

Nanosymposium

012. Therapeutics of Parkinson's Disease: Clinical Studies

Location: N230

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 12.01

Topic: C.03. Parkinson’s Disease

Support: Lewi Body Disease Foundation

Title: Nilotinib significantly alters blood and CSF α-Synuclein and p-Tau levels, inhibits dopamine breakdown and increases neuro-restorative markers in an open-labelled Parkinson’s disease with dementia and Lewy body dementia trial

Authors: *F. L. PAGAN;
Georgetown Univ. Hosp. Neurol. Dept., Medstar Georgetown Univ. Hosp., Washington, DC

Abstract: Parkinson’s disease is characterized by loss of dopamine neurons and accumulation of α-Synuclein in LBs. Nilotinib is a potent inhibitor of Abl tyrosine kinase and it is FDA-approved for adult CML. Nilotinib penetrates the brain and inhibits Abl, leading to autophagic clearance of amyloid proteins. It also increased brain dopamine and modulated immune markers, and reversed motor and cognitive decline. We conducted a clinical trial with the primary objective to determine the safety and efficacy of Nilotinib in advanced PD, PDD and LBD patients. Our studies include measurement of CSF and plasma biomarkers at baseline, 2 and 6 months with 150mg and 300mg Nilotinib daily. These doses are significantly lower of Nilotinib for CML treatment (800-1200mg/ day). We excluded patients with prolonged QTc and other medical

contradictions. 8 patients have passed the 2 months period. More than half the patients screened were excluded due to cardiac complications. Nilotinib has a good safety profile in enrolled subjects with no QTc prolongation or myelosuppression. Nilotinib CSF penetration is 0.5-1.5%. A significant reduction (>60%) in plasma α-Synuclein was detected, correlating more frequent bowel movements. There is also a significant decrease in CSF p-Tau181, while total Tau is unchanged. CSF Abeta40 is reduced (18%) with no change in the plasma, while CSF and plasma Abeta42 remain stable. The level of CSF α-Synuclein is unchanged, suggesting stabilization of α-Synuclein levels. CSF homovanillic acid (HVA) is reduced (26%) at 2 months despite a decrease in dopamine replacement therapy, suggesting inhibition of dopamine breakdown. This effect on dopamine also correlates with clinical outcomes, including stabilization with less or no Azilect and L-Dopa. Nilotinib also increases CSF concentration (30-55%) of neuro-restorative markers (PDGF-AB/BB, G-CSF, IL-7, GRO, CCL2 and CCL5), while it reduces markers of neurodegeneration (NSE and S100B). Overall these data indicate safety, tolerability and biomarkers efficacy, and provide a collectively compelling rationale to examine Nilotinib in larger placebo-controlled, double blind studies in earlier stages of diseases.

Disclosures: **F.L. Pagan:** A. Employment/Salary (full or part-time): Georgetown University Hospital. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Lewy Body Foundation, Georgetown University Hospital. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Georgetown University Medical Center's CRU. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Teva, Acadia, US World Meds, Lunbeck, Abvie, Merz.

Nanosymposium

12. Therapeutics of Parkinson's Disease: Clinical Studies

Location: N230

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 12.02

Topic: C.03. Parkinson's Disease

Support: Walter S. and Lucienne Driskill Foundation

Michael J. Fox Foundation

Mr. Charles Ackerman

Mr. Ray Sidhom

Mr. John Anderson

Title: Stopping progression of Parkinson's disease with the drug phenylbutyrate

Authors: *C. R. FREED[1], M. WANG[1], J. CUMMISKEY[1], K. B. BJUGSTAD[1], B. A. SYMMES[1], C. A. JOHNSON[2], R. C. MURPHY[2], M. A. LEEHEY[3], W. ZHOU[1];
[1]Div. of Clin. Pharmacol., [2]Dept. of Pharmacol., [3]Dept. of Neurol., Univ. Colorado Sch. of Med., Aurora, CO

Abstract: Parkinson's disease has excellent symptomatic treatment with drugs such as L-DOPA, but the underlying disease process causes a relentless downhill course. Several drugs have been tested in an effort to alter disease progression, but all have failed. We have developed a new concept for stopping the progression of Parkinson's disease by turning on a neuroprotective gene with an FDA-approved drug. In Parkinson's disease, the protein alpha-synuclein forms abnormal deposits called Lewy bodies as well as toxic fibrils which contribute to the death of dopamine neurons. We have discovered that the drug phenylbutyrate can prevent aggregation of alpha-synuclein in transgenic mice which are genetically programmed to develop a form of Parkinson's disease as they age. The drug works by upregulating the neuroprotective gene DJ-1. Gene activation leads to an increase in lysosome and exosome activity, promoting transfer of alpha-synuclein from neurons into the bloodstream where the protein is eliminated. In mice, phenylbutyrate increased plasma alpha-synuclein by about 100 per cent compared to non-treated control animals. To see if phenylbutyrate has the same effect in people, we have given the drug for three weeks to 20 people with newly diagnosed Parkinson's disease and to 20 age-matched subjects without the disease. We found that the drug increased the level of alpha-synclein in plasma of all 40 subjects from 50 to 150 per cent of baseline values, just as it had done in transgenic mice, strongly suggesting that the drug can mobilize alpha-synuclein from neurons into blood plasma. While baseline plasma alpha-synuclein varied between subjects, the average alpha-synuclein plasma concentrations at baseline and during phenylbutyrate administration did not differ between patients with Parkinson's disease and normal subjects. Results are compatible with a neuroprotective effect of phenylbutyrate by accelerating clearance of alpha-synuclein from brain into plasma. A double-blind, placebo-controlled trial in newly diagnosed Parkinson patients will be needed to prove whether phenylbutyrate can stop the progression of Parkinson's disease in humans.

Disclosures: **C.R. Freed:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Hyperion Pharmaceuticals. **M. Wang:** None. **J. Cummiskey:** None. **K.B. Bjugstad:** None. **B.A. Symmes:** None. **C.A. Johnson:** None. **R.C. Murphy:** None. **M.A. Leehey:** None. **W. Zhou:** None.

Nanosymposium

12. Therapeutics of Parkinson's Disease: Clinical Studies

Location: N230

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 12.03

Topic: C.03. Parkinson's Disease

Support: NIH F31 NS089111

NIH R01 DK095172

NIH P30 AG024827

Title: The relationship between physical fitness and neurocognitive function in humans with Parkinson's disease

Authors: *A. M. WEINSTEIN[1,2], G. GROVE[1], S. BURKE[1], S. WINTER[1], K. I. ERICKSON[1]; [1]Dept. of Psychology, Univ. of Pittsburgh, Pittsburgh, PA; [2]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA

Abstract: Parkinson's disease (PD) is a neurodegenerative disease affecting almost half a million Americans (Dorsey et al., 2007). PD is characterized by motor disturbances, but executive function deficits are also a prominent symptom of PD. Unfortunately, PD medications have only a minimal effect on cognitive symptoms. However behavioral factors, such as physical activity, are emerging as possible methods for improving the function of the frontal-striatal system and cognition. This study aims to establish whether aerobic fitness positively relates to frontal-striatal functioning and executive function in adults with PD. Seventeen adults diagnosed with early stage PD (median age = 67) and 6 neurologically healthy controls (median age = 66) underwent neuropsychological evaluations, mobility and balance assessments, VO2 submax exercise testing, and MRI scans. All evaluations occurred while PD patients were on medication. Executive function was assessed with the Parkinson's Disease Cognitive Rating Scale (PDCRS). Physical fitness was assessed with the Oxygen Uptake Efficiency Slope (OUES), as derived from the VO2 submax test. Frontal-striatal functional connectivity was assessed during a resting state paradigm using the rostral and caudal portions of the caudate nucleus as seed regions (voxelwise threshold: $z = 2.3$; clusterwise threshold: $k > 30$). The relationship between fitness, executive function, and functional connectivity to the caudate nucleus was examined using Spearman's correlations and linear regression, controlling for age, education, and motor symptoms. Within the PD group, higher fitness (OUES) levels were associated with better performance on the PDCRS ($r = .668$, $p = .003$). In a hierarchical regression analysis, higher OUES was marginally predictive of better PDCRS-fs performance ($F(4,12) = 1.697$, $p = .215$; OUES: beta = .440, $p = .095$). Sixteen frontal regions showed greater caudate connectivity with higher fitness levels including the precentral gyrus, middle frontal gyrus, frontal pole, and orbitofrontal cortex. The connectivity in eight of these regions was also positively related to PDCRS performance. This

pilot study found that higher fit PD patients performed better on cognitive tests and exhibited greater fitness-related functional connectivity between the caudate nucleus and frontal lobe. These results indicate that aerobic fitness may not only be associated with better motor function, but also cognitive function, in PD patients. Future work in a larger sample is needed to examine whether an exercise intervention improves frontal-striatal functioning in PD.

Disclosures: A.M. Weinstein: None. **G. Grove:** None. **S. Burke:** None. **S. Winter:** None. **K.I. Erickson:** None.

Nanosymposium

12. Therapeutics of Parkinson's Disease: Clinical Studies

Location: N230

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 12.04

Topic: C.03. Parkinson's Disease

Support: Virginia Horne Henry Grant

Title: Exercise modality differentially improves bradykinesia and hypokinesia in Parkinson's disease: rct comparing pilates to general exercise

Authors: *K. L. DOYLE, K. A. PICKETT, J.-A. C. LAZARUS;
Kinesiology, Univ. of Wisconsin -- Madison, Madison, WI

Abstract: Introduction. Bradykinesia (slow movements) and hypokinesia (small movements) deleteriously affect upper limb coordination and activities of daily living in individuals with Parkinson disease (PD). This randomized control trial tested upper limb function before and after participation in Pilates exercises compared to general PD therapeutic exercises with moderate intensity aerobics. Methods. 14 individuals with PD (10 females, 52-70 y.o., H&Y stages I-III) were evaluated "on" medication. Participants were randomly assigned to either instructor-led group Pilates or group therapeutic exercise following American Parkinson Disease Association recommendations. Both groups completed 2, 1-hour classes per week for 12 weeks. Pre- and post-test upper limb kinematics were assessed across four motor tasks: index finger tapping (IFT), dysdiadokokinesis (DDK), finger flexion/extension, and rapid wrist extension (RWE). Bradykinesia, and hypokinesia measures were collected. Left and right hand data were aggregated for subjects within each group. Small group size, non-Gaussian distribution, and lack of homogeneity of variance warranted Wilcoxon signed ranks tests ($\alpha \leq .05$). Results. Pilates improved hypokinesia, evidenced by larger displacement in IFT (P=.017), DDK (P=.001), and RWE (P=.018). Additionally, Pilates improved speed SD of velocity: DDK (P=.045); and

increased acceleration and its SD: WGB (P=.011 and P=.026) and RWE (P=.008 and P=.0004). General exercisers improved speed [frequency: DDK (P=.003) and WGB (P=.01)]; velocity and its SD: IFT (P=.026 and P=.002) and DDK (P=.002 and P=.003); and acceleration and its SD: IFT (P=.004 and P=.025) and WGB (P=.025 and P=.039). Discussion. Previous studies employing cognitive movement strategies, like Pilates, suggest efficacy at attenuating hypokinesia and, to some extent, bradykinesia. In contrast, general therapeutic exercises combined with aerobics may mitigate bradykinesia more so than protocols employing gait training or aerobics-only interventions. Conclusion. Results support exercise prescription specificity for people with PD based on symptoms. Pilates may be more effective for individuals presenting with hypokinesia; whereas general exercises plus aerobics may be better for people with bradykinesia.

Disclosures: **K.L. Doyle:** None. **K.A. Pickett:** None. **J.C. Lazarus:** None.

Nanosymposium

12. Therapeutics of Parkinson's Disease: Clinical Studies

Location: N230

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 12.05

Topic: C.03. Parkinson’s Disease

Title: Postoperative management of deep brain stimulation candidates; visits during the first year and beyond

Authors: *E. L. HARGREAVES[1], R. J. DIPAOLA[2], D. P. SCHNEIDER[2], S. F. DANISH[1], D. L. CAPUTO[2];
[1]Neurosurg., Robert Wood Johnson Med. School- Rutgers Univer, New Brunswick, NJ;
[2]Neurol., Robert Wood Johnson Med. School-Rutgers Univer, New Brunswick, NJ

Abstract: Deep Brain Stimulation (DBS) is an established adjunct neurosurgical treatment for movement disorders. Much of the effectiveness and long term outcome of the therapy depends upon the postoperative management. Our current program has been operating for some six years. We retrospectively analyzed the number of visits and visit intervals during the initial year when DBS therapy and medications are optimized together and compared these to the subsequent years, where the overall therapy is maintained. Additionally, two other contrasts were made 1) the initial set of patients who entered at the start of the program six years ago were compared to those entering just some two years ago 2) of the more recent patients those implanted in the GPi were compared to those implanted in the STN. In total the records from 30 implanted Parkinson’s patients were retrospectively examined, 5 were implanted in the Globus Pallidus

interna (GPi), while the remaining 25 were implanted in the Subthalamic Nucleus (STN). Fourteen patients comprised the initial set at the start of the program, all of whom were implanted in the STN. Sixteen patients comprised the latter group 11 of which were implanted in the STN. Overall there were almost 12 visits during the first year (mean 11.86), with ¾ of the visits occurring within the first 6 months (mean 8.06). During the second year, as expected, the number of visits dropped dramatically (mean 5.08). No differences were found between the GPi or STN implanted patients for any visit comparisons (t(14) p=ns). However, there were statistically less visits for the early STN patients compared to the later STN patients during the first year (mean 10.50; 12.87 t(28)=2.33; p=0.029). This difference was largely attributable to more visits during the initial 6 months than the latter 6 months. No differences were found during the second year. For the more recent patients the outcome of those implanted in the STN (n=11) was contrasted to those implanted in the GPi (n=5). Not surprisingly, levodopa equivalent units indicated that a statistical reduction occurred for the STN implants at a year (t(10)=5.42; p=0.0003), but not the GPi implants. (t(4)=1.70; p=ns). Pre-implant Dopamine challenge UPDRS III scores did not reveal a difference between the groups for either “Off” or “On” scores (analyses not shown). However, the best “On” score at the one year mark favored the STN implants with statistically lower scores than the GPi implants (mean 9.09; 16.30 t(14)=2.22; p=0.043). Large clinical trials have shown the equivalency of these target sites. Our lattermost results may reflect differences in patient selection, postoperative management, or simply a very small number of GPi implants.

Disclosures: E.L. Hargreaves: None. **R.J. DiPaola:** None. **D.P. Schneider:** None. **S.F. Danish:** None. **D.L. Caputo:** None.

Nanosymposium

12. Therapeutics of Parkinson's Disease: Clinical Studies

Location: N230

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 12.06

Topic: C.03. Parkinson’s Disease

Support: NSF 1135581

NSF 1264432

MnDrive Neuromodulation Fellowship

NSF IGERT DGE-1069104

NIH 5T32GM008471-19

Title: Phase optimized closed-loop deep brain stimulation for Parkinson's disease

Authors: *A. HOLT BECKER[1], M. SHINN[1], T. I. NETOFF[2];
[2]Biomed. Engin., [1]Univ. of Minnesota, Minneapolis, MN

Abstract: Deep brain stimulation (DBS) is a neuromodulation therapy effective at treating motor symptoms of parkinsonian patients. Currently, an open-loop approach is used to set stimulus parameters, where stimulation settings are pre-programmed by a clinician using a time intensive trial-and-error process and do not adjust in response to fluctuating symptoms [1]. There is a need for a closed-loop, systematic approach to tune stimulation parameters based on a patient's physiology. A closed-loop approach has many potential advantages, such as reducing side effects, improving efficacy, reducing battery use, and providing a patient-specific approach. With the development of a DBS system for Parkinson's disease (PD) that can simultaneously stimulate and record a neural signal, a closed-loop approach based on patient recordings will be possible in a clinical setting [2]. An effective biomarker in the neural signal recorded is needed for a closed-loop approach. Pathological oscillations, particularly in the beta frequency range (12-36 Hz), have been implicated in motor symptoms of PD [3]. It is thought that DBS may work by disrupting these oscillations. We propose a novel, closed-loop approach to suppressing these oscillations. Using a simple measure of how a stimulus affects the phase of the oscillation, called a phase response curve (PRC), we are able to predict a range of phases over which to apply a burst of stimulus pulses to desynchronize the oscillation. We call this method Phasic Burst Stimulation (PhaBS). First, we show the PRC can be used to predict phases at which to apply PhaBS to disrupt entrainment of a neuron in the substantia nigra pars reticulata from an oscillatory input. Next, we show PhaBS can be used to disrupt an emergent pathological oscillation in a computational model of the basal ganglia. From the PRC, we are able to predict both an optimal stimulus phase as well as burst frequency. While we present this approach to suppress beta oscillations seen in PD, it can be used to disrupt or enhance any oscillatory biomarker. 1. Volkmann J, Herzog J, Kopper F, Deuschl G: **Introduction to the programming of deep brain stimulators**. *Movement disorders : official journal of the Movement Disorder Society* 2002, **17 Suppl 3**:S181-187. 2. Ryapolova-Webb E, Afshar P, Stanslaski S, Denison T, de Hemptinne C, Bankiewicz K, Starr PA: **Chronic cortical and electromyographic recordings from a fully implantable device: preclinical experience in a nonhuman primate**. *J Neural Eng* 2014, **11**(1):016009. 3. Dostrovsky J, Bergman H: **Oscillatory activity in the basal ganglia--relationship to normal physiology and pathophysiology**. *Brain : a journal of neurology* 2004, **127**(Pt 4):721-722.

Disclosures: A. Holt Becker: None. **M. Shinn:** None. **T.I. Netoff:** None.

Nanosymposium

12. Therapeutics of Parkinson's Disease: Clinical Studies

Location: N230

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 12.07

Topic: C.03. Parkinson's Disease

Support: NIH R01 NS058706-01

NIH R01 NS073717-01

NIH R01 HD061363-01

DOD 006469

Title: Active contact location, depression, and cognitive performance in subthalamic nucleus deep brain stimulation

Authors: *D. FLODEN[1], C. M. MATIAS[3], C. WATHEN[2], A. G. MACHADO[1];
[2]Cleveland Clin. Lerner Col. of Med., [1]Cleveland Clin., Cleveland, OH; [3]Ribeirão Preto Med. Sch., Univ. of Sao Paulo, Sao Paulo, Brazil

Abstract: High frequency deep brain stimulation of the subthalamic nucleus is an effective treatment for the motor symptoms of Parkinson disease. The cognitive and behavioral side effects that can accompany this treatment are often hypothesized to arise from current spread from the intended sensorimotor (dorsal/lateral/posterior) division of the nucleus to the associative and limbic (ventral/medial/anterior) divisions. The objective of this study was to determine whether stimulation at ventral, medial, or anterior locations adversely affects cognitive performance and mood. Anatomical coordinates of 73 active electrode contacts (32 right; 41 left) were determined for 46 patients with idiopathic Parkinson disease treated with deep brain stimulation. Contact locations were then correlated with post-surgical changes in neuropsychological performance and depression ratings. A significant association existed between worsening depression and more lateral and anterior contact locations in both hemispheres. Semantic fluency decline, the most commonly reported cognitive change, was associated with more medial contacts in the left hemisphere. Finally, single trial learning change was not associated with contact location but did show a relationship with stimulation voltage in the right hemisphere. These data suggest that specific cognitive and mood worsening may indeed arise from unintended stimulation of non-motor regions in one or both hemispheres. However, the fact that voltage, but not location, was also relevant for single trial learning further points to a potential role for disease burden in explaining cognitive changes with stimulation treatment.

Disclosures: **D. Floden:** None. **C.M. Matias:** None. **C. Wathen:** None. **A.G. Machado:** F. Consulting Fees (e.g., advisory boards); Spinal Modulation, Functional Neuromodulation. Other; Distribution rights Enspire.

Nanosymposium

12. Therapeutics of Parkinson's Disease: Clinical Studies

Location: N230

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 12.08

Topic: C.03. Parkinson's Disease

Support: Neurological Foundation of New Zealand 1318-PG

Title: Impulsivity after administration of the dopamine agonist ropinirole

Authors: ***W. D. BYBLOW**[1], H. J. MACDONALD[1], C. M. STINEAR[1], J. P. COXON[2], A. X. REN[1], S. CRAMER[3], J. KAO[4], L. MACDONALD[4], B. SNOW[4];
[1]Univ. of Auckland, Auckland, New Zealand; [2]Monash Univ., Mellbourne, Australia; [3]Univ. of California-Irvine, Irvine, CA; [4]Auckland City Hosp., Auckland, New Zealand

Abstract: Our aim was to identify mechanisms that contribute to the development of impulse control disorders when taking commonly prescribed dopaminergic medications for Parkinson's disease. Specifically, we investigated the effects of ropinirole on objective measures of cognitive and motor impulsivity in healthy adults aged 40 - 75, and whether the effects were dependent on their genetically determined dopamine profile. Routine administration of dopamine agonists for Parkinson's disease can lead to poor inhibitory control, impulsivity and impulse control disorders. We hypothesized that motor and cognitive measures of impulsivity may be mediated by single nucleotide polymorphisms of genes involved in dopamine regulation. This was a double-blind, randomized, counter-balanced, placebo-controlled clinical trial (ACTRN12614000046606) to measure the effect of 0.5mg and 1.0mg doses of ropinirole on motor and cognitive impulsivity. At baseline participants completed the Barratt Impulsiveness Scale (BIS-11) and provided a blood sample for genotyping of catechol-O-methyltransferase, dopamine transporter genes, and dopamine D1, D2 and D3 receptor genes (Pearson-Fuhrhop et al., PLoS ONE e61197). Motor and cognitive impulsivity were objectively measured using a response inhibition task and the Balloon Analogue Risk Task respectively, following medication and placebo administration. Other executive functions were assessed using components of the Central Nervous System Vital Signs test battery. Mixed model linear regression analyses were performed to examine the influence of gene score on behavioral measures. Thirty participants (13 male) mean age 61 y (range 44 - 75 y) completed the study and were without neurological or

cognitive impairment: Montreal Cognitive Assessment (mean 28, range 27 - 30); Baratt Impulsiveness Scale (59, 38 - 77); Beck Depression Inventory (4, 0 - 22); motor section of the Unified Parkinson's Disease Rating Scale (4, 0 - 15). Chi squared tests confirmed all 5 genes were in Hardy-Weinberg equilibrium. The allele score ranged from 3 - 8 (full range 0 - 10) for the sample. Investigators will be unblinded to medication status June 1, 2015. We will report on associations between measures of motor and cognitive impulsivity and dopamine gene score for each medication status. Associations with composite measures of executive function will be reported. Our results are expected to inform whether behavioral measures, combined with genotyping, can be used to predict those people at most risk of developing impulse control disorders, which in turn could lead to more individualized treatment of Parkinson's disease.

Disclosures: W.D. Byblow: None. **H.J. MacDonald:** None. **C.M. Stinear:** None. **J.P. Coxon:** None. **A.X. Ren:** None. **S. Cramer:** None. **J. Kao:** None. **L. Macdonald:** None. **B. Snow:** None.

Nanosymposium

12. Therapeutics of Parkinson's Disease: Clinical Studies

Location: N230

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 12.09

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation for Parkinson's research

IZKF University Hospital Würzburg

Grigioni Foundation for Parkinson's Disease

Title: Increased nicotinic acetylcholine α4β2 receptor density in patients with Parkinson's disease and L-Dopa induced dyskinesia

Authors: *I. U. ISAIAS[1], J. BRUMBERG[2], N. G. POZZI[1], F. STEIGERWALD[1], G. MAROTTA[3], S. KLEBE[1], M. M. REICH[1], C. LAPA[2], K. HERRMANN[2], A. BUCK[2], J. VOLKMANN[1], S. SAMNICK[2];
[1]Neurol., [2]Nuclear Med., Uni. Hosp. and Julius-Maximillian-University, Wuerzburg, Germany; [3]Dept. of Nuclear Med., Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico,, Milano, Italy

Abstract: Background. L-dopa induced dyskinesia (LID) are abnormal involuntary movements that may develop with L-Dopa therapy for PD. Extensive evidence indicates that aberrant

presynaptic dopaminergic activity plays a major role in the development of LID. Presynaptic mechanism of particular relevance include the nigrostriatal dopaminergic neuronal loss that results in a decrease dopamine buffering capacity and in an increase of extracellular dopamine levels that may arise from L-Dopa treatment. Preliminary results on animals suggest that nicotinic acetylcholine α4β2 receptor (nAChR) desensitization and/or down regulation by nicotine, nAChR agonists or antagonist, can lead to reducing striatal dopaminergic activity and therefore ameliorate LID. Methods. We investigated a group of 11 PD subjects with LID (2 males; age: 60±8 years; disease duration: 11±7 years; UPDRS-III: 25±15 [after overnight suspension of all dopaminergic drugs]; UPDR-IV >3; LEDDs=885.6±274.4 mg) and a second group of nine subjects without LID (2 males; age: 67±8 years; disease duration: 7±4 years, UPDRS-III 25±11; UPDRS-IV=0; LEDDs=607.2±306.1). All subjects were cognitively intact and non-depressed (according to Mattis Dementia Rating Scale and Beck Depression Inventory). Single-Photon Emission Computed Tomography (SPECT) and 5-[123I]Iodo-3-[2(S)-2-azetidinylmethoxy]pyridine ([123I]IAP) or N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) tropane ([123I]FP-CIT) were applied to measure respectively nAChR and dopamine reuptake transporters (DAT) density. SPECT data were semiquantitatively analyzed and expressed as specific uptake ratios using the software package PMOD. Results. In PD patients with LID, we found a selective increase of nAChR binding in the caudate nucleus. In particular, nAChR density was significantly higher in the caudate with lower DAT measurement (nAChR: 1.02±0.13 vs. 0.80±0.25, $p<0.05$ Wilcoxon test; DAT: 1.53±0.54 vs. 1.85±0.68), also when weighted for demographic or clinical variables. The density of nAChR did not differ in any other brain area between PD with and without LID. Conclusions. Our preliminary findings further confirm a role of the cholinergic system in the pathophysiology of LID. An increased nAChR binding, possibly suggesting an up-regulated cholinergic status counterbalancing a dopaminergic innervation loss, may facilitate the evolution of LID in predisposed PD patients.

Disclosures: **I.U. Isaias:** None. **J. Brumberg:** None. **N.G. Pozzi:** None. **F. Steigerwald:** None. **G. Marotta:** None. **S. Klebe:** None. **M.M. Reich:** None. **C. Lapa:** None. **K. Herrmann:** None. **A. Buck:** None. **J. Volkmann:** None. **S. Samnick:** None.

Nanosymposium

12. Therapeutics of Parkinson's Disease: Clinical Studies

Location: N230

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 12.10

Topic: C.03. Parkinson’s Disease

Support: CIRM Grant RM1-01735

Title: Human leukocyte antigen-a critically determines neural stem cell transplant acceptance in a humanized mouse model

Authors: *K. W. IM, K. R. DOTY, D. GATE, J. C. BIANCOTTI, T. TOWN;
USC, Los Angeles, CA

Abstract: Human embryonic stem (hES) cells hold promise in the fight against neurodegenerative diseases. Specifically, their ability to self-renew and differentiate into all neural lineages makes them attractive targets for transplantation therapy. One of the most successful applications of stem cell therapy is transplantation of non-matched fetal brain tissue into patients with Parkinson's Disease (PD). In this scenario, the patient is given immunosuppressive drugs, such as FK506 or Cyclosporin A, to promote transplant acceptance. Although chronic immunosuppression is necessary to reduce acute rejection of human tissue allografts, it has severe side-effects, including infections and malignancies. One alternative to immunosuppressive therapy is matching donor and recipient immune molecules. Arguably the most important of these are human leukocyte antigens (HLAs); in particular, HLA-A and HLA-B. Our overall objective is to establish a pre-clinical platform to test the relative contribution of HLA haplotypes to neural stem cell transplant tolerance. To that end, we have endeavored to determine how many degrees of freedom from a perfect HLA match are permissible without eliciting transplant rejection. We engrafted NOD scid gamma (NSG) mice with human umbilical cord blood to generate mice with human immune systems. These 'humanized' mice were then used in HLA haplotype 'mix and match' adoptive transfer experiments. Specifically, HLA-typed humanized mice were transplanted with human embryonic stem cell-derived neural precursor cells in the striatum. Our data show that HLA-A is expressed at the highest level compared to other HLA alleles in neural stem cells. Remarkably, we find tolerance of stem cell transplants with as much as 50% mismatch at the HLA-A locus; irrespective of degree of mismatch for HLA-B, -C, -DR, or DQ. Taken together, our results show that humanized mice are an important pre-clinical tool to understand HLA-dependent stem cell transplant rejection.

Disclosures: K.W. Im: None. **K.R. Doty:** None. **D. Gate:** None. **J.C. Biancotti:** None. **T. Town:** None.

Nanosymposium

013. Rett Syndrome

Location: S102

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 13.01

Topic: C.06. Developmental Disorders

Support: NIH Grant MH085802

Simons Foundation

Research Fellowship from International Brain Research Organization

Title: Robustly dysregulated miRNAs downstream of MeCP2 control human prenatal brain development through differential effects on autism-related signaling pathways

Authors: *N. MELLIOS[1], D. FELDMAN[2], S. D. SHERIDAN[3], P. K. IP[2], S. KWOK[2], B. ROSEN[2], B. CRAWFORD[2], Y. LI[4], R. JAENISCH[4], S. J. HAGGARTY[3], M. SUR[2];
[1]Brain and Cognitive Sci., MIT/ Picower Inst. For Learning and Memory, Cambridge, MA; [2]MIT, Cambridge, MA; [3]Chem. Neurobio. Laboratory, Ctr. for Human Genet. Research, Departments of Neurol. & Psyc, Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA; [4]Whitehead Inst. for Biomed. Res., Cambridge, MA

Abstract: Rett Syndrome (RTT) is a neurodevelopmental disorder primarily caused by mutations in methyl-CpG-binding protein 2 (MECP2), a potent epigenetic regulator whose role in prenatal brain development is poorly understood. Given the known effects of MeCP2 on miRNA biogenesis, we hypothesized that neurogenesis may be impacted in RTT via MeCP2-regulated miRNAs that are enriched in early brain development; and hence modulate critical molecular components of neuronal progenitor proliferation and differentiation. Focusing on the most dysregulated miRNAs we found two prenatal brain-enriched miRNAs - miR-199 and miR-214 - to be robustly increased in human patient-derived culture, cerebral organoid, and mouse models of MeCP2 deficiency. Increases in miR-199 and miR-214 in MeCP2 mutant or deficient neuronal progenitors were a consequence of altered miRNA biogenesis and were associated with reduced expression of their targets PAK4 and PTEN, which in turn resulted in differential changes in Erk and Akt phosphorylation. Inhibiting miR-199 or miR-214 expression in induced pluripotent stem cell-derived neuronal progenitors deficient in MeCP2 restored Akt and Erk activation, respectively, and ameliorated the observed alterations in neuronal differentiation. Collectively, our data suggest that MeCP2-mediated dysregulation of miR-199 and miR-214 expression influences early neurogenesis through the differential regulation of molecular pathways with known links to autism spectrum disorders.

Disclosures: **N. Mellios:** None. **D. Feldman:** None. **S.D. Sheridan:** None. **P.K. Ip:** None. **S. Kwok:** None. **B. Rosen:** None. **B. Crawford:** None. **Y. Li:** None. **R. Jaenisch:** None. **S.J. Haggarty:** None. **M. Sur:** None.

Nanosymposium

13. Rett Syndrome

Location: S102

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 13.02

Topic: C.06. Developmental Disorders

Support: IRSF

Title: Characterization of a novel phosphorylation site of MeCP2 that might be involved in neuronal morphogenesis and chromatin related functions

Authors: *G. STEFANELLI[1], M. S. CHEEMA[2], M. COSTA[3], C. KILSTRUP-NIELSEN[4], J. AUSIÓ[2], N. LANDSBERGER[1];
[1]San Raffaele Rett Res. center, San Raffaele Scientific Inst., Milano, Italy; [2]department of biochemestry and microbiology, Univ. of Victoria, Victoria, BC, Canada; [3]department of neuroscience, Natl. research center CNR, Pisa, Italy; [4]department of genetic and epigenetic control of gene expression, Univ. of Insubria, Varese, Italy

Abstract: Rett's syndrome (RTT) is an X-linked neurodevelopmental autistic like disorder that causes severe neurological dysfunction in females. RTT is caused primarily by mutations in MeCP2, a transcriptional regulator that binds to methylated DNA and is capable of recruiting chromatin-modifying complexes thereby regulating chromatin structure and gene expression. Previous reports showed that MECP2 responds to neuronal activity by changing its phosphorylation states on several residues of which only few have so far been further characterized. In this study, we report the initial characterization of a new phosphorylation site of MECP2 that might be relevant for RTT syndrome pathology. MECP2 becomes highly phosphorylated on this residue only in brain. In addition, phosphorylation of this residue is developmentally regulated, displaying high levels between DIV 7-9 in neuronal culture and P 4-7 in total brain extracts; this period corresponds to postnatal synapse development, indicating that this phosphorylation might be required for proper neuronal maturation. Interestingly, this period is followed by a rapid dephosphorylation of MeCP2 on this residue. MeCP2 is reported to bind mononucleosomes in brain with high affinity. Interestingly, the pool of MeCP2 that is highly phosphorylated on this residue represents a pool of the protein that is not able to bind mononucleosomes in brain and it binds nucleosomes free DNA. In addition, phosphorylation of this residue of MECP2 appears to influence its binding to DNA as confirmed by salt extractions performed on total brain extracts and from FRAP assays. Overall the data collected so far indicate that this phosphorylation event can influence MeCP2 function during postnatal brain development synaptogenesis.

Disclosures: G. Stefanelli: None. **M.S. Cheema:** None. **M. Costa:** None. **C. Kilstrup-Nielsen:** None. **J. Ausió:** None. **N. Landsberger:** None.

Nanosymposium

13. Rett Syndrome

Location: S102

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 13.03

Topic: C.06. Developmental Disorders

Support: International Rett Syndrome Foundation Basic Research Grant # 2916

NINDS R01NS075062

UAB Civitan Emerging Research Scholar Award

UAB Cancer Center Support grant CA13148

CFAR Core Grant AI027767

Title: Aberrant astrocyte maturation contributes to Rett Syndrome pathogenesis

Authors: *N. L. PACHECO, L. HOLT, D. K. CROSSMAN, M. L. OLSEN;
Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Rett syndrome (RTT) is an X-linked neurodevelopmental disorder caused by mutations in the transcriptional regulator MeCP2. RTT is characterized by having apparently normal development until 6-18 months, when a progressive decline in motor and language functions begins and breathing abnormalities and seizures present. Astrocytes, the most abundant cell type in the CNS, have recently been shown to express MeCP2. Importantly, postnatal re-expression of MeCP2 in astrocytes in globally Mecp2-deficient mice ameliorated many RTT disease symptoms, indicating that deficiencies in astrocytic function contribute to the pathophysiology of RTT. However, the causative mechanisms are currently unknown. Given the broad transcriptional regulatory role of MeCP2, we predict that many astrocytic genes are dysregulated. To test this prediction, we have utilized RNA-Seq analysis to examine global gene expression changes in enriched cortical astrocytes compared to whole cortex tissue from symptomatic Mecp2-deficient mice compared to wild-type (WT) littermate controls. We have identified over 1,700 significant and differentially expressed genes in cortical astrocytes. Pathway analysis in our cortical astrocyte dataset has identified disrupted pathways involved in inflammation and metabolism as well as gastrointestinal, neurological, and immunological diseases. Furthermore, molecular and cellular functions associated with proper astrocytic maturation were also identified as being disrupted. Current work underway is directed at understanding when in the disease process these changes occur. Through the identification of key groups of astrocytic genes, proteins and pathways, we can begin to tease apart the mechanisms in

which astrocytes contribute to RTT pathogenesis, possibly identifying new and much needed therapeutic targets for RTT patients.

Disclosures: **N.L. Pacheco:** None. **L. Holt:** None. **D.K. Crossman:** None. **M.L. Olsen:** None.

Nanosymposium

13. Rett Syndrome

Location: S102

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 13.04

Topic: C.06. Developmental Disorders

Support: International Rett Syndrome Foundation (IRSF)

Shire (Lexington MA USA)

Title: To move or not to move: Is acetylated tubulin the answer For Rett Syndrome?

Authors: ***W. GOLD**[1,2], T. LACINA[3], S. WILLIAMSON[4], L. CANTRILL[5], J. CHRISTODOULOU[4,2,6];
[1]Western Sydney Genet. Program, NSW Ctr. For Rett Syndrome Res., Westmead, Australia; [2]Discipline of Paediatrics & Child Health, Univ. of Sydney, Australia., Sydney, Australia; [3]Hochschule Mannheim - Univ. of Applied Sciences, faculty of Biotech., Mannheim, Germany; [4]NSW Ctr. for Rett Syndrome Research, Western Sydney Genet. Program, Children's Hosp. at Westmead, Sydney, Australia, Westmead, Australia; [5]Microscope Facility, Kids Res. Institute, Children's Hosp. at Westmead, Sydney, Australia, Westmead, Australia; [6]Discipline of Genet. Medicine, Sydney Med. School, Univ. of Sydney, Australia, Westmead, Australia

Abstract: Background: Rett syndrome (RTT) is a severe neurodevelopmental disorder, predominantly caused by mutations in the Methyl-CpG-binding protein 2 (MECP2). Despite the genetic cause being identified, the pathophysiology of the disorder remains to be completely elucidated. A predominance of neuronal and synaptic dysfunction, with altered excitatory-inhibitory neuronal synaptic transmission and synaptic plasticity are overarching features of RTT in children and in mouse models. Tubulin and the microtubule network play an essential role in neuronal function whereby the acetylation state of microtubules dictates the efficiency of synaptic targeting and molecular motor trafficking of mitochondria and Brain Derived Neurotrophic Factor containing vesicles, amongst other cargo. Recent reports showing reduced tubulin acetylation and microtubule instability in Mecp2-deficient cells, suggest a link between these irregularities and the neurobiology in RTT. Aims: To investigate the stability of the

microtubule network and whether the inhibition of histone deacetylase 6 (HDAC6), a tubulin deacetylase, can restore microtubule dynamics and microtubule-regulated mitochondrial trafficking in cortical neurons of a RTT mouse model. Methods: Acetylated tubulin and HDAC6 levels were measured in RTT patient fibroblasts and in cortical neurons of Mecp2T158A mice. Microtubule stability experiments were performed in patient fibroblasts and using live cell imaging, the trafficking speed of mitochondria was measured in cultured cortical neurons isolated from pups of the Mecp2T158A mice. Finally, to assess the potential therapeutic efficacy of HDAC6 inhibition, we are currently conducting a mouse trial using a novel, highly specific HDAC6 inhibitor. Results: Reduced acetylated tubulin and increased HDAC6 expression was observed in both patient cells and Mecp2T158A mouse cortical neurons. In addition we found a reduction in mitochondrial velocity and increased microtubule instability in these cells. We report that HDAC6 inhibition restores tubulin acetylation levels and improved microtubule stability. Preliminary studies in the HDAC6 trial reveal that treated Mecp2T158A mice show improvement in their motor performance. Summary: HDAC6 provides a novel potential therapeutic option for restoring neuronal trafficking deficits in RTT.

Disclosures: W. Gold: None. **T. Lacina:** None. **S. Williamson:** None. **L. Cantrill:** None. **J. Christodoulou:** None.

Nanosymposium

13. Rett Syndrome

Location: S102

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 13.05

Topic: C.06. Developmental Disorders

Support: NIH/NINDS grant (5R01NS057819)

Title: Deficiency of mecp2 in glutamatergic neurons leads to severe neurological dysfunctions caused by altered neuronal activity

Authors: *X. MENG[1,2], W. WANG[3,2], H. LU[3,2], H. ZOGHBI[3,2,4];
[1]NEUROSCIENCE, BAYLOR COLLEGE OF MEDICINE, Houston, TX; [2]Jan and Dan Duncan Neurolog. Res. Institute, Texas Children's Hosp., Houston, TX; [3]Mol. Human Genet., Baylor Col. of Med., Houston, TX; [4]Howard Hughes Med. Inst., Houston, TX

Abstract: Background: Rett Syndrome (RTT) is a postnatal neurological disorder caused by loss of function mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2). Deleting Mecp2 only from brain tissue at embryonic day 12 leads to phenotypes identical to those of the

null mutation, indicating that loss of MeCP2 from the CNS is responsible for the RTT phenotypes. Neuronal subtype-specific Mecp2 deletion replicates select aspects of the null phenotype. For instance, deletion of Mecp2 only from inhibitory GABAergic neurons recapitulates many RTT phenotypes including the stereotypies and altered social interaction, but spares anxiety-like behaviors and tremor. The role that excitatory glutamatergic neurons play in the pathogenesis of RTT has not been explored in detail. Method: We conditionally deleted Mecp2 in glutamatergic neurons in the mouse brain using a vGlut2-Cre line, and characterized the mice by a comprehensive battery of behavioral assays as well as neurophysiological methods. Results: The glutamatergic conditional knockout mice (CKO) became obese, and developed impaired acoustic startle and motor deficits. Interestingly, unlike the GABAergic CKO, the glutamatergic CKO showed anxiety-like behaviors as early as 5 weeks of age, and developed severe tremor. Furthermore, they died early with half of them dead by 10 weeks. These phenotypes are identical to the disease progression pattern of the Mecp2 null mutation. Patch-clamp recording from the layer V pyramidal neurons revealed reduced spontaneous activity in the CKO mice, which replicated the circuit deficit of null mutation. Conclusion: These data demonstrate that dysfunction of MeCP2 in excitatory glutamatergic neurons contributes to numerous neuropsychiatric phenotypes. Especially, it drives the onset of anxiety-like behaviors, tremor, and obesity in RTT, indicating an excitatory neuron-dependent mechanism underlying these phenotypes of Rett syndrome.

Disclosures: **X. Meng:** None. **W. Wang:** None. **H. Lu:** None. **H. Zoghbi:** None.

Nanosymposium

13. Rett Syndrome

Location: S102

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 13.06

Topic: C.06. Developmental Disorders

Support: Simons Foundation

Title: Impaired vocal perception in a mouse model of Rett syndrome is caused by abnormal plasticity of auditory cortical inhibitory circuits

Authors: *B. Y. LAU, K. KRISHNAN, S. D. SHEA;
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Neurodevelopmental disorders result from inappropriate synaptic connectivity that initially emerges in early brain development. However, circuit mechanisms by which behavioral

symptoms are later exacerbated by deficits in experience-dependent plasticity remain unclear. We aim to answer this question by using neuronal recordings to assess the effects of *MeCP2* mutation on maternal experience-induced changes to the encoding of pup ultrasonic distress vocalizations (USVs). We previously showed that impaired pup retrieval behavior in a mouse model of Rett syndrome (*MeCP2* heterozygous females, $MeCP2^{+/-}$) is caused by dysregulated adult plasticity of inhibitory networks in the auditory cortex. Specifically, in response to maternal experience, adult $MeCP2^{+/-}$ exhibited transient increases in perineuronal nets and parvalbumin, inhibitory markers that are typically associated with limited plasticity. How these molecular changes affect the function of neural circuits in $MeCP2^{+/-}$ remain unclear. Here, we performed *in vivo* loose patch recordings from individual neurons in the auditory cortex of head-fixed, awake mice. Our preliminary results suggest that there are abnormal changes in the inhibitory responses to USVs in $MeCP2^{+/-}$ after maternal experience. These results further support a model in which transient experience-dependent changes to inhibitory networks in $MeCP2^{+/-}$ act as brakes on auditory cortical plasticity, hindering adult learning. We are continuing to assess neuronal activity in $MeCP2^{+/-}$, comparing different identified cell types, as well as neurons expressing either the mutant or wild type allele of *MeCP2*, before and after maternal experience.

Disclosures: **B.Y. Lau:** None. **K. Krishnan:** None. **S.D. Shea:** None.

Nanosymposium

13. Rett Syndrome

Location: S102

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 13.07

Topic: C.06. Developmental Disorders

Support: Gujarat State Biotechnology Mission (GSBTM), Gandhinagar

Animal House of Biochemistry Department, The M. S. University of Baroda

Title: Role of MeCP2 in mitochondrial impairments and myelin defects

Authors: *A. R. DAVE, L. K. BUCH, K. M. SHARMA, P. P. PILLAI;
Zoology, The Maharaja Sayajirao Univ. of Baroda, Vadodara, India

Abstract: Glial cells play pivotal role in neuronal functions in central nervous system. Oligodendrocytes, enable the fast conduction of nerve impulses by ensheathing axons by lipid rich multi-layered structure- myelin sheath. CpG methylation is involved in long-term silencing

of genes during mammalian development. The methyl-CpG-binding protein 2 (MeCP2) interacts specifically with methylated DNA and represses or activates target genes transcription. Mitochondrial dysfunction through glutathione depletion, glutamate excitotoxicity, altered gene expression of electron transport chain complexes, abnormal Ca+2 elevation, oxidative stress, decreased ATP levels are possible underlying mechanisms for demyelination mediated neurodegenerative diseases. Recent reports provide an insight into mitochondrial dysfunction in brain of MeCP2 null mouse and Rett syndrome patients. Mutations in MeCP2 gene cause Rett Syndrome and impaired mitochondrial function is one of the many manifestations. However, whether MeCP2 altered expression causes mitochondrial dysfunction through altering gene expression of electron transport chain in oligodendrocytes and thereby causing demyelination is not much clear. We hypothesised that expression patterns of key respiratory complex genes and calcium flux in mitochondria are altered in the MeCP2 knock-down oligodendrocytes. In order to test the hypothesis we investigated the expression of genes encoding mitochondrial respiratory complex subunits; Ubiquinol-cytochrome c reductase core protein (Uqcrc1) and NADH dehydrogenase (ubiquinone) flavoprotein 2 (Ndufv2), protein expressions and enzyme activities of respiratory complexes of mitochondria by RT-PCR, western blot and spectrophotometric assays respectively. Also, we assessed the effects of MeCP2 knock down in cortical astrocytes on myelin genes in astrocyte -myelinating spinal cord co- culture. Our data shows elevated transcript levels of respiratory genes- ndufv-2 (complex 1) and uqcrc-1 (complex 3) in MeCP2 knockdown oligodendrocytes. The respiratory complex- I enzyme specific activity was found to be increased in MeCP2 knock down which is in accordance with the increased transcript level of complex-1 gene. Data from the current study also indicates down-regulation of myelin proteins i.e. Myelin basic protein (MBP) and Proteolipid Protein (PLP) in myelinating spinal cord co-culture grown on MeCP2 knock down astrocytic bed which also indicates the role of MeCP2 in CNS myelination.

Disclosures: **A.R. Dave:** None. **L.K. Buch:** None. **K.M. Sharma:** None. **P.P. Pillai:** None.

Nanosymposium

13. Rett Syndrome

Location: S102

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 13.08

Topic: C.06. Developmental Disorders

Support: Treatment Grant, Autism Speaks (CMN)

NIH Grant R21 NS078262 (CMN)

Basic Research Grant

Rettsyndrome.org (CMN), Mentored Training Fellowship

Rettsyndrome.org (RGG)

NIH Grant T32-MH065215 (RGG)

NIH Grant T32-MH09336604 (RGG)

Weatherstone Pre-doctoral Fellowship (RK)

Title: A novel mGlu5 positive allosteric modulator improves phenotype and rescues synaptic plasticity defects in a mouse model of Rett syndrome

Authors: *R. G. GOGLIOTTI[1,2], R. KLAR[1,2], A. GHOSHAL[1,2], R. ZAMORANO[1,2], J. M. ROOK[1,2], S. STAUFFER[1,2], C. MALOSH[1,2], P. N. VINSON[1,2,3,4], C. K. JONES[1,2], C. W. LINDSLEY[1,2,5], P. CONN[1,2], C. M. NISWENDER[1,2];
[1]Dept. of Pharmacol., [2]Vanderbilt Ctr. for Neurosci. Drug Discovery, [3]Dept. of Biochem., [4]Vanderbilt Inst. of Chem. Biol., [5]Dept. of Chem., Vanderbilt Univ., Nashville, TN

Abstract: Rett syndrome is a monogenic form of autism that is characterized by severe developmental regression, loss of communicative ability, stereotyped hand movements, and prolonged apneas. Reduced number and strength of excitatory synapses have been reported in several regions of the brain in Rett syndrome model mice which are not believed to have accompanying alterations in intrinsic excitability. Excitingly, we have generated preliminary data indicating that attenuated forms of protein synthesis-dependent synaptic plasticity and decreased AKT/mTOR signaling are also characteristic of these brain regions. These findings suggest that mechanisms to normalize protein synthesis-dependent synaptic plasticity will be viable Rett syndrome therapeutics. Here we explore one such mechanism in metabotropic glutamate receptor 5 ($mGlu_5$) positive allosteric modulators (PAMs). While $mGlu_5$ PAMs have been investigated for many years, drug discovery in this area has been plagued by the presence of excitotoxic and convulsive adverse effects. To address this, we have undertaken significant efforts to understanding the interplay between $mGlu_5$ signaling and seizures, and have now generated $mGlu_5$ PAMs that possess large enough therapeutic windows to test *in vivo* without adverse effects. This safety profile appears to stem from signaling bias away from NMDA receptor activation. We show that one such compound, VU0462807, retains a favorable safety profile, even in mouse models where convulsive liability is high, such as the *Mecp2*$^{-/y}$ mouse model of Rett syndrome. Furthermore, we demonstrate that $mGlu_5$ expression is reduced in *Mecp2*$^{-/y}$ mice and in the motor cortex of Rett Syndrome autopsy samples. Additionally, we have established that chronic dosing in P39-55 old *Mecp2*$^{-/y}$ mice with 3.3 mg/kg VU0462807 significantly ameliorates the presence of hind paw clasping, normalizes disrupted gait dynamics, has anxiolytic properties in the open field assay, as well as a restoration of attenuated DHPG-LTD at

the SC-CA1 synapse in the hippocampus in acute slices. Importantly, VU0462807 accomplishes phenotypic rescue without altering respiratory function in Rett mice, which is believed to be disrupted by brain stem hyperexcitability and at risk for exacerbation by increased glutamatergic signaling. These exciting data suggest that selective $mGlu_5$ potentiation may be a potential novel therapeutic strategy for Rett syndrome.

Disclosures: **R.G. Gogliotti:** None. **R. Klar:** None. **A. Ghoshal:** None. **R. Zamorano:** None. **J.M. Rook:** None. **S. Stauffer:** None. **C. Malosh:** None. **P.N. Vinson:** None. **C.K. Jones:** None. **C.W. Lindsley:** None. **P. Conn:** None. **C.M. Niswender:** None.

Nanosymposium

014. Auditory System: Sensory Transduction and Hair Cell Differentiation

Location: S402

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 14.01

Topic: D.02. Auditory System

Support: NIH NIDCD R00 DC012534

Alfred P. Sloan FR- 2015- 65794

Title: Mechanisms and mechanosensitivity: exceptional cadherins for hearing and balance

Authors: ***M. SOTOMAYOR**, R. ARAYA-SECCHI, Y. NARUI, C. CHEN, C. KLANSECK, L. WIMALASENA;
Chem. and Biochem., The Ohio State Univ., Columbus, OH

Abstract: Cadherins form a large superfamily of proteins essential for morphogenesis, neuronal connectivity, and tissue integrity. Two atypical members of this superfamily, cadherin-23 and protocadherin-15, are also involved in hereditary deafness and blindness. In the inner ear, these two proteins interact to form the tip link, a fine filament that pulls open transduction channels to initiate a cascade of events leading to sensory perception. Here we present structural, computational, and biophysical experiments that reveal unique properties of the tip link extracellular cadherin (EC) repeats. Our crystal structures, simulations, and binding assays show how the tip of protocadherin-15 and some of its variants form a mechanically strong and calcium-dependent heterophilic complex with the cadherin-23 tip. In addition, structures and simulations of protocadherin-15 EC repeats show how non-canonical inter-repeat linker regions may alter protocadherin-15 tertiary structure and elasticity. Overall, our results provide a

molecular view of tip link mechanics and identify the structural determinants of tip link function in vertebrate mechanosensation.

Disclosures: **M. Sotomayor:** None. **R. Araya-Secchi:** None. **Y. Narui:** None. **C. Chen:** None. **C. Klanseck:** None. **L. Wimalasena:** None.

Nanosymposium

14. Auditory System: Sensory Transduction and Hair Cell Differentiation

Location: S402

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 14.02

Topic: D.02. Auditory System

Support: NIDCD/NIH (R01 DC009434)

Title: TRPA1 channels regulate cochlear amplification through active shape changes of supporting cells in the inner ear

Authors: ***A. C. VELEZ-ORTEGA**[1], S. E. EDELMANN[1], C. PARK[2], R. STEPANYAN[1], K. Y. KWAN[3], G. P. SINHA[1], D. P. COREY[3], G. I. FROLENKOV[1];
[1]Dept. of Physiol., Univ. of Kentucky, Lexington, KY; [2]Dept. of Head & Neck Surgery, UCLA, Los Angeles, CA; [3]Harvard Med. Sch., Boston, MA

Abstract: TRPA1 channels are sensors for noxious stimuli in a subset of nociceptive neurons and they are also expressed in cells of the mammalian inner ear. Given that *Trpa1*$^{-/-}$ mice exhibit normal hearing, balance and sensory mechanotransduction, the function of TRPA1 channels in the inner ear remains unknown. We assessed TRPA1 expression in the organ of Corti using antibodies against the human PLAP reporter expressed in *TrpA1*$^{-/-}$ mice, and found broad PLAP labeling in the sensory hair cells as well as in the following non-sensory supporting cells: cells of the Kolliker's organ (CKO), Deiters' cells (DCs), pillar cells (PCs), Hensen's cells (HeCs) and Claudius' cells (CCs). Functional TRPA1 channels can be detected by FM1-43 dye that permeates through these channels in the presence of an agonist. TRPA1-mediated FM1-43 uptake was observed in wild type hair cells, HeCs and CKO, but not in any of the cells from *Trpa1*$^{-/-}$ mice. Patch clamp recordings also revealed TRPA1-mediated inward currents in wild type HeCs and DC. Ca^{2+} imaging showed that HeCs of wild type but not *Trpa1*$^{-/-}$ mice generate robust and long-lasting Ca^{2+} responses after stimulation with 4-HNE, an endogenous TRPA1 agonists produced by lipid peroxidation. Thus, HeCs seem to be the major sensors of oxidative damage in the cochlea. TRPA1-initiated Ca^{2+} responses are often propagated from HeCs to other types of supporting cells and are accompanied by prominent shape changes in DCs and PCs.

Using flash photolysis of caged Ca^{2+} compounds, we confirmed that PCs possess Ca^{2+}-dependent contractile machinery. We hypothesized that TRPA1-initiated changes of the supporting cell shape would alter the geometry of the organ of Corti and modify cochlear amplification after acoustic trauma, which is known to increase the oxidative stress in the cochlea and to cause the generation of 4-HNE for several days. Therefore, we exposed young adult mice to mild noise and evaluated the recovery of hearing thresholds and cochlear amplification over time. Consistent with our hypothesis, we found a longer-lasting inhibition of cochlear amplification in wild type mice than in *Trpa1*$^{-/-}$ littermates. Our results indicate that the non-sensory supporting cells of the hearing organ detect tissue damage via the activation of TRPA1 channels and subsequently modulate cochlear amplification through active cell shape changes. We believe that this novel mechanism of cochlear regulation may protect or fine-tune the organ of Corti after acoustic trauma or other types of cochlear injuries.

Disclosures: **A.C. Velez-Ortega:** None. **S.E. Edelmann:** None. **C. Park:** None. **R. Stepanyan:** None. **K.Y. Kwan:** None. **G.P. Sinha:** None. **D.P. Corey:** None. **G.I. Frolenkov:** None.

Nanosymposium

14. Auditory System: Sensory Transduction and Hair Cell Differentiation

Location: S402

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 14.03

Topic: D.02. Auditory System

Support: NIH/NIDCD Grant # R01DC013521

NIDCD intramural fund #Z01-DC000060-10

Title: Tmc1 mutagenesis and cysteine modification highlight amino acid residues critical for sensory transduction in mouse inner ear hair cells

Authors: X.-P. LIU[1], B. PAN[1], Y. ASAI[1], K. KURIMA[2], A. J. GRIFFITH[3], *J. R. HOLT[1]; [1]Dept. of Otolaryngology, Boston Children's Hosp. / Harvard Med. Schoo, Boston, MA; [2]Dept. of Regenerative Med., Univ. of the Ryukyus, Ryukyus, Japan; [3]NIDCD, NIH, Bethesda, MD

Abstract: Identification of the molecular components of the sensory transduction complex in hair cells of the mammalian inner has been the focus of intensive research. Recently, Transmembrane channel-like 1 and 2 (TMC1 and TMC2) emerged as possible components of the hair cell sensory transduction channel based on the following observations. Mice deficient in

both *Tmc1* and *Tmc2* are deaf and lack vestibular function. Hair cells of double mutants lack sensory transduction, despite intact hair bundles and tip-links (Kawashima et al., 2011). Mice that express only TMC1 or TMC2 have distinct single-channel conductances and calcium selectivity. A methionine-to-lysine substitution at position 412 in TMC1 reduces the single-channel current amplitude and calcium permeability of transduction (Pan et al., 2013). These data support a model in which TMCs are essential components of the sensory transduction channel in auditory and vestibular hair cells, but their exact role is not yet clear. They may form a vestibule at the mouth of the pore, the pore of the ion channel itself or both (Holt et al., 2014). Alternatively, TMCs may function as accessory or trafficking subunits (Kim et al., 2013). To probe TMC1 structure and function we combined electrophysiological recording with mutagenesis and cysteine modification in native hair cells. Cysteine substitutions were introduced into the wild-type mouse *Tmc1* sequence and the sequence was packaged into AAV vectors. The vectors were transfected into organotypic cultures harvested from *Tmc1/Tmc2* doubly-deficient mice and sensory transduction was assayed eletrophysiologically 6-10 days post-transfection. We found that the mutant *Tmc1* sequences restored mechanosensitivity to positive hair bundle deflections in virally-transfected hair cells and that acute application of cysteine modification reagents irreversibly altered the biophysical properties of sensory transduction within seconds. The data provide further support for a direct role for TMC1 in sensory transduction in mammalian hair cells and highlight several residues that regulate current amplitude and ionic selectivity. The data may also suggest revised models of TMC1 topology with up ten transmembrane domains.

Disclosures: X. Liu: None. **B. Pan:** None. **Y. Asai:** None. **K. Kurima:** None. **A.J. Griffith:** None. **J.R. Holt:** None.

Nanosymposium

14. Auditory System: Sensory Transduction and Hair Cell Differentiation

Location: S402

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 14.04

Topic: D.02. Auditory System

Title: Hair cell encoding of intensity in the zebrafish lateral line

Authors: *J. G. TRAPANI, A. ORDOOBADI, T. SOMMERS, R. AZIZ-BOSE;
Amherst Col., Amherst, MA

Abstract: Hair cells, the sensory receptors of the auditory, vestibular, and lateral line systems, quickly and precisely transform mechanical stimuli into trains of action potentials (spikes) in

afferent neurons. Importantly, how stimulus features are encoded within the temporal patterns of spike trains is not well understood. Here, we examined hair cell encoding of stimulus intensity in wild type and transgenic zebrafish with hair-cell expression of Channelrhodopsin-2 (ChR2). Specifically, we performed *in vivo* recordings from single afferent neurons in the lateral line while delivering both mechanical stimuli using a fluid jet and optical stimuli using controlled flashes of ~470 nm light to innervated hair cells. Stimulus intensity was then varied between a minimum level that did not evoke spiking above background and a maximum level that evoked saturating spike train responses. Our experiments tested the hypothesis that intensity would be correlated with the latency to the first evoked spike (FSL), the time between the first two evoked spikes, and the number of spikes evoked by each stimulus presentation. Furthermore, we compared spike trains between mechanically and optically evoked spike trains from transgenic hair cells, which allowed us to examine the role of the concerted activation of mechanoelectrical transduction (MET) channels in stimulus encoding. Altogether, our results suggest that lateral line hair cells encode intensity within the temporal pattern of evoked spike trains and that the MET channel plays an important role in the precision of this encoding.

Disclosures: **J.G. Trapani:** None. **A. Ordoobadi:** None. **T. Sommers:** None. **R. Aziz-Bose:** None.

Nanosymposium

14. Auditory System: Sensory Transduction and Hair Cell Differentiation

Location: S402

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 14.05

Topic: D.02. Auditory System

Support: Fonds leon fredericq

Fonds national de la recherche scientifique

Belgian science policy (P7/07)

Title: Cochlear cell differentiation and regeneration: role of ephrins and Eph receptors

Authors: *B. MALGRANGE[1], S. MATEO-SANCHEZ[1], L. SCHOONAERT[2], W. ROBBERECHT[2], A. DAVY[3], L. NGUYEN[1], J. DEFOURNY[1];
[1]Univ. of Liege, LIEGE, Belgium; [2]Lab. of Neurobio., Univ. of Leuven, Leuven, Belgium; [3]Ctr. for Developmental Biol., Univ. of toulouse, Toulouse, France

Abstract: In mammals, cochlear sensory hair cells that are responsible for hearing are postmitotic and are not replaced after loss. One of the most promising strategies to regenerate hair cells is to identify and inhibit the factors preventing the conversion of adjacent non-sensory supporting cells into hair cells. Here we demonstrate that mammalian hair cells can be directly generated from supporting cells by inhibition of ephrin-B2 signalling. Using either ephrin-B2 conditional knockout mice, shRNA-mediated gene silencing or soluble inhibitors, we found that down- regulation of ephrin-B2 signalling at embryonic stages results in supporting cell translocation into hair cell layers and subsequent switch in cell identity from supporting cell to hair cell fate. As transdifferentiation is here a result of displacement across boundary, this original finding presents the interest that newly generated hair cells directly integrate either hair cell layer, then would be likely more rapidly able to fit into functional circuitry.

Disclosures: B. Malgrange: None. **S. Mateo-sanchez:** None. **L. Schoonaert:** None. **W. Robberecht:** None. **A. Davy:** None. **L. Nguyen:** None. **J. Defourny:** None.

Nanosymposium

14. Auditory System: Sensory Transduction and Hair Cell Differentiation

Location: S402

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 14.06

Topic: D.02. Auditory System

Support: NIDCD/NIH 1R01 DC013275

Title: Epigenetic DNA demethylation induces inner ear stem cells to differentiate into sensory hair cells

Authors: Z. HU[1], *Y. ZHOU[2];
[1]Otolaryngology, Wayne State Univ. Sch. of Med., Detroit, MI; [2]Otolaryngology, Wayne State Univ., Detroit, MI

Abstract: DNA methyltransferase (DNMT) inhibitor 5-azacytidine (5-aza) induces genomic demethylation to regulate gene expression. However, it remains unclear whether 5-aza affects gene expression and cell fate determination of stem cells. In this study, 5-aza was applied to mouse inner ear stem/progenitor cells, MUCs, to investigate whether 5-aza stimulates MUCs to become sensory hair cells. After treatment, MUCs increased expressions of sensory hair cell genes and proteins. FM1-43 permeation assays suggested that 5-aza-treated MUCs possessed potent mechanotransduction channels, which are specifically shown in functional sensory hair cells. To understand the mechanism of induced changes, quantitative DNA methylation assays

were performed and treated MUCs showed a 28.57% decrease in genomic methylation level. In treated MUCs, western blotting revealed remarkably reduced DNMT1 expression and the DNMT activity was significantly decreased. These data suggested that 5-aza affects protein expression and the activity of DNMTs to cause DNA demethylation of MUCs, which may contribute to up-regulation of sensory hair cell markers and differentiation of hair cell. This study not only demonstrates a possible epigenetic approach to induce tissue specific stem/progenitor cells to become sensory hair cells, but also provides a cell model to epigenetically modulate stem cell fate determination without changing DNA sequence. **Key words** 5-azacytidine; demethylation; epigenetics; hair cell; methylation; stem cell; regeneration
Acknowledgements This study is supported by NIDCD/NIH (1R01 DC013275). **Conflict of interest** The authors indicate no potential conflicts of interest.

Disclosures: Z. Hu: None. **Y. Zhou:** None.

Nanosymposium

14. Auditory System: Sensory Transduction and Hair Cell Differentiation

Location: S402

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 14.07

Topic: D.02. Auditory System

Title: Gap junction gene Panx1 deficiency can induce hearing loss

Authors: *H.-B. ZHAO, Y. ZHU, C. LIANG, J. CHEN;
Univ. Kentucky Med. Sch., Lexington, KY

Abstract: Gap junctions play a critical role in hearing. Connexin gap junction gene mutations can induce a high incidence of hearing loss. Pannexin (Panx) gene also encodes gap junction proteins in vertebrates. Panx1 is a predominant pannexin isoform and has extensive expression in the cochlea. Here, we report that deletion of Panx1 in the cochlea could produce a progressive hearing loss. The auditory brainstem response (ABR) recording showed that hearing loss was moderate to severe and severe at high-frequencies. Distortion product otoacoustic emission (DPOAE), which reflects the activity of active cochlear mechanics that can amply acoustic stimulation to enhance hearing sensitivity and frequency selectivity, was also reduced. Panx1 deletion could also reduce ATP release and endocochlear potential. We further found that Panx1 deficiency could activate Caspase-3 cell apoptotic pathway in the cochlea to cause hair cells and other types of cells degeneration. These data indicate that like connexins Panx1 deficiency can also induce hearing loss. These data also suggest that pannxins play important rather than redundant roles in the cochlea and hearing.

Disclosures: **H. Zhao:** None. **Y. Zhu:** None. **C. Liang:** None. **J. Chen:** None.

Nanosymposium

015. Insula: Somatotopy, Emotion, and Cognition

Location: S401

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 15.01

Topic: D.03. Multisensory Systems

Support: NIH Grants K01AT008225

R90DA023427

P41EB015896

P01AT006663

K01EB011498

R01EB019437

S10RR023401

Title: High-resolution mapping of somatotopic organization in the human insular cortex using ultra-high-field (7 Tesla) fMRI

Authors: ***G. DESBORDES**[1,2], J. KIM[3], J. R. POLIMENI[1,2], V. NAPADOW[1,2];
[1]Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Dept. of Med. Res., Korea Inst. of Oriental Med., Daejeon, Korea, Republic of

Abstract: The insular cortex, or insula, is a small cortical lobe that acts as a central hub integrating somatosensory, viscerosensory, autonomic, and cognitive-affective functions. Impairments within the insula have been linked to a broad variety of disorders, including chronic pain, mood disorders, addiction, frontotemporal dementia, etc. Technical challenges associated with imaging the insula in the living human brain at high spatial resolution have precluded a detailed functional mapping which would be necessary to test proposed models linking insular subregions to different functions (e.g. Menon & Uddin 2010 Brain Struct Funct). Based on animal studies and a few human fMRI studies (Henderson et al. 2007 Pain; Baumgärtner et al. 2010 J Neurophys), it is believed that a posterior-dorsal subregion of the insula presents somatotopic organization. In addition, Craig (2002 Nat Rev Neuro) proposed that the same map

is re-represented in a mid-dorsal region of the insula, although to our knowledge this has not been conclusively demonstrated in humans. Here we tested in four human subjects the feasibility of high-resolution functional mapping of somatotopy in the insula. We used ultra-high-field (7T) BOLD fMRI with cutaneous electrostimulation as a highly localized somatosensory stimulus. Electrostimulation was performed sequentially at 6 different locations: 3rd/4th fingers, upper leg, and lower back on each side of the body at a non-painful intensity. The 7T fMRI acquisition used gradient-echo Blipped-CAIPI Simultaneous-Multi-Slice EPI (Setsompop et al. 2012 Magn Reson Med) with 1.2×1.2×1.2 mm^3 voxels, *R*=3 acceleration with FLEET-ACS, MultiBand-3, full brain (TR=2.51 s, 123 slices; 3 subjects) or cerebrum only (TR=1.79 s, 87 slices; 1 subject), with concurrent recording of cardiac and respiratory signals. We used FSL and FreeSurfer to compute cortical surface-based statistical maps based on same-session anatomical (MPRAGE) data with 750 μm isotropic voxels. We found preliminary evidence of fine-grained somatotopic organization in the contralateral posterior-dorsal and mid-dorsal insula, with minimal overlap between the cortical representation of each stimulation site (fingers, leg, lower back), supporting Craig's re-representation hypothesis. Our findings support the use of localized electrostimulation in conjunction with 7T fMRI to perform high-resolution mapping of somatosensory regions of the human insula. This method could be used to achieve a comprehensive mapping of the full somatotopic organization hypothesized to be present in different insular subregions, as has been done for primary and secondary somatosensory and motor cortices.

Disclosures: G. Desbordes: None. **J. Kim:** None. **J.R. Polimeni:** None. **V. Napadow:** None.

Nanosymposium

15. Insula: Somatotopy, Emotion, and Cognition

Location: S401

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 15.02

Topic: D.03. Multisensory Systems

Support: Social Science Matrix, UC Berkeley

Title: Neuroeconometrics of neural networks underlying asset trading: toward the prediction and prevention of major asset-price bubbles

Authors: *J. L. HARACZ[1,2], C. BATTISTA[3], M. HOFFMAN[4], D. MARINAZZO[5];
[1]Goldman Sch. of Publ. Policy, UC Berkeley, Berkeley, CA; [2]Dept. of Psychological and Brain Sci., Indiana Univ., Bloomington, IN; [3]Dept. of Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA; [4]Gen. and Biol. Psychology, Bergische Univ., Wuppertal, Germany; [5]Dept. of Data Analysis, Ghent Univ., Ghent, Belgium

Abstract: Many authors suggested that theoretical and empirical (e.g., predictive) challenges within economics could be at least partly overcome by bringing neuroeconomics into increased interactions with economics (e.g., Glimcher et al., 2005, 2007; Caplin & Dean, 2007; Bernheim, 2009; Brocas, 2012; Camerer, 2013; Krajbich et al., 2014; Smith et al., Am. Economic J.: Microeconomics, 2014a). These challenges underscore the need for a coordinating effort that reviews studies in a category that could be called "neuroeconometrics", due to the potential that these studies show for improving prediction by including neural measures in econometric models. The current review includes initial neuroeconometric studies and recommendations for extending this research to better understand neural networks involved in asset trading that underlies financial-market price bubbles and crashes. Within microeconometrics, the longstanding goal of predicting choices by individuals or households occasionally is augmented by studying new types of data. Nonchoice behaviors (e.g., reaction times; Krajbich et al., 2014), eye-tracking measures (Balcombe et al., 2015), and neuroimaging results (Smith et al., 2014a) have shown potential for improving the capacity of models to predict choices. For example, neural-activity measures, recorded by functional magnetic resonance imaging (fMRI) in ventral striatum, subgenual cingulate cortex, orbitofrontal cortex, insula, and inferior parietal lobe in response to viewing food items, improved the prediction of subsequent choices between food items (Smith et al., 2014a). Neural measures from traders were proposed to assist potentially the forecasting of short-term stock-market movements (Bernheim, 2009). This proposal was supported by a lab asset-trading study of markets with asset-price bubbles (Smith et al., Proc. Natl. Acad. Sci. USA, 2014b), which revealed that fMRI-measured nucleus accumbens (NA) activity, when calculated as a moving average across all subjects, tracked bubble-related price changes and predicted crashes. Price peaks were preceded by elevated anterior insula (AI) activity in subjects who sold assets before peaks. Several fMRI studies found AI activations associated with the need to exert cognitive control, which is dependent on activity in the frontoparietal network, whereas NA was activated during herding (i.e., following others' decisions). In conclusion, studies with wearable functional near-infrared spectroscopy technology should test whether low frontoparietal activity may serve as a bubble-related biomarker that can be exploited by countercyclical policies aimed at preventing major bubbles.

Disclosures: **J.L. Haracz:** None. **C. Battista:** None. **M. Hoffman:** None. **D. Marinazzo:** None.

Nanosymposium

15. Insula: Somatotopy, Emotion, and Cognition

Location: S401

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 15.03

Topic: D.03. Multisensory Systems

Support: FONDECYT N°1130724

UNAB DI-603-14/N

Title: Role of the Insula in Anxiety

Authors: *J. STEHBERG[1], R. MORAGA-AMARO[2], R. DIAZ-GALARCE[2], S. ROJAS[2], D. QUINTANA[2];
[2]Ctr. de Investigaciones Biomedicas, [1]Univ. Andres Bello, Santiago, Chile

Abstract: Recent evidence suggests that the insula may be involved in anxiety. Here, using *in vivo* pharmacology of the Insula in rodents, we identified the area within the insula that is involved in anxiety and determined to which extent the insula modulates the behavioral effects of stress hormones in anxiety. We also assessed the behavioral effects of intra-insular microinjections of noradrenaline and corticosterone. Finally, we also performed a study in humans using a special coil of Deep transcranial magnetic stimulation (dTMS) uniquely designed to stimulate the rostral insula non-invasively in volunteers suffering from work stress, showing that Insula stimulation leads to a fast and significant decline in anxiety and significant improvements in anxiety-related insomnia, irritability and coping. In consequence, here we show a role for the Insula in response to stress and anxiety, from rodents, to humans, suggesting that the Insula may be a critical site regulating anxiety and a novel target for treatment of stress, anxiety and anxiety-related disorders.

Disclosures: J. Stehberg: None. **R. Moraga-Amaro:** None. **R. Diaz-Galarce:** None. **S. Rojas:** None. **D. Quintana:** None.

Nanosymposium

15. Insula: Somatotopy, Emotion, and Cognition

Location: S401

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 15.04

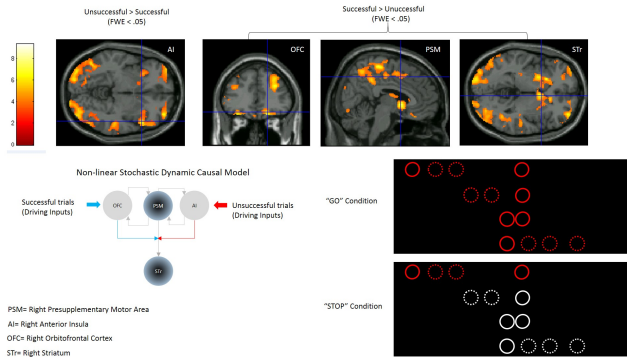
Topic: D.03. Multisensory Systems

Support: FONDECYT 1130920

Title: The right anterior insula modulates cortico-striatal glutamatergic connections during unsuccessful behavior inhibition: an fMRI effective connectivity study

Authors: *R. LIMONGI, F. J. PÉREZ;
Univ. Diego Portales Facultad De Psicología, Santiago, Chile

Abstract: Behavior flexibility is critical to surviving a volatile and unpredictable environment. The neural mechanism that gives rise to the control of behavior (i.e., stopping or changing an ongoing behavior) is one of the most investigated subjects in neuroscience. Glutamatergic cortico-striatal projections mediate behavior inhibition via striatal activation. Meta-analytic data show that the right anterior insula (rAI) takes control of the cortico-striatal mechanism when behavior inhibition fails. The rAI have anatomical connectivity with the right presupplementary motor area (rPreSMA). However, the effective connectivity between the rAI and the rPreSMA during unsuccessful control of behavior has not been studied. Specifically, we do not know how the rAI-rPreSMA communication affects the striatal activity during unsuccessful control of behavior. In this work, we evaluated the hypothesis that the insular cortex modulate the rPreSMA-striatal endogenous glutamatergic connections during unsuccessful response inhibition. In our task, 20 subjects predicted the timing of a rear-end collisions and engaged temporal behavior preparation. In a minority of trials, the participants were cued to stop the execution of the prepared behaviors. Functional connectivity analysis of the successful vs. unsuccessful trials (FWE < 0.05) revealed activity of the orbitofrontal cortex (OFC), the rPreSMA, and the striatum whereas the reverse contrast (i.e., unsuccessful vs. successful, FEW < 0.05) showed activity in the rAI. Non-linear stochastic dynamic causal modeling revealed that the OFC modulate the rPreSMA-striatal connections when the participants succeeded at inhibiting their behaviors, the rAI modulated the same connections when the participants failed. The analysis reveals the modulatory role of rAI in the indirect pathway of behavior inhibition. Because the rAI is involved during decisions under temporal uncertainty, uncertainty could be considered as a driving internal state that dampens the control of behavior.



Disclosures: **R. Limongi:** None. **F.J. Pérez:** None.

Nanosymposium

15. Insula: Somatotopy, Emotion, and Cognition

Location: S401

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 15.05

Topic: F.03. Motivation and Emotion

Support: Israel Science Foundation grant 1370/12

Title: Neural attunement to the emotions of others

Authors: *Y. GOLLAND[1], N. LEVIT-BINNUN[2], T. HENDLER[3,6,4,5], Y. LERNER[6,7];
[1]Baruh Ivcher Sch. Of Psychology, Interdisciplinary Ctr. (IDC),Herzliya, Herzliya, Israel; [2]Sagol Ctr. for Brain and Mind, Baruh Ivcher Sch. Of Psychology, Interdisciplinary Ctr. (IDC), Herzliya, Israel; [3]Sch. of Psychological Sci., [4]Fac. of Med., [5]Sagol Sch. of Neurosci., Tel Aviv Univ., Tel Aviv, Israel; [6]Functional Brain Ctr., [7]Dept. of Neurol., Tel Aviv Sourasky Med. Ctr., Tel Aviv, Israel

Abstract: Research suggests that the emotions of others can be highly contagious, affecting one's own emotional and neural responses. Yet, the neural mechanisms underlying interpersonal emotional transmissions have been mainly studied using static images in non-social setups. Here we investigated how the human brain responds to dynamic emotional input, coming from another, co-present individual. Using an innovative approach recently developed in our lab, we provided participants with continuous emotional feedback from another participant while they watched emotional movie in the fMRI scanner. To disentangle between the socially-driven effects and the stimulus-driven effects we introduced a control group, in which participants received identical stimulus, but thought that the feedback is generated by a computer algorithm. We mapped the brain regions which exhibited reliable activity in the experimental and control groups. In addition, we assessed neural response synchronization with the time-course of the social-emotional feedback and compared it across groups. Behavioral Results: Although the feedback time-line was identical in the experimental and control groups, the experimental group participants rated the feedback as matching their own emotional experience to a larger degree than the control group participants (experimental=6.4±2, control=2.68±0.7, $p<0.0001$). Imaging Results: Comparing the experimental and the control groups, we found that response time-courses in the bilateral insula, amygdala, thalamus and dMPFC exhibited moment-by-moment alignment with the feedback time-line. In addition, right lateral prefrontal regions were reliably recruited in the experimental (social) but not in the control (non-social) groups. Finally, alignment with the feedback in the right amygdala and in the MPFC was strongly associated with the emotional effects of the feedback, reported after the experiment ($r=0.75$, $p<0.01$). Conclusions: Continuous processing of emotional input from another, co-present individual recruited a set of brain systems, including core regions associated with emotion generation, medial prefrontal cortex associated with social-emotional evaluation as well as lateral prefrontal

control system consistently linked with emotion regulation. Moreover, the activity in the limbic, insular and dorsomedial prefrontal regions was dynamically aligned with the time-course of the social input. Taken together, the results of this study suggest that the emotions of others shape one's own responses by evoking response synchronization in the core emotion brain regions and recruitment of prefrontal emotion regulation mechanisms.

Disclosures: Y. Golland: None. **N. Levit-Binnun:** None. **T. Hendler:** None. **Y. Lerner:** None.

Nanosymposium

15. Insula: Somatotopy, Emotion, and Cognition

Location: S401

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 15.06

Topic: F.03. Motivation and Emotion

Support: NIH/NIMH R21MH102634

NCATS CTSA UL1 TR000142

Title: Category-independent value and salience signals in the human brain

Authors: *Z. ZHANG[1,3], D. B. EHRLICH[1,3], J. FANNING[3], W. CHEN[3,6], D. LEE[4,2,5], I. LEVY[3,4];
[1]Interdepartmental Neurosci. Program, [2]Dept. of Psychology, Yale Univ., New Haven, CT; [3]Section of Comparative Med., [4]Dept. of Neurobio., [5]Kavli Inst. for Neurosci., Yale Sch. of Med., New Haven, CT; [6]Dept. of Psychology, Southwest Univ., Chongqing, China

Abstract: The ability to compute and assign values in a common scale to predictive cues and outcomes across different categories is essential for value-based decision making. An extensive literature has focused on the neural mechanisms of value computations at both outcome anticipation and receipt, and a 'valuation system' in the brain has emerged from these studies. Few studies, however, included both rewards and punishments in their design to disentangle value and salience signals, which are highly correlated in either the positive or the negative domain alone. Even fewer studies assessed the degree to which those signals are category-dependent. Here we present evidence from a human fMRI study for category-independent value and saliency signals in different brain regions. 18 healthy participants were scanned while performing the reward and punishment task. Participants were presented with cues that predicted the probabilistic delivery of different types of outcomes. Four outcome categories were used: monetary gains and losses, presentations of pleasant faces and electric shocks. Four magnitude or

intensity levels were used for each outcome type, so that a wide range of value and salience were experienced by the participants. On third of the trials outcome was provided after a delay period. Pleasantness ratings were collected both at the cue (anticipation) phase and at the outcome (receipt) phase, and trial-by-trial value and saliency were estimated from these ratings. In the cue phase, blood oxygen level-dependent (BOLD) signals in the orbitofrontal cortex (OFC), the ventromedial prefrontal cortex (vmPFC), and the posterior parietal cortex monotonically increased from extreme negative to extreme positive values, consistent with a linear value signal. The rostral anterior cingulate cortex (rACC), and the anterior insula showed a U-shaped salience-like activity profile, in which signals increased for anticipation of both increasing positive and increasing negative outcomes. Finally, the striatum encoded both value and salience signals. Importantly, the observed signals were on a unified scale that applied to different categories. Similar analysis also revealed that, in the outcome phase, the vmPFC, striatum, and the posterior cingulate cortex (PCC) represented value and the rACC represented salience, both in a category-independent manner. In a complementary set of analyses we used representation similarity analysis (RSA) to compare predictions for regional activation patterns generated by several potential models. Based on this analysis we propose a computational model in which the reliability of value representations is modulated by salience.

Disclosures: Z. Zhang: None. **D.B. Ehrlich:** None. **J. Fanning:** None. **W. Chen:** None. **D. Lee:** None. **I. Levy:** None.

Nanosymposium

15. Insula: Somatotopy, Emotion, and Cognition

Location: S401

Time: Saturday, October 17, 2015, 1:00 PM - 2:45 PM

Presentation Number: 15.07

Topic: F.01. Human Cognition and Behavior

Title: Correlates of the social stereotype threat and socioeconomic status effects in the human brain: a meta-analysis

Authors: *A. N. SOKOLOV[1], M. A. PAVLOVA[2], E. SIMOES[1];
[1]Women's Hospital, Univ. of Tübingen Med. Sch., Tübingen, Germany; [2]Univ. of Tübingen Med. Sch., Tübingen, Germany

Abstract: Social experience and social interactions can shape our brain, its function, and behavior. Only most recently, however, advances in neuroimaging have suggested the existence of systematic individual differences in the brain structure, function, and development related to social (e.g., gender and race) identity and stereotypes, socioeconomic status (SES), and their

implications for health and disease. We present a meta-analytic review of neuroimaging evidence on these issues as found in PubMed and Medline databases over the past ten years. Social stereotypes such as “women usually outperform men in social cognition tasks” or “Asians compared to Whites, typically excel in math” are often viewed threatening by another population group (e.g., Pavlova et al., 2014). Research shows that activating such a stereotype can evoke a stress-related physiological response, engaging a number of brain regions, notably the amygdala, prefrontal, anterior insular and dorsal anterior cingulate cortex (PFC, AI, and dACC; e.g., Wraga et al., 2007). One activation pathway may arise from dACC connections with both the amygdala and hypothalamus (LeDoux, 2000). The amygdala with its projections to brainstem regions such as the locus coeruleus (LC, a key region for norepinephrine production; Ulrich-Lai & Herman, 2009), modulates the sympathetic nervous system activity. The amygdala also projects to the bed nucleus of stria terminalis and further to the paraventricular nucleus (PVN) of hypothalamus. These prompt the hypothalamic-pituitary-adrenal (HPA) axis responses that ultimately increase cortisol production (Burgos-Robles et al., 2009). The AI is implicated in representing efferent outputs of brain regions triggered by stress and arousal as the insula itself is viewed to represent the physiological condition of the body (Craig, 2009). The neurobiological effects of stereotype threat may be gender dependent (e.g., Cattaneo et al., 2011). Environment and social context factors such as SES are likely to shape the brain structure and function as well. Recent evidence indicates the SES effects on structural brain development, mostly brain connectivity as reflected in the white matter structure and integrity (e.g., Gianaros et al., 2013; Johnson et al., 2013), and functional task-related activity, primarily in the frontal lobe (e.g., Kishiyama et al., 2009; Muscatell et al., 2012). A mechanistic understanding of these relationships will offer novel insights into the brain response to the social challenges and help to develop better strategies for treating and managing such devastating diseases as major depression, cardiovascular disease, and cancer.

Disclosures: **A.N. Sokolov:** None. **M.A. Pavlova:** None. **E. Simoes:** None.

Nanosymposium

016. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.01

Topic: D.17. Voluntary Movements

Title: Sensorimotor cortical hemodynamics following hand and orofacial motor tasks and pulsed cutaneous stimulation

Authors: *A. ODER ROSNER, S. M. BARLOW;
Univ. of Nebraska-Lincoln, Lincoln, NE

Abstract: OBJECTIVE: To examine hemodynamic differences between hand and face cortical representations during motor and passive somatosensory conditions, as measured with functional near-infrared spectroscopy (fNIRS). The recorded data will help create a computational model of cortical adaptation for future neurodiagnostic and neurotherapeutic applications. METHODS: The ongoing study design includes 20 neurotypical adults (ages 19-30) and 20 neurotypical children (ages 6-12). A T1-weighted anatomical image will localize individual's primary motor (M1) and somatosensory (S1) cortices and ensure precise placement of the fNIRS probe over those areas. A TechEn CW6 device will be used for fNIRS data acquisition. A 5x3 optode montage with 2 short separation measurements (1 cm) will be placed over left M1 and S1 to sample hemodynamic response functions (HRFs) during 4 stimulation conditions: 1. bilabial compressions on a lip force strain gage at 5% max voluntary contraction (MVC) force, 2. right hand squeezing on a grip force strain gage at 5% MVC, 3. Galileo™ pneumatic stimulation of the lower face near the right oral angle, and 4. Galileo™ pneumatic stimulation of the right thumb, index, and middle fingers. The experimental paradigm consists of passive pneumotactile stimulation (biphasic pneumatic pulse train -80 to 140 cmH2O, 50-ms pulse width, 9 ms rise/fall time) or performance of motor tasks, each at 2 Hz (20 s ON/ 20 s OFF, repeated 10x). Relative concentrations of oxy- (HbO) and deoxy-hemoglobin (HbR) will be measured during stimulus ON and OFF periods, and averaged over all 10 blocks. RESULTS: Preliminary results from 12 neurotypical adults (mean = 22.7 yrs) reveal significant oxygenation differences across stimulus conditions in putative corresponding cortical regions. Face motor tasks yielded significantly greater levels of HbO in face M1 than hand motor tasks in hand M1 ($t[1500]=190.57$, $p< .000$), as well as greater levels of HbO in face S1 than hand S1 ($t[1500]=94.43$, $p<.000$), during motor activity periods. Pneumotactile stimulation of the face yielded significantly greater HbO levels in face S1 than did the same stimulation of the hand in hand S1 ($t[1500]=43.24$, $p< .000$), during pneumotactile stimulation periods. CONCLUSIONS: Many significant differences were found in hand and face M1 and S1 across the different motor and sensory conditions, including distinctive HRFs, adaptation patterns, and cortical refill responses. These differential effects are likely due to differences in regional arterial/venous anatomy, cortical vascular beds, extent and orientation of somatotopy, task dynamics, and mechanoreceptor typing in hand and face.

Disclosures: A. Oder Rosner: None. **S.M. Barlow:** None.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.02

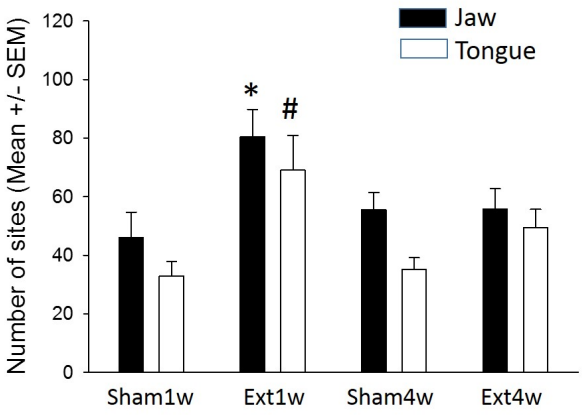
Topic: D.17. Voluntary Movements

Support: CIHR 4908, Faculty of Dentistry Bertha Rosenstadt Endowment Fund

Title: Neuroplasticity of face sensorimotor cortex induced by tooth extraction in C57BL/6 mice

Authors: Y. HAYASHI[1], J.-C. LEE[2], D. CHOCRON[3], P. CHERKAS[2], B. SESSLE[3], *L. AVIVI-ARBER[3];
[1]Kanagawa Dent. Univ., Yokosuka, Kanagawa Prefecture, Japan; [3]Fac. of Dentistry, Dept. of Prosthodontics, [2]Univ. of Toronto, Toronto, ON, Canada

Abstract: We have recently documented the neuroplastic capacity of the face sensorimotor cortex (face-SMCx) following tooth extraction in rats (Avivi-Arber et al. JCN 2010, 2015), but no study has addressed the extraction-induced neuroplastic capacity of this brain region in mice. We used intracortical microstimulation (ICMS) and recordings of evoked electromyographic (EMG) activity to test if the ICMS-defined jaw (anterior digastric, AD) and tongue (genioglossus, GG) motor representations within the cytoarchitectonically defined face-SMCx are altered following extraction of the right maxillary molar teeth in adult male C57BL/6 mice. Under local and halothane anaesthesia, 13 mice had molar tooth extractions and 13 sham control mice had general anaesthesia with no actual tooth extraction. Systematic ICMS mapping was carried out within the contralateral left hemisphere under ketamine general anaesthesia 1 or 4 weeks following tooth extraction (ie, Ext1w, n=6; Ext4w, n=7) or sham operation (ie, Sham1w, n=6; Sham4w, n=7). Cortical sites from which ICMS evoked EMG activity in AD or GG and onset latencies of the evoked EMG activities were noted. There were no significant differences across the study groups in the AD and GG onset latencies (ANOVA $p>0.05$), but Tooth extraction was associated 1 week later with significantly increased AD and GG motor representations (see Figure). These changes were transient and were not observed 4 weeks after extraction. Our novel findings suggest that tooth extraction in mice produces transient neuroplastic changes in face-SMCx that may be related to how mice adapt to the altered dental state.



*ANOVA, *post-hoc* Duncan: Ext1w vs Sham1w, Sham4w and Ext4w p=0.01, 0.04, 0.03 respectively. #Ext1w vs Sham1w, Sham4w and Ext4w p=0.003, 0.003, 0.05 respectively.

Disclosures: **Y. Hayashi:** None. **J. Lee:** None. **D. Chocron:** None. **P. Cherkas:** None. **B. Sessle:** None. **L. Avivi-Arber:** None.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.03

Topic: D.17. Voluntary Movements

Support: NIH Grant F32 DC014399 (Kelm-Nelson) , UW Department of Surgery Pilot Funds (Kelm-Nelson) , UW Department of Surgery (Ciucci)

Title: Molecular inquiry of vocal dysfunction in the periaqueductal gray of a PINK1 knockout rat model of Parkinson's disease

Authors: *C. A. KELM-NELSON[1], S. A. STEVENSON[2], M. R. CIUCCI[1];
[1]Dept. of Surgery, Div. of Otolaryngology, [2]Dept. of Zoology, Univ. Wisconsin-Madison, Madison, WI

Abstract: Voice disorders in Parkinson disease (PD) manifest in the early stages of the disease. PD pathology is widespread including not only central dopamine loss, but early-onset neuropathology including alpha synuclein aggregation and alterations in catecholamine function. However, the underlying pathology that contributes to early-onset vocal dysfunction is poorly

understood. We use a genetic rat model of PD, *PINK1* knockout (-/), to model early-onset vocal deficits. Rats produce social 50-kHz ultrasonic vocalizations and our recent data show that male *PINK1* -/- rats exhibit early, progressive deficits compared to non-affected wildtype (WT). Specifically, at 8 months of age *PINK1* -/- rats have significant reductions in peak frequency, bandwidth and intensity. Within the brainstem, the periaqueductal gray (PAG) is responsive during the production of vocalizations and is hypothesized to be involved in the central coordination of vocalizations as well as integration of motivational state. Our recent data show significant aggregations in insoluble alpha synuclein immunoreactivity within the PAG, suggesting a possible link to vocalization deficits. To gain insight into the mechanism related to vocal deficits, we investigated changes in genetic expression within the PAG. At 8 months of age, microdissected brain tissue from *PINK1* -/- rats and age-matched WT controls was collected for real time qPCR; products were sequenced using Sanger sequencing for confirmation. Mean Ct values for each sample were transformed via the Pfaffl Method to yield individual relative expression normalized to reference genes. Our results show that *PINK1* -/- animals had significantly increased expression of mRNAs encoding tyrosine hydroxylase and dopamine receptor 2, but not dopamine receptor 1, as compared to WT. These findings are consistent with the hypothesis that upregulation of dopamine receptor 2 results in a reduction of neurotransmission. Future experiments will explore the role of norepinephrine in catecholamine compensation as a model of upregulation of tyrosine hydroxylase as well as markers of dopamine turnover. Moreover, there was no difference in relative expression of mRNAs encoding alpha synuclein. These results are the first to suggest that alpha synuclein aggregation in this model is not a result of increased transcription, and future experiments will explore lysosomal autophagy markers as a mechanism of pathogenesis. Altogether, these findings are consistent with the hypothesis that differences in neural substrate sensitivity contribute to the early pathogenesis of vocalizations and motivation to communicate in the *PINK1* -/- rat model of PD.

Disclosures: C.A. Kelm-Nelson: None. **S.A. Stevenson:** None. **M.R. Ciucci:** None.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.04

Topic: D.17. Voluntary Movements

Title: The motor organization of positive and negative vocalizations in the midbrain periaqueductal gray

Authors: *H. H. SUBRAMANIAN[1], M. ARUN[1], P. A. SILBURN[2], G. HOLSTEGE[2];
[2]UQ Ctr. for Clin. Res., [1]The Univ. of Queensland, Herston, Australia

Abstract: Neurochemical microstimulation in different parts of the midbrain periaqueductal gray (PAG) in cat can generate four different types of vocalization, mews, howls, cries and hisses. The mews signify a positive vocal expression while the howls and cries signify negative vocal communications. Hisses are usually combined with howls and also represent negative emotions. Mews were produced from the lateral column of the intermediate PAG. Howls were produced from the ventrolateral column of the intermediate PAG. Cries were produced from two regions, the lateral column of the rostral PAG and the ventrolateral column of the caudal PAG. Hisses were also produced from the same area, which produced howls, however were not seen from areas which produced either mews or cries. An 'only hissing episode' was never seen. In order to define the specific motor patterns belonging to mews, howls and cries, the frequency, intensity, activation cascades, turns and amplitude analysis of the electromyograms (EMG's) during these vocalizations of the following muscles were analyzed: larynx (cricothyroid, thyroarytenoid and posterior cricoarytenoid), tongue (genioglossus), jaw (digastric) and respiration involved muscles (diaphragm, internal intercostal, external abdominal oblique and internal abdominal oblique). The results show that each type of vocalization consists of a specific circumscribed motor coordination. The nucleus retroambiguus (NRA) in the caudal medulla, by way of its direct projections to the motoneurons innervating pharynx, larynx, diaphragm, abdominal muscles and pelvic floor, serves as the final premotor interneuronal output system for vocalization. Also in the NRA neurochemical microstimulation can generate vocalizations (guttural sounds). Analysis of their EMG's demonstrated that these vocalizations consist of only small parts of the emotional vocalizations generated by neurochemical stimulation in the PAG. These results demonstrate that circuits mediating the expression of positive and negative vocalizations are segregated within the PAG. The PAG is able to elicit the same mews, howls, and cries as conscious cats, and that it uses the NRA as a tool to gain access to the motoneurons generating vocalization.

Disclosures: H.H. Subramanian: None. **M. Arun:** None. **P.A. Silburn:** None. **G. Holstege:** None.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.05

Topic: D.17. Voluntary Movements

Title: Encoding saltatory tactile velocity in the human orofacial somatosensory system using fMRI

Authors: *R. CUSTEAD[1], H. OH[2], S. M. BARLOW[3];
[1]Communication Disorders, Neurosci., [2]Bioengineering, [3]Communication Disorders, Neuroscience, Bioengineering, Human Biol., Univ. of Nebraska, Lincoln, NE

Abstract: BACKGROUND: The processing of continuous tactile inputs is a key function of somatosensory systems. Closely tied to movement and skilled motor activity, tactile percepts of velocity are crucial mechanisms in healthy movement production and recovery of function following neurological insult. Little is known about tactile velocity coding in trigeminal somatosensory networks that process complex cutaneous afferent information associated with facial sensation and proprioception. OBJECTIVE: To use functional magnetic resonance imaging (fMRI) to investigate neural substrates of velocity encoding in the healthy human orofacial somatosensory system during saltatory, pneumotactile inputs to the unilateral orofacial skin. METHODS: Participants - 15 neurotypical, right-handed adults, age 19-30 years. A multichannel pneumatic amplifier (Galileo Somatosensory) was programmed to generate sequential punctate inputs (50 ms duration, 9 ms rise/fall time) to the hairy skin of the right lower face. An array of 7 small, acetyl pneumatic capsules (6 mm ID) were arranged along a line (medial-lateral) spanning the right perioral skin and cheek. Programmed time delays between pressure pulses resulted in a saltatory stimulus sequence at 3 velocities (25, 45, 105 cm/s) in a randomized block design (40 s). An MPRAGE sequence (1 mm isotropic, TE=30ms, TR=2400ms) was followed by 3 functional scans using a 3T Siemens Skyra (32-ch head coil). Functional images: T2*-weighted EPI sequence, 36 slices (1.7x1.7x.2.0mm, TE=24ms, TR=2500ms, FOV=220mm). Using SPM12, 990 acquired brain volumes/subject were realigned, and smoothed with an isotropic Gaussian kernel (FWHM=6 mm). RESULTS: Common areas of activation for all velocities were predominately localized to the contralateral face primary somatosensory cortex (SI). Peak intensities of activated regions were velocity dependent, with the largest local maxima seen at the slowest velocity (25cm/sec: [MNI (mm) = -61, -18, 42; T= 8.14, p<.001]). The magnitude of the peak activations were less at the faster velocities (45cm/s: [MNI (mm)= -61, -18, 44; T= 5.56, p= .001]), (105cm/s: [MNI (mm)= -61, -20, 42; T=6.36, p<.001]), and showed more variable spatial organization. CONCLUSIONS: Unilateral, sequential saltatory inputs to the right lower face produced localized, contralateral BOLD responses whose spatiotemporal organization was highly dependent on velocity. These differences may be related to unique velocity processing networks associated with tactile discrimination of movement across orofacial skin. Supported by: Barkley Trust Foundation (Barlow)

Disclosures: R. Custead: None. **H. Oh:** None. **S.M. Barlow:** None.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.06

Topic: D.17. Voluntary Movements

Support: NIH R01 NS04853, NIH R01 DE023816

Title: Spectral profiles of local field potentials of somatosensory and motor cortices during feeding

Authors: *K. TAKAHASHI[1], Y. NAKAMURA[1,2], K. A. BROWN[3], F. I. ARCE-MCSHANE[1], C. F. ROSS[1], N. G. HATSOPOULOS[1];
[1]Organismal biology and anatomy, Univ. of Chicago, Chicago, IL; [2]Grad. Sch. of Med. and Dent. Sci., Niigata Univ., Niigata, Japan; [3]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The orofacial areas of the primary motor cortex (MIo) and somatosensory cortex (SIo) are involved in controlling and monitoring of voluntary, semiautomatic and rhythmic movements of the tongue and jaw during key feeding behaviors such as ingestion, chewing and swallowing. However it remains unclear as to the function of or relation of aggregated signals such as local field potentials (LFPs) to orofacial behaviors. Our previous results from MIo showed that beta oscillations (15-30 Hz) were modulated around swallow cycles and low gamma oscillations (30-80 Hz) were often modulated at ingestion or transition from transport to a first chew cycle in a feeding sequence. To investigate if spectral properties of SIo during feeding behavior were similar to those of MIo, we analyzed LFPs recorded simultaneously from Utah arrays implanted in MIo and SIo in one macaque monkey performing a manual feeding task. Tongue and jaw kinematics were captured using videofluoroscopy and a 3D motion tracking system, and the kinematics were used to quantify the jaw cycles including ingestion, transport, chew, and swallow cycles. We found that during 43 feeding sequences, compared to MIo, the power spectrum of SIo signals shared almost identical peak beta frequency at 19 Hz, and showed more beta power from the baseline pink noise. Furthermore, the band width of the beta band of SI LFPs was narrower (+- 2.5 Hz) compared to that of MI (+- 4.1 Hz). Coherence around the beta band between MIo and SIo LFPs was highest during one chewing sequence prior to the swallow. A weak low gamma peak from both areas at 65-75 Hz showed similar power deviation form the respective baseline spectra and coherence increased slightly at the time of ingestion and more at transition from transport to a first chew cycle. Our results suggest that gross spectral profiles of MI and SI LFPs are similar, but their detailed oscillations patterns are different at key behavioral state such as swallowing and transition from transport to chewing cycles. Therefore change in

their involvement or their communication patterns would give us further insights for their roles and interactions during feeding behavior.

Disclosures: **K. Takahashi:** None. **Y. Nakamura:** None. **K.A. Brown:** None. **F.I. Arce-McShane:** None. **C.F. Ross:** None. **N.G. Hatsopoulos:** None.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.07

Topic: D.17. Voluntary Movements

Support: KAKENHI 26462824

Title: Pyramidal neurons in the agranular insular cortex receives sensory inputs from the tongue: an *in vivo* whole-cell patch-clamp study

Authors: ***K. ADACHI**[1,2], M. KOBAYASHI[2], H. SAKAGAMI[1], N. KOSHIKAWA[2];
[1]Meikai Univ. Sch. of Dent., Sakado/ Saitama, Japan; [2]Pharmacol., Nihon Univ. Sch. of Dent., Tokyo, Japan

Abstract: The insular cortex (IC) has morphologically and functionally unique features compared with other sensory areas including somatosensory and visual cortices. Cytoarchitectural difference based on the pattern of granular cell layer (layer IV) divides IC into three subregions: granular (GI), dysgranular (DI) and agranular IC (AI). These subregions are connected each other, and also reciprocally connected between limbic system and thalamus. Recent studies report that IC processes multimodal sensory information including gustation, olfaction, visceral and thermal sensation, and nociception. In particular, the responses to nociceptive stimulation are recorded in the rostral part of IC. We performed *in vivo* whole-cell patch clamp recording from rostral region of AI (approximately 1 mm rostral from middle cerebral artery) to elucidate physiological and morphological features of layer II/III pyramidal neurons responding to tongue stimulation. To reconstruct morphological feature of recorded cells, only one AI neuron was recorded in each animal. AI pyramidal neurons exhibited spontaneous membrane oscillation similar with pyramidal neurons in GI and DI (Adachi et al., 2013). Electrical stimulations (7 V) of caudal IC (around middle cerebral artery) elicited evoked excitatory postsynaptic potentials (eEPSPs: 11.5 ± 2.9 mV, n = 8). Repetitive electrical stimulation with 5 pulses at 50 Hz induced summation of eEPSP. Electrical stimulation of tongue (5 pulses at 33 Hz) was applied to 6 of 8 animals and induced tongue twitch in all animal. Then,

50% of AI neurons responded to tongue stimulation. Tongue stimulation at 1.6 mA induced EPSPs with the amplitude of 7.4 ± 1.0 mV in 1 animal. The evoked EPSPs were followed by IPSPs. On the other hand, tongue stimulation at 1.2-1.6 mA induced IPSPs with amplitude of -6.8 ± 0.6 mV or -0.4 ± 0.0 mV in other 2 animals. These findings suggest that the rostral AI processes sensory, maybe nociceptive, information from the tongue.

Disclosures: K. Adachi: None. **M. Kobayashi:** None. **H. Sakagami:** None. **N. Koshikawa:** None.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.08

Topic: D.17. Voluntary Movements

Title: In search of functional neural biomarkers of dysphagia to quantify treatment effects in mouse models

Authors: *T. E. LEVER[1], K. L. ROBBINS[1], M. J. ALLEN[1], R. SHARMA[2], K. TAKAHASHI[3], M. M. THAKKAR[2], G. N. DESOUZA[4];
[1]Otolaryngology - Head and Neck Surgery, [2]Neurol., Univ. of Missouri Sch. of Med., Columbia, MO; [3]Biol. Sci., Univ. of Chicago, Chicago, IL; [4]Electrical and Computer Engin., Univ. of Missouri, Columbia, MO

Abstract: Objectives: The neural components and pathologic mechanisms contributing to dysphagia (feeding and swallowing impairment) in various diseases - amyotrophic lateral sclerosis (ALS), for example -- are largely unknown. Consequently, treatments for dysphagia are limited to palliative interventions such as diet modifications (e.g., thickened liquids), behavioral adaptations (e.g., tucking the chin when swallowing), and feeding tubes. We propose to accelerate the search for preventative and curative treatments using a novel assay that combines electrophysiological recordings with videofluoroscopic (VF) imaging in mouse models of human diseases. **Methods:** Healthy control mice (n=4) and a SOD1-G93A transgenic mouse model of ALS (n=4) were stereotaxically implanted with electrodes targeting the hypoglossal nucleus in the brainstem. Electrographic recordings (single units and field potentials) were performed in awake, freely-behaving conditions and temporally synchronized with concurrent VF imaging while mice voluntarily ate and drank in a custom chamber. **Results**: Temporally synchronized electrophysiologic and VF imaging data were recorded over 6 months in all mice. In our initial analysis, we were able to easily identify and distinguish between distinct neuronal waveform

patterns corresponding to either licking, chewing, or swallowing, suggesting that different neuronal events/groups are involved in different feeding and swallowing behaviors.
Conclusions: We have successfully synchronized electrophysiological recordings from the hypoglossal nucleus with VF feeding and swallowing behaviors in freely behaving, self-feeding mice. Although preliminary, this line of research has tremendous clinical relevance and therapeutic potential. Protocol optimization is underway using high speed (>400 fps) video tracking to correlate distinct electrophysiological events from multiple brainstem with patterns of anatomic motion of radiopaque markers implanted into soft tissues of the oral cavity, pharynx, and larynx. This approach will reveal differences in the neural control of feeding and swallowing between healthy mice and mouse models of human diseases, which will serve as novel functional neural biomarkers for future treatment efficacy studies.

Disclosures: **T.E. Lever:** A. Employment/Salary (full or part-time): University of Missouri. **K.L. Robbins:** A. Employment/Salary (full or part-time): University of Missouri. **M.J. Allen:** A. Employment/Salary (full or part-time): University of Missouri. **R. Sharma:** A. Employment/Salary (full or part-time): University of Missouri. **K. Takahashi:** A. Employment/Salary (full or part-time): University of Chicago. **M.M. Thakkar:** A. Employment/Salary (full or part-time): University of Missouri. **G.N. DeSouza:** A. Employment/Salary (full or part-time): University of Missouri.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.09

Topic: D.17. Voluntary Movements

Support: Michael J Fox Foundation

Title: Inflammation as a contributor to ingestive dysfunction in a PINK1 knockout rat model of Parkinson's disease

Authors: ***K. YANG**[1], M. R. CIUCCI[2];
[1]Neurosci. Training Program, Univ. of Wisconsin-Madison, Madison, WI; [2]Dept. of Surgery - Otolaryngology, Univ. of Wisconsin - Madison, Madison, WI

Abstract: Deficits in ingestive behaviors, including those in functional swallowing that contribute to aspiration pneumonia, occur in the early stages of Parkinson Disease (PD) and have a complex underlying neuropathology that occurs outside of the classical central dopamine loss

framework. Late-stage PD patient brain tissue shows that vagal nuclei that provide afferent and efferent projections to structures of ingestion have degeneration of neurons that may result from pathological aggregation of abnormal alpha synuclein (a-syn). Additionally, significant increases in neuroinflammation including microgliosis, a central immune response that releases pro-inflammatory cytokines, may lead to an increase in neuronal cell death within these nuclei. Furthermore, human PD patients show an increased amount of circulating pro-inflammatory interleukins; modulating this may be a possible avenue of treatment or prevention. Thus, we hypothesize that abnormal a-syn aggregation will be present in vagal nuclei controlling swallowing and digestion in the rat, including the dorsal motor nucleus of the vagus (DMV), the nucleus ambiguus (NA), and the nucleus of the solitary tract (NTS). This aggregation may stimulate increased levels of microgliosis and pro-inflammatory molecule secretion. To test these predictions, we used a genetic animal model of PD, the PINK1 -/- rat, which shows early and progressive deficits in oropharygeal swallowing as well as aggregation of a-syn within muscles innervated by various branches of the vagus nerve. We performed immunohistochemistry for a-syn phosphorylated at serine 129 and activated microglia marker OX-42 within these nuclei in 14 10-month-old PINK1 -/- and 14 age-matched wild-type controls. Two bilateral serial sections where the central canal was present were analyzed using custom designed software in ImageJ to quantify total pixel area and mean optical density of the immunolabelling in each section. Preliminary results suggest that there are significant increases in total pixel area and mean optical density measures of a-syn and of OX-42 immunolabeling within the DMV, the NA, and the NTS in PINK1 -/- but not in wild-type rats. These findings are consistent with the hypothesis that microgliosis co-occurs in brain regions with aggregated a-syn. We will investigate the specific pro-inflammatory factors secreted by activated microglia colocalized with markers of cell death in these regions to better understand the sequaela of cell death. These findings will contribute to our understanding of how central inflammation and protein aggregation contribute to ingestive deficits in the PINK1 -/- rat model of PD.

Disclosures: K. Yang: None. **M.R. Ciucci:** None.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.10

Topic: D.17. Voluntary Movements

Support: NSF Grant BCS-0926196

NIH Grant R01-DC010145

NIH Grant F32-DC011249

Title: Auditory predictions of self-produced speech are task-dependent

Authors: *C. A. NIZIOLEK, S. S. NAGARAJAN, J. F. HOUDE;
Univ. of California San Francisco, San Francisco, CA

Abstract: How does the brain evaluate the success of a motor act? An action's sensory consequences, such as the auditory feedback heard while speaking, are thought to be predicted by the motor system. If the feedback matches the prediction, the neural response in sensory cortices is suppressed, a phenomenon known as speaking-induced suppression (SIS). However, it is unclear how this suppression occurs neurally, and what sensory parameters are compared to evaluate a "match." For example, when speaking English, the pitch of the voice has much more freedom to vary than when singing; is pitch encoded in the auditory prediction in the same way during these two tasks? Here, we used natural speech production to probe the nature of internal predictions and how they are encoded in auditory cortex. We used magnetoencephalography (MEG) to measure how SIS varied over repeated word productions in two different contexts. In Experiment 1, ten subjects produced 200 repetitions of three different words; in Experiment 2, ten subjects were cued by tonal prompts to produce 150 repetitions of a single word on three different pitches. These productions were then played back to the subjects. SIS was defined as the suppression of the auditory M100 response to spoken or sung words relative to the playback condition. When the prediction does not encode pitch, SIS should not change across pitch space: every production will be equally accurate. However, when the prediction does encode a pitch target, then SIS should be strongest at the center of the pitch distribution (most accurate pitches) and attenuated at the periphery (sharpest and flattest attempts at producing a pitch), where the feedback least matches the prediction. We found that pitch encoding depended on task context: SIS varied across utterances only in Experiment 2, in which pitch was an explicit target. This is consistent with a forward model in which the auditory prediction is weighted by acoustic parameters that contribute to a higher-level goal.

Disclosures: C.A. Niziolek: None. **S.S. Nagarajan:** None. **J.F. Houde:** None.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.11

Topic: D.17. Voluntary Movements

Support: NIH RO1DE023816

CIHR Grant MOP-4918

Title: Coherent activity in the orofacial sensorimotor cortex follows a spatiotemporal pattern

Authors: F. ARCE-MCSHANE[1], N. G. HATSOPOULOS[1], K. TAKAHASHI[2], B. J. SESSLE[4], *C. F. ROSS[3];
[1]Organismal Biol. & Anat., [3]Organismal Biol. and Anat., [2]Univ. of Chicago, Chicago, IL; [4]Univ. of Toronto, Toronto, ON, Canada

Abstract: We have shown that inter-areal coherence between the primary motor (MIo) and somatosensory (SIo) areas of the orofacial sensorimotor cortex exhibits a specific temporal organization (Arce-McShane et al., 2014 SfN Abstract). Here we examined whether this inter-areal coherence also exhibits a spatial pattern. Coherence (2-6 Hz) between spiking of MIo and SIo neurons and between spiking of MIo or SIo neurons and local field potentials (LFPs) were measured with microelectrode arrays in monkeys (Macaca mulatta) trained to perform a tongue-protrusion task. Using regression analysis, we found a significant effect of the position of MIo or SIo neurons on the array on the time-of-peak coherence ($p<0.05$); peak spike-spike coherence occurred earliest in MIo neurons located closest to the central sulcus and in caudal SIo neurons. MIo and SIo neurons exhibited significant spatial gradients for the time-of-peak coherence increasing in the rostrolateral direction for MIo neurons and in the mediolateral direction for SIo neurons. The spatial gradient in MIo may be related to our previous findings that MIo neurons whose spiking activity led the tongue-protrusive force were located closer to the central sulcus than neurons whose spiking activity lagged the force (Arce-McShane et al., 2014). Moreover, receptive fields (RFs) of the lips and tongue were located on the medial and lateral border of MIo, respectively. RFs in SIo increased in size caudally from the central sulcus and contralateral oral structures were largely represented in the medial region of SIo. Similar spatial gradients were also observed for the neuron component of the spike-field coherence; time-of-peak coherence progressed rostrolaterally in MIo neurons of the MIospike-SIoLFP coherence and mediolaterally for SIo neurons of the SIospike-MIoLFP coherence. For the LFP component of the spike-field coherence, the spatial gradient was opposite to the direction of the coherence in the neurons; time-of-peak coherence progressed medially and towards the central sulcus for MIospike-SIoLFP coherence and medially for SIospike-MIoLFP coherence. We also found significant spatial gradients with peak coherence ($p<0.05$); peak coherence of SIo neurons and LFPs progressed rostrally and were highest near the central sulcus where SIo neuronal RFs are smaller and less complex. Significant spatial gradients were observed for MIo neurons and LFPs, however the directions were not consistent across monkeys. The results suggest a spatiotemporal organization of coherence that may be related to the temporal relation of MIo neurons' spiking to tongue force and to the spatial features of MIo and SIo neurons' receptive fields.

Disclosures: **F. Arce-McShane:** A. Employment/Salary (full or part-time); NIH RO1DE023816. **N.G. Hatsopoulos:** A. Employment/Salary (full or part-time); University of Chicago. **K. Takahashi:** A. Employment/Salary (full or part-time); NIH RO1DE023816. **B.J. Sessle:** None. **C.F. Ross:** A. Employment/Salary (full or part-time); University of Chicago. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CIHR Grant MOP-4918, NIH RO1DE023816.

Nanosymposium

16. Oral Motor and Speech

Location: N226

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 16.12

Topic: D.17. Voluntary Movements

Support: MEXT (Nos. 24791984 and 26293397)

Title: Developmental changes of dendritic properties in rat jaw-closing motoneurons

Authors: ***S. NAKAMURA**[1], S. NAGATA[2], K. NAKAYAMA[1], A. MOCHIZUKI[1], M. KIYOMOTO[1], M. YAMAMOTO[2], T. INOUE[1];
[1]Dept. of Oral Physiology, Showa Univ. Sch. of Dent., Tokyo, Japan; [2]Dept. of Periodontology, Showa Univ. Sch. of Dent., Tokyo, Japan

Abstract: The dendrites of trigeminal motoneurons are well developed and ramify extensively in the trigeminal motor nucleus and surrounding reticular formation. It is possible that the dendrites of jaw-closing motoneurons possess active properties, which change with development of the orofacial musculoskeletal system during the early postnatal period. Thus, we investigated the developmental changes of somatic voltage responses evoked by focal dendritic photostimulation using laser photolysis of caged glutamate and somatic whole-cell recordings in the rat retrogradely-labeled masseter motoneurons (MMNs). Transverse brain stem slices (400 μm) were prepared from postnatal day (P) 2-5 (n = 22) and 9-12 (n = 18) Wistar rats. We made whole-cell patch clamp recordings from MMNs in the brainstem slice preparations and then stimulated 39 spots arranged around the recorded neurons in a concave shape array for each neuron with a laser power of 13.1 μJ. In P2-5 MMNs, we found that laser photostimulation of 9.7 spots per neuron induced membrane depolarization in the presence of tetrodotoxin (TTX) in all MMNs tested. These photostimulation-evoked responses were reduced by the application of N-methyl D-aspartate (NMDA) receptor antagonist D(-)-2-amino-5-phosphonovaleric acid

(APV). With increasing photostimulation intensity, the responses grew in amplitude up to a certain threshold, where a step-like increase in the somatic voltage amplitude, known as the NMDA spikes/plateau potentials, occurred in 75% (6/8) of P2-5 MMNs. The step-like depolarization was completely suppressed by application of 20 μM APV. The photostimulation-evoked responses became significantly smaller in amplitude and shorter in duration at P9-12 than at P2-5. Furthermore, only a few P9-12 MMNs exhibited NMDA spikes compared to P2-5 MMNs. These results suggest that the characteristics of responses evoked by photostimulation of the MMN dendrites change during the first 2 postnatal weeks, and such changes in the dendritic signal processing of the synaptic inputs to the MMNs are involved in the conversion from sucking to chewing and biting during early postnatal development.

Disclosures: **S. Nakamura:** None. **S. Nagata:** None. **K. Nakayama:** None. **A. Mochizuki:** None. **M. Kiyomoto:** None. **M. Yamamoto:** None. **T. Inoue:** None.

Nanosymposium

017. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.01

Topic: E.08. Biological Rhythms and Sleep

Support: NIH Grant GM10499102

Title: Kv12-encoded K+ channels regulate neuronal excitability in the suprachiasmatic nucleus

Authors: ***T. HERMANSTYNE**[1], D. GRANADOS-FUENTES[2], E. D. HERZOG[2], J. M. NERBONNE[1];
[1]Dept of Developmental Biol., Washington University, St. Louis Sch. of Med., Saint Louis, MO; [2]Biol., Washington University, St. Louis, St. Louis, MO

Abstract: The suprachiasmatic nucleus (SCN) is a bilateral structure in the hypothalamus that controls circadian rhythms in mammalian physiology and behavior and in the expression of molecular clock genes/proteins. The repetitive firing rates of SCN neurons are higher during the day and lower at night and these daily changes in electrical activity have been shown to drive circadian rhythms in physiology and behavior. Although previous studies suggest that the daily variations in the firing properties of SCN neurons are mediated by day-night changes in the expression of K+ channels that function at sub-threshold membrane potentials, the critical K+ channel(s) have not been identified. K+ channels encoded by the subunits of the KCNH (Kv12) subfamily have been shown to be highly expressed in the SCN and provide steady-state K+

currents in the sub-threshold voltage range, suggesting a physiological role for Kv12-encoded K+ channels in regulating neuronal firing in the SCN. To explore this hypothesis that subunits of the Kv12 subfamily are important regulators of repetitive firing in the SCN, we developed a RNA-interference based strategy using short hairpin RNAs (shRNAs) to "knockdown" Kv12.1 or Kv12.2 α-subunits *in vivo* in the SCN using adeno-associated viral delivery. Virally-transduced SCN neurons were visually identified by the presence of GFP and whole-cell current clamp recordings were obtained from wild-type (WT) and Kv12-targeted shRNA-expressing SCN neurons. Similar to WT SCN neurons, the mean ± SEM repetitive firing rate of Kv12-targeted shRNA-expressing SCN neurons was significantly ($P<0.05$) higher during the day than at night. Interestingly, however, the mean nighttime firing frequency was significantly ($P<0.01$) higher in SCN neurons expressing Kv12-targeted shRNAs (1.8 ± 0.4 Hz), compared with WT SCN neurons (0.45 ± 0.4 Hz). In addition, the mean input resistance measured at night was ~75% higher in Kv12-targeted shRNA-expressing SCN neurons, compared with WT SCN neurons ($P< 0.01$) and the mean ± SEM nighttime action potential threshold was significantly ($P< 0.05$) more hyperpolarized in Kv12-targeted shRNA-expressing (-31.6 ± 1.3 mV), than in WT (-24.1 ± 2.1 mV) SCN neurons. These results reveal that the targeted knockdown of Kv12.1 and Kv12.2 α-subunits expression regulate nighttime firing rates in the SCN, suggesting a role for K+ channels encoded by Kv12.1 and Kv12.2 α-subunits in the circadian regulation of electrical activity, molecular clock gene expression and behavior. This work was supported by NIH grant GM10499102 to EDH and JMN.

Disclosures: T. Hermanstyne: None. **D. Granados-Fuentes:** None. **E.D. Herzog:** None. **J.M. Nerbonne:** None.

Nanosymposium

17. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.02

Topic: E.08. Biological Rhythms and Sleep

Support: NSF Grant IOS-1145796

Title: Desynchronized suparachiasmatic nucleus and affective disorder pathogenesis

Authors: *M. BEN HAMO, L. S. DUGE, H. O. DE LA IGLESIA;
Dept. of Biol., Univ. of Washington, Seattle, WA

Abstract: The master control of circadian rhythms by the hypothalamic suprachiasmatic nucleus (SCN) allows for entrainment of rhythms of physiology and behavior to the light-dark (LD) cycle, as well as for a constant and normal phase relationship between different rhythmic modalities within an organism, known as circadian internal synchronization. There is substantial body of evidence that links disruptions to endogenous circadian rhythms, such as sleep, circulating hormone levels, and locomotor activity with affective disorders. In fact, interventions designed to realign endogenous circadian rhythms with external cues such as light therapy, sleep phase advance, social rhythm therapy and in some cases sleep deprivation therapy, are all effective treatments for affective disorders. Studies of depression have thus utilized animal models which have undergone some genetic, anatomical, pharmacological or behavioral intervention, such as gene knockouts, neural lesions, administration of corticosterone, social defeat and isolation. These manipulations do not necessarily concur with the etiology of affective disorders in humans, and finding a suitable animal model is still a major challenge, hampering the study of the mechanisms underlying psychiatric disorders. We used the 'forced desynchrony' protocol, where mere exposure of rats to symmetric 22 h LD cycle causes neuronal oscillators within the SCN to dissociate into two regional oscillators: the ventrolateral SCN (vlSCN) and the dorsomedial SCN (dmSCN), which are otherwise coupled. Thus, this protocol leads to the stable and predictable desynchrony of the vlSCN and dmSCN and their respective outputs, offering a unique opportunity to assess the effect of circadian internal desynchronization on the behavioral manifestation of affective disorders. We compared the behavior of 22 h LD rats to 24 h LD controls using four different tests: 1) Saccharin preference test to assess anhedonia, 2) Open Field test to assess levels of anxiety, 3) Sexual behavior test to assess sexual activity and motivation, and 4) Forced swim test to assess levels of despair. Preliminary results indicate that the recurrent misalignment of circadian rhythms in 22 h LD rats is associated with oscillations in their affective responses. Since the misalignment of endogenous circadian rhythms in the forced desynchronized rats is the result of the desynchronization of neuronal oscillators within the suprachiasmatic nucleus, our results suggest that circadian desynchronization within the master circadian clock contributes to the pathogenesis of affective disorders in neurologically and genetically intact animals.

Disclosures: **M. Ben Hamo:** None. **L.S. Duge:** None. **H.O. de la Iglesia:** None.

Nanosymposium

17. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.03

Topic: E.08. Biological Rhythms and Sleep

Support: BBSRC Grant BB/J003441/1

BBSRC Grant BB/G004307/1

Title: Scheduled locomotor exercise improves aberrant rhythms in neural and locomotor circadian function through alteration of GABAergic activity in the suprachiasmatic nuclei

Authors: *A. T. HUGHES[1], R. E. SAMUELS[2], M. D. C. BELLE[2], S. WEGNER[2], H. D. PIGGINS[2];
[2]Fac. of Life Sci., [1]Univ. of Manchester, Manchester, United Kingdom

Abstract: The hypothalamic suprachiasmatic nuclei (SCN) contain a network of cellular circadian oscillators which ultimately control daily rhythms in physiology and behaviour. Appropriate SCN function, including a coherent output rhythm and high amplitude oscillations at the single cell level, depends on synchrony between thousands of autonomous cellular oscillators that comprise these nuclei. Such synchrony is achieved largely by the neuropeptide vasoactive intestinal polypeptide (VIP) signalling through its cognate $VPAC_2$ receptor. Circadian rhythms generated by the SCN must be coordinated with the external environment via the actions of exogenous time cues and feedback from endogenous clock-controlled outputs. Daily scheduled exercise is one such influence and it is well established that regularly scheduled locomotor activity entrains behavioral rhythms in wild-type (WT) mice. Whilst VIP promotes synchrony within the SCN, the most abundant neurotransmitter in this structure, GABA, is currently postulated to oppose this synchrony, acting to make changes to the phase of the SCN, which are necessary during entrainment, easier to achieve. Thus, appropriate SCN function, and hence circadian output, rely on a balance between these synchronizing and desynchronizing factors. As such, mice lacking $VPAC_2$ receptors (*Vipr2*$^{-/-}$) generate only low amplitude, desynchronized rhythms in SCN cellular and molecular activities that result in aberrant rhythms in behavior. We have previously shown that placing these mice on a regimen of daily scheduled voluntary exercise (SVE) promoted robust near 24h rhythms in behavior. Here, we demonstrate that this is achieved through an SVE-mediated remodeling of SCN temporal architecture; SVE significantly recovered the proportion, synchrony and amplitude of rhythmic neurons in the *Vipr2*$^{-/-}$ SCN towards WT values. This effect is achieved through alteration of GABAergic signaling in the SCN; using voltage clamp recordings we demonstrate a significant increase in the amplitude of GABAergic events in the ventral part of the SCN accompanied by a significant decrease in the frequency of such events in the dorsal part. Further, using *in vitro* recordings of a luciferase reporter of SCN molecular activity, we demonstrate that, in contrast to control (non-SVE) *Vipr2*$^{-/-}$ tissue, post-SVE *Vipr2*$^{-/-}$ SCN show WT-like responses to blockade of $GABA_A$ signaling. We conclude that SVE promotes behavioral rhythmicity through partial restoration of SCN function in *Vipr2*$^{-/-}$ mice. These data are consistent with an SVE-mediated alteration in GABA signaling leading to long-term reorganization of SCN temporal activity.

Disclosures: **A.T. Hughes:** None. **R.E. Samuels:** None. **M.D.C. Belle:** None. **S. Wegner:** None. **H.D. Piggins:** None.

Nanosymposium

17. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.04

Topic: E.08. Biological Rhythms and Sleep

Support: NIH Grant NS036607

NIH Grant RR023432

NIH Grant RR025440

NIH Grant NS061800

Title: Astrocytes regulate the tonic GABA current in suprachiasmatic nucleus neurons

Authors: C. N. ALLEN[1], O. CRAVETCHI[1], M. WILLIAMS[2], R. P. IRWIN[1], S. A. AICHER[2], *M. MOLDAVAN[3];
[1]Oregon Inst. of Occup. Hlth. Sci., [2]Dept. of Physiol. and Pharmacol., [3]Oregon Health&Science Univer., Portland, OR

Abstract: Neurons in the hypothalamic suprachiasmatic nucleus (SCN), utilize GABA as a neurotransmitter to regulate the magnitude of light-induced phase shifts and synchronization of the dorsal and ventral regions of the SCN. The GABA released from presynaptic axon boutons is terminated by diffusion from the synapse and uptake from the extracellular space by specific GABA transporters (GATs). We investigated the role that these GATs play in regulating the extracellular GABA concentration and fast synaptic and tonic currents mediated by GABA(A) receptors in the SCN. Both light and electron microscopy in combination with immunocytochemistry demonstrated that the GABA transporters GAT1 and GAT3 in the SCN were located in astrocytes but not in neurons. The GAT1 and GAT3 were observed in astrocytic processes surrounding neuronal cell bodies, axons and axo-dendritic synapses. Application of the selective GAT1 inhibitors SKF89976A, NNC711, or the GAT3 inhibitor (S)-SNAP5114 applied alone even at high concentrations induced very small changes in the GABA(A) receptor-mediated baseline current. Simultaneous application of SKF89976A and (S)-SNAP5114 or nipecotic acid, a nonselective GAT blocker, significantly increased the amplitude of the GABA(A) receptor-mediated tonic current. These data demonstrate, that GAT1 and GAT3

located in astrocytes play an important role in regulating the amplitude of the tonic GABA currents in SCN neurons. These data also demonstrate that astrocytes expressing both GATs play an important role in regulation of SCN neural network activity.

Disclosures: **C.N. Allen:** None. **O. Cravetchi:** None. **M. Williams:** None. **R.P. Irwin:** None. **S.A. Aicher:** None. **M. Moldavan:** None.

Nanosymposium

17. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.05

Topic: E.08. Biological Rhythms and Sleep

Title: Simulated light therapy enhances recognition memory and alters daily rhythms in hippocampal gene expression

Authors: ***J. A. EVANS**, A. DELLAPOLLA, B. CALLIF, M. HURLEY, K. BAKER; Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: Light therapy improves cognitive function in humans, but the neurobiological basis of this effect is not well understood. One obstacle to gaining insight into this process is that nearly all rodent models used to date have employed lighting conditions that cause cognitive deficits rather than improvements. Here we have developed a mouse model where light improves cognitive function, which provides insight into the mechanisms underlying the positive effects of light therapy. First, we find that recognition memory is enhanced in mice receiving simulated light therapy consisting of exposure to long day lengths (i.e., summer photoperiods). In the hippocampus of mice receiving simulated light therapy, we see pronounced suppression of core clock gene transcription, which indicates that the molecular circadian clock of the hippocampus is markedly altered. Moreover, simulated light therapy specifically elevated daily transcription of a growth factor (Insulin-like growth factor II, IGF-II) known to be necessary and sufficient for memory consolidation. Up-regulation of IGF-II occurs in tandem with suppression of its transcriptional repressor (Wilm's tumor 1, WT1). These findings provide important insight into how the molecular circadian clock regulates learning by controlling cellular processes required for memory consolidation. Furthermore, this study highlights novel neurobiological and molecular mechanisms underlying the effects of bright light therapy.

Disclosures: **J.A. Evans:** None. **A. DellaPolla:** None. **B. Callif:** None. **M. Hurley:** None. **K. Baker:** None.

Nanosymposium

17. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.06

Topic: E.08. Biological Rhythms and Sleep

Support: Wellcome Trust

Carnegie Trust

University of Glasgow

Title: Dim light at night inhibits hippocampal neurogenesis in mice

Authors: C. A. WYSE, N. KANGASMAA, L. DESBONNET, S. MACDONALD, A. RUSSELL, *S. M. BIELLO;
Univ. Glasgow, Glasgow, United Kingdom

Abstract: Disruption of circadian rhythms is a defining feature of the urban lifestyle, in which artificial light facilitates eating, sleeping, working and exercise at physiologically inappropriate times. Disruption of the light dark cycle in hamsters induced learning and memory deficits that were associated with suppression of hippocampal neurogenesis and cell proliferation,[1] while human shiftworkers were at increased risk of reporting anxiety, depression and poor mental health.[2] These findings support that disruption of the synchronisation between endogenous and environmental cycles might contribute to the detrimental effects of urbanisation on human behaviour and mental health.[3] The aim of this study was to investigate the effects of chronic dim light at night on the rate of hippocampal neurogenesis in mice, and to assess if social interaction by group housing modulates any effects. Adult mice (n=32) were housed for 10 weeks in either a dim light at night (12D:12L at 5 lux) or control conditions of a 12:12 light dark cycle. The animals were further allocated to be singly housed, or housed in groups of 4. After 10 weeks, the animals were sacrificed and their brains processed for detection of a marker of immature neurons (doublecortin) in the dentate gyrus of the hippocampus using immunohistochemistry. Confocal microscopy was used to acquire images of the entire hippocampus, and the number of cell bodies immunopositive for doublecortin expression were quantified and normalised to the length of the granule cell layer. Circadian rhythmicity was monitored using passive infra red sensors to monitor locomotor activity at 1 minute intervals for periods of 10 days. The mice in this study that were exposed to dim light at night showed evidence of disruption of rhythms in locomotor activity, with more activity occurring in day time, and less consolidated activity at night ($p < 0.05$). These different light conditions were associated with decreased expression of doublecortin

in the hippocampus ($F(1,28)=7.81, p<.01$). Doublecortin expression was also lower in the animals that were singly housed in comparison to those housed in groups ($F(1,28)=4.58, p<0.04$). These results support an effect of dim light at night on circadian rhythms and on neurogenesis, mechanisms that might mediate previously reported effects of urbanisation and shiftwork on behaviour in humans. Group housing might be a useful intervention to attenuate these effects, possibly by amplification of timing cues through social entrainment. 1.Gibson et al, PLoS One (2010) 2.Bara & Arber, Scand J Work Env Health (2007) 3.Galea et al, Ann Epidemiol (2007) 4.Karatsoreos et al, Proc Natl Acad Sci (2011)

Disclosures: C.A. Wyse: None. **N. Kangasmaa:** None. **L. Desbonnet:** None. **S. MacDonald:** None. **A. Russell:** None. **S.M. Biello:** None.

Nanosymposium

17. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.07

Topic: E.08. Biological Rhythms and Sleep

Support: NIH R01NS082413

Title: Regulation of hippocampal circadian rhythms by glycogen synthase kinase 3 (GSK3)

Authors: *K. L. GAMBLE[1], R. C. BESING[2], C. O. ROGERS[2], J. R. PAUL[2], L. M. HABLITZ[2], R. L. JOHNSON[2], L. L. MCMAHON[2];
[1]Psychiatry, UAB Med. Ctr., Birmingham, AL; [2]Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: The hippocampus exhibits daily rhythms in gene expression, long-term potentiation (LTP), and learning and memory, all of which may be regulated by the circadian molecular clock. Glycogen synthase kinase 3-beta (GSK3β), a serine/threonine kinase, modulates hippocampal synaptic plasticity and contextual memory as well as phosphorylates key components of the molecular clock. Therefore, we sought to test the hypothesis that the phosphorylation status of GSK3β varies across the 24-h day in the hippocampus and regulates the hippocampal molecular clock as well as day-night differences in synaptic plasticity and memory. First, we found that phosphorylation of GSK3β (but not GSK3α) exhibits a significant 24-h rhythm in the CA1 region of the hippocampus in mice housed in constant darkness for at least two weeks. Next, we examined the effect of chronic GSK3 activation on BMAL1 expression in CA1 by utilizing a transgenic mouse model in which GSK3 is constitutively

activated (GSK3-KI). Interestingly, BMAL1 expression within CA1 of GSK3-KI mice showed no significant rhythm and were disrupted compared to WT (wild-type) mice. Moreover, GSK3-KI mice (versus WT mice) exhibited greater LTP magnitude and impaired contextual fear recall. However, day-night differences in LTP magnitude and contextual fear memory remained intact. Finally, pharmacological GSK3 inhibition significantly shortened the period length of organotypic hippocampal PER2::luciferase cultures, reduced LTP magnitude during the night, and facilitated spontaneous alternation performance during the day. Taken together, these results support the model that circadian rhythmicity of hippocampal GSK3β inactivation regulates the molecular clock and day/night differences in synaptic plasticity and memory.

Disclosures: K.L. Gamble: None. **R.C. Besing:** None. **C.O. Rogers:** None. **J.R. Paul:** None. **L.M. Hablitz:** None. **R.L. Johnson:** None. **L.L. McMahon:** None.

Nanosymposium

17. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.08

Topic: E.08. Biological Rhythms and Sleep

Support: Smith College CFCD

Title: Exercise impacts alters organization of circadian system in female mice housed under 20 h light cycles

Authors: *M. E. HARRINGTON[1], F. CHIFAMBA[2], W. WANG[2], S. HUYNH[2], P. MOLYNEUX[2], T. L. LEISE[3];
[1]Neurosci Prog, [2]Smith Col., Northampton, MA; [3]Amherst Col., Amherst, MA

Abstract: Circadian disruption is a common factor in modern life, with frequent exposure to light at night, sleep restriction, jet lag and social jet lag. Health problems, such as disruption of metabolism and incidence of type 2 diabetes, are linked with this circadian disruption. We examined how frequent exercise versus a more sedentary lifestyle interacts with the coherence of the circadian system by exposing mice to a cycle with 10 h of light alternating with 10 h of dark. The circadian clocks of mice are typically unable to entrain to such 20 h cycles; however, exercise can strengthen the circadian system (Leise et al., Age, 2013) and can extend the ranges of cycle periods the circadian system is able to entrain to (Chiesa et al., Chronobiol. Int. 2007). We housed female mice under 10:10 LD, either with or without a running wheel that can induce high levels of voluntary exercise. We hypothesized that exercise would enable animals to entrain

to the exotic light cycle. We measured rhythms from peripheral tissues (esophagus, thymus, spleen) and from central pacemaker tissue (suprachiasmatic nucleus, anterior and posterior coronal slices) *in vitro* using mice with a per2-luciferase transgene (Yoo et al., PNAS 2004). We analyzed locomotor activity and body temperature as reported by i.p. implanted telemetry probes. Maximum entropy spectral analysis revealed multiple periodicities within some records, particularly in those of mice unable to entrain to the 10:10 LD. We also measured the spectral coherence to assess coordination between the temperature and activity rhythms at each of the periods present. Tissues exhibited circadian rhythms *in vitro* with widely varied times of peak. These studies provide evidence for an interaction of spontaneous voluntary exercise with entrainment as well as internal circadian synchrony.

Disclosures: M.E. Harrington: None. **F. Chifamba:** None. **W. Wang:** None. **S. Huynh:** None. **P. Molyneux:** None. **T.L. Leise:** None.

Nanosymposium

17. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.09

Topic: E.08. Biological Rhythms and Sleep

Support: DGAPA-UNAM IG200314

CONACyT 234456

Title: In a rat model of shift-work clock genes expression is altered in a tissue specific manner

Authors: *C. CÓRDOBA[1], M. BASUALDO[2], E. ESPITIA-BAUTISTA[3], R. M. BUIJS[2], C. ESCOBAR[4];
[1]Dept. of Anat., Facultad De Medicina, Univ. Nacional Autónom, Mexico City, Mexico; [2]Inst. de Investigaciones Biomédicas, UNAM, Mexico City, Mexico; [3]Anat., Facultad de Medicina, UNAM, Mexico; [4]Anat., Facultad de Medicina, UNAM, Mexico City, Mexico

Abstract: In a rat model of shift-work internal desynchronization is observed due to forced activity in a rotating drum during the rest phase after a 5 week working regimen. While the biological clock remains fixed to the LD cycle, metabolic functions uncouple from the clock, resulting a flattened glucose rhythm and shift of the TAG rhythms toward the day. In the liver of working rats clock genes expression is shifted to the forced activity hours. In this study we aimed to determine the effect of the working protocol on the rhythmic profile of clock genes in other

peripheral oscillators. We determined the temporal expression of per2, cry1, bmal1 and clock in the heart, white adipose tissue and skeletal muscle (gastrocnemius). We found that forced activity during the light phase changes the expression of clock genes in a tissue specific manner. In adipose tissue, bmal1 was in antiphase when compared to the control group while per2 and cry1 acrophases were advanced. Per2 in the heart and skeletal muscle maintained his acrophase within the beginning of the dark phase, but cry1 was advanced and bmal1 had a delayed acrophase in both tissues, although skeletal muscle genes remained closer to the acrophase in the control group. Given the results, peripheral oscillators disengage from the LD cycle by different mechanisms and their expression and function is tissue dependent.

Disclosures: C. Córdoba: None. **M. Basualdo:** None. **E. Espitia-Bautista:** None. **R.M. Buijs:** None. **C. Escobar:** None.

Nanosymposium

17. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.10

Topic: E.08. Biological Rhythms and Sleep

Support: R01 AG-036670, T32 AG-023477

Title: Hypothalamic neurons and locomotor activity in old female rhesus macaques

Authors: *D. H. EGHLIDI[1], L. LUNA[2], D. BROWN[2], S. KOHAMA[1], H. URBANSKI[1]; [1]Div. of Neurosci. Oregon Natl. Primate Res. Ctr., Beaverton, OR; [2]Univ. de Valparaíso, Valparaíso, Chile

Abstract: Like humans, many rhesus macaques show an age-related attenuation of daily activity that is associated with perturbed physiological functions such as cognitive decline and decreased immune function. To gain insights into the underlying causal mechanism, we examined the orexin neurons in the lateral hypothalamic area (LHA), and calbindin neurons in the suprachiasmatic nucleus (SCN) of old (>20 years) female rhesus macaques that had been classified as active or sedentary, based on their daytime locomotor activity patterns. Orexin neurons play a key role in arousal, and so we hypothesized that the sedentary animals would show a significant reduction in the number of orexin immunopositive neurons. Using immunohistochemistry (IHC) we counted the number of orexin-B immunopositive neurons in the LHA of each animal, focusing on five 25-µm sections (collected at 300-µm intervals) spanning the distribution peak. We also used IHC to describe the organization of neurons in the

SCN and to assess the number of calbindin neurons in active versus sedentary aged animals from one 25-µm section with the highest number of core and shell calbindin expressing cells. SCN neurons project to the arousal circuitry of the LHA, and play a role in controlling locomotor activity. Overall, we observed no difference in the number of orexin-B or calbindin immunopositive neurons between animals in the two groups. The data suggest that reduced activity in the elderly is unlikely to stem from a loss of orexin or calbindin neuronal perikarya in the LHA and SCN, respectively. However, it is possible that other output signals of the SCN or orexin neuronal projections to arousal centers of the brain, such as the locus coeruleus, are associated with activity patterns in aged monkeys.

Disclosures: D.H. Eghlidi: None. **L. Luna:** None. **D. Brown:** None. **S. Kohama:** None. **H. Urbanski:** None.

Nanosymposium

17. Circadian Entrainment Mechanisms and Consequences

Location: S404

Time: Saturday, October 17, 2015, 1:00 PM - 3:45 PM

Presentation Number: 17.11

Topic: E.08. Biological Rhythms and Sleep

Support: March of Dimes, NIGMS

Title: Ontogeny of circadian rhythms and the timing of birth

Authors: C.-A. VANIA[1], C. A. MARTIN-FAIREY[1], S. K. ENGLAND[2], A. T. C. SUN[1], C. L. SIMMS[1], *E. D. HERZOG[1];
[1]Dept. of Biol., Washington Univ. In St. Louis, St Louis, MO; [2]Deparment of Obstetrics and Gynecology Basic Div., Washington University, Sch. of Med., Saint Louis, MO

Abstract: Our lab previously demonstrated that circadian rhythms affect both maternal and fetal tissues during pregnancy. However it is not clear when circadian rhythms initiate and synchronize within the developing fetus and whether they affect the timing of delivery. Based on reports that daily rhythms in physiology and metabolism initiate *in utero* in mammals, we hypothesize that synchrony among circadian cells occurs prior to birth and contribute to the daily rhythm in the timing of birth. This work addresses two key questions: 1) when do circadian rhythms develop and synchronize and 2) how does circadian genotype affect gestation length? To examine development and synchronization of circadian rhythms, we monitored a bioluminescent reporter for PERIOD2 levels (PER2::Luc) in individual cells within fetal hypothalamic suprachiasmatic nucleus (SCN) explants. We found that SCN explants isolated on

embryonic day 13.5 (E13.5, where E0 is the time of conception) did not express circadian rhythms *in vitro* and at E14.5, 30% of SCN had circadian cells with a broad distribution of periods (18-32h). By E17.5, all recorded SCN were circadian with a narrow distribution of periods (24-25.5 h) indicating that the fetal SCN synchronize circadian rhythms approximately two days prior to birth. To assess whether circadian genotypes affect gestation length, mice were bred and maintained in a 7am-7pm light cycle. WT C57BL/6J, with a 23.7h circadian period, delivered 466.7±16.5h after conception with 100% delivering in the night with minimal variability between the first and second pregnancies. In contrast, preliminary results indicated that Per1-/-Per2-/-, with an arrhythmic circadian rhythm, have similar gestational lengths to WT (472.4 ±9.8h) on the first litter, but have a contracted second parity (371.45h) despite having a full litter. Intriguingly, in contrast to WT mice, 25% of Per1-/-Per2-/- dams delivered during the day. Our results indicate that the embryonic SCN is capable of producing daily rhythms in gene expression starting at E14.5 and, by E17.5, synchrony among SCN cells and that circadian rhythms may be involved in the timing of delivery.

Disclosures: **C. Vania:** None. **C.A. Martin-Fairey:** None. **S.K. England:** None. **A.T.C. Sun:** None. **C.L. Simms:** None. **E.D. Herzog:** None.

Nanosymposium

018. Multivariate Approaches to Studying Medial Temporal and Prefrontal Contributions to Human Memory

Location: N227

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 18.01

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant F32-MH100904, NIH Grant R01-MH100121, NSF CAREER Award 1056019

Title: The dynamics of hippocampal and prefrontal neural representations track the evolution of attentional biases during learning

Authors: ***M. L. MACK**[1], A. R. PRESTON[1], B. C. LOVE[2];
[1]The Univ. of Texas At Austin, Austin, TX; [2]Univ. Col. London, London, United Kingdom

Abstract: Learning theories posit that attention is tuned to relevant information during the course of learning. Formal category learning models make explicit the computational architecture whereby attention shapes feature representation over the course of learning. These models suggest that attentional biases formed during learning are reflected by an evolving

representational space that is increasingly biased towards diagnostic features. Although recent evidence suggests that after learning, attention-weighted category knowledge is present in neural representations, a link between the evolution of attention and the dynamics of neural representation during learning has yet to be demonstrated. Here, we use neural pattern similarity and model-based fMRI analyses to investigate the neural mechanisms of learning-based shifts in category representations over time. During fMRI scanning, participants learned to categorize complex objects composed of multiple features across three category learning tasks, with each task requiring attention to different combinations of object features. A learning model was fit to participants' behavior to derive latent measures of attention weights to object features, which were used to construct similarity matrices characterizing each participant's attention-biased object representations throughout learning. A searchlight analysis compared similarity matrices of the neural representations of the objects over time with model-derived similarity matrices. We found correspondence between model and neural similarity in lateral occipital cortex, a region associated with higher-level object representations. Model and neural similarity also converged in areas of ventral striatum, posterior parietal cortex, and lateral prefrontal cortex, consistent with a striatal-based circuit that learns attention weights and a prefrontal-parietal control network that biases neural representations in visual cortex. Interestingly, hippocampal representations were consistent with model predictions, perhaps reflecting an underappreciated role for MTL-based processes in encoding attention-biased memory representations during learning. These results provide strong neural evidence for the attentional tuning of neural representations proposed by prominent learning theories.

Disclosures: **M.L. Mack:** None. **A.R. Preston:** None. **B.C. Love:** None.

Nanosymposium

18. Multivariate Approaches to Studying Medial Temporal and Prefrontal Contributions to Human Memory

Location: N227

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 18.02

Topic: F.01. Human Cognition and Behavior

Support: NIMH Grant R00 MH083945

Title: Temporal context processing within hippocampal subfields

Authors: *F. WANG, K. WOISARD, R. DIANA;
Dept. of Psychology, Virginia Tech., Blacksburg, VA

Abstract: The hippocampus is involved in processing the temporal context of an event but the role of individual subfields is unknown. The current study investigates the function of CA1 and DG/CA3 in encoding temporal context, specifically separation of similar temporal contexts into representations of different events. Participants viewed groups of three pictures with the third picture in each triplet serving as the target and the first two pictures serving as the temporal context of the target picture. The similarity of the temporal context preceding each target picture was manipulated across two presentations: repeated context, high similarity context, and low similarity context. Hippocampal activation was measured during presentation of the target picture. We expected processing of the target item to be influenced by the manipulation of temporal context in hippocampal subfields that process temporal information. We predicted that the activation of CA1 would increase linearly as temporal context similarity decreased and that the activation in DG/CA3 would increase whenever temporal context was altered but not be modulated by the similarity of the new context to the original context. Neuroimaging results supported the prediction that DG/CA3 separates repeated temporal context from new contexts that are either high or low in similarity. However, we did not find changes in CA1 activation due to processing of temporal context. Multivoxel pattern analyses were also used to compare temporal context processing in DG/CA3 and CA1.

Disclosures: **F. Wang:** None. **K. Woisard:** None. **R. Diana:** None.

Nanosymposium

18. Multivariate Approaches to Studying Medial Temporal and Prefrontal Contributions to Human Memory

Location: N227

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 18.03

Topic: F.01. Human Cognition and Behavior

Support: CIHR Grant MOP125958, CIHR Post-Doctoral Fellowship to MJS

Title: The neural correlates of episodic memory transformation in humans

Authors: *M. J. SEKERES[1,2], J. A. E. ANDERSON[1,2], G. WINOCUR[1,2,3], M. MOSCOVITCH[1,2], C. L. GRADY[1,2];
[1]Rotman Res. Inst., Toronto, ON, Canada; [2]Psychology, Univ. of Toronto, Toronto, ON, Canada; [3]Psychology, Trent Univ., Peterborough, ON, Canada

Abstract: As memories for events age and lose detail, how do the brain networks supporting these memories change? We used fMRI to test the neural correlates of episodic memory

transformation in the human brain. During fMRI scanning, participants viewed a series of film clips of episodes. Immediately after, they were cued to retrieve the memory for half of the film clips they had just seen. Seven days later, participants returned to the scanner and were cued to retrieve the other half of the film clips. During the immediate memory test, participants report richly detailed episodic memories for the film clips, and have high hippocampal activation during memory retrieval. Seven days later, participants show a reduction in memory for the details of the film clips, but retention of memory for the general storyline, supported by a reduction of hippocampal activation, and an emergence of activity in the prefrontal cortex, a brain region found to be activated during remote episodic memory retrieval in humans. Critically, when the memories retained their vividness, hippocampal activity was comparable during immediate retrieval and 7d retrieval sessions, suggesting that the hippocampus continues to be important for the retrieval of detailed episodic memory.

Disclosures: **M.J. Sekeres:** None. **J.A.E. Anderson:** None. **G. Winocur:** None. **M. Moscovitch:** None. **C.L. Grady:** None.

Nanosymposium

18. Multivariate Approaches to Studying Medial Temporal and Prefrontal Contributions to Human Memory

Location: N227

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 18.04

Topic: F.01. Human Cognition and Behavior

Support: NSF CAREER Award (1056019) , NIH Grant (R01 MH100121) , Department of Defense NDSEG Fellowship

Title: Learning-related changes in item representations reveal dissociable integration and separation signatures in hippocampus and prefrontal cortex

Authors: *M. L. SCHLICHTING[1], J. A. MUMFORD[2], A. R. PRESTON[1];
[1]Univ. Texas Austin, Austin, TX; [2]Univ. Wisconsin-Madison, Madison, WI

Abstract: The episodic memory system is thought to enable accurate retrieval while maintaining flexibility by representing both episode specifics and generalizations across related (i.e., overlapping) events. On the one hand, overlapping events may recruit overlapping populations of neurons, thereby integrating across related memories and promoting flexible behaviors. This scheme predicts that specific elements of related memories will take on similar neural representations. However, dominant theory suggests that memories for related episodes are

instead maintained as orthogonalized, pattern-separated representations to minimize interference and allow for retrieval of event details. Under this coding scheme, neural representations for indirectly related items are predicted to be highly dissimilar. While hippocampus (HPC) and medial prefrontal cortex (MPFC) have been implicated in the encoding of related memories, it remains unknown whether these regions represent related content via integration or separation. One theoretical account suggests that HPC is dedicated to representing specifics while MPFC generalizes; however, alternate accounts posit that HPC can also integrate related memories. Here, we used high-resolution fMRI to investigate whether complementary integration and separation coding schemes occur simultaneously within subregions of HPC and MPFC. Computational models predict that the manner in which the overlapping episodes are experienced may also influence the nature of representations for individual memory elements. Thus, we manipulated the strength versus recency of the initial memory at the time of overlapping experience by teaching participants overlapping AB and BC pairs of novel objects in blocked (strong AB) and intermixed (recent AB) learning conditions. Pre- and post-learning, participants viewed individual A, B and C items during scanning. Using neural pattern similarity analysis, we found evidence of pattern separation--indirectly related A and C items becoming less similar--in posterior hippocampus and anterior MPFC. Conversely, strong initial memories biased anterior hippocampus and posterior MPFC to integrate, with A and C items becoming more similar to one another following learning in the blocked condition. We also show dissociable coding signatures in ventrolateral PFC, a region previously implicated in interference resolution. These data highlight how memory elements are represented across different brain regions to simultaneously promote generalization across memories and protect from interference.

Disclosures: M.L. Schlichting: None. **J.A. Mumford:** None. **A.R. Preston:** None.

Nanosymposium

18. Multivariate Approaches to Studying Medial Temporal and Prefrontal Contributions to Human Memory

Location: N227

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 18.05

Topic: F.01. Human Cognition and Behavior

Support: NIH R01 EY021755, NIH F32 EY023162, NIH S10 OD016277

Title: Action-based predictive coding from different timescales of memory

Authors: *N. C. HINDY[1], F. Y. NG[2], N. B. TURK-BROWNE[1,2];
[1]Princeton Neurosci. Inst., [2]Dept. of Psychology, Princeton Univ., Princeton, NJ

Abstract: Our actions provide a rich source of expectations because they can determine what visual input we receive. For example, when you open the door to your office, you expect to see your desk, chair, computer monitor, etc. But how does the brain generate these expectations? One neural source of expectation could be the hippocampus: Its associative learning mechanisms bind items over space and time, and once these links are formed, one or more items can reactivate other absent but associated items, generating memory-based predictions about forthcoming stimuli. Here we use high-resolution fMRI to examine the role of the hippocampus in generating predictions based on actions, for both recently learned associations (from a training session immediately before the scan) and longer-term associations (from a training session three days before the scan). We reasoned that, if the hippocampus generates expectations about stimuli based on actions, predictive actions should enhance functional connectivity between the hippocampus and visual cortex. And since the hippocampus is thought to be more active in supporting new memories than old ones, we predicted that connectivity would be greater for recent than remote associations. During training, cue stimuli appeared individually, participants executed an action (pressed a specific button), and the cue was transformed into another stimulus. For predictive cues, one particular outcome appeared when a left button was pressed and a different outcome appeared when a right button was pressed. For non-predictive cues, either outcome appeared with equal probability irrespective of which button was pressed. We measured functional connectivity between the hippocampus and stimulus-selective visual cortex to assess prediction for recent and remote associations. To measure connectivity during the task, we removed confounding variables as well as stimulus-evoked responses, and then measured temporal correlations between brain areas in the residual BOLD timeseries. Functional connectivity between the hippocampus and visual cortex was stronger for predictable than for unpredictable trials, but surprisingly only for remote associations. This interaction was driven by a reduction in connectivity for remote unpredictable trials, suggesting that hippocampal prediction may occur by default, and that learning may involve gradually disregarding cues not useful for prediction. Since knowledge on longer timescales may be represented outside of the hippocampus as well, follow-up experiments examine connectivity with other systems that represent complex, semantic associations between actions and objects learned over a lifetime.

Disclosures: **N.C. Hindy:** None. **F.Y. Ng:** None. **N.B. Turk-Browne:** None.

Nanosymposium

18. Multivariate Approaches to Studying Medial Temporal and Prefrontal Contributions to Human Memory

Location: N227

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 18.06

Topic: F.01. Human Cognition and Behavior

Support: Templeton Grant ID #36751, The McDonnell Foundation

Title: Changing the past: The interplay of replay and uncertainty in retrospective revaluation

Authors: *I. MOMENNEJAD[1], A. R. OTTO[2], N. DAW[2], K. A. NORMAN[1];
[1]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]New York Univ., New York City, NY

Abstract: Learning to make advantageous decisions in sequentially structured tasks, like mazes, requires integrating information acquired across multiple learning trials or episodes. This is a challenging problem for learning approaches - like many popular models - that work fully "online" by adjusting representations that summarize ongoing experience. One proposed mechanism to support such integration is to replay previous or simulated experiences, "offline," e.g. during intermittent rest periods or between trials. Here we used a decision task called retrospective revaluation in which participants must integrate initial experience about a task with later experience about a change in its goals. We hypothesized that replay of past experience during intermittent rest periods would help 'piece together' trajectories that were not directly experienced, enabling the integration of new relevant information to change previously learned values. A second question for such an account is how the brain prioritizes whether or which experiences to replay. Based on research in machine learning, we hypothesized that the brain should preferentially devote resources to replay under conditions of uncertainty, when it has the most potential to improve decisions. To test this, we acquired functional magnetic resonance imaging (fMRI) data as participants performed a sequential decision task with a 2x2 design in which reward revaluation and uncertainty were both manipulated. We used multi-voxel pattern analysis (MVPA) to examine (a) whether replay during rest periods supports optimal retrospective revaluation behavior, and (b) whether the extent of replay depends on reward uncertainty. We predict a correlation between replay and accurate retrospective revaluation behavior. Also, we predict more neural evidence for replay in the retrospective revaluation condition and under higher reward uncertainty, and less evidence for replay in the no-retrospective-revaluation condition and under lower reward uncertainty.

Disclosures: I. Momennejad: None. **A.R. Otto:** None. **N. Daw:** None. **K.A. Norman:** None.

Nanosymposium

18. Multivariate Approaches to Studying Medial Temporal and Prefrontal Contributions to Human Memory

Location: N227

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 18.07

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R01-MH094480

Title: Differentiation of neural patterns during reinstatement vs scene construction

Authors: *A. ZADBOOD[1,2], Y.-C. LEONG[3], J. CHEN[2,1], U. HASSON[2,1];
[1]Psychology Department, Princeton Univ., Princeton, NJ; [2]Princeton Neurosci. Institue, Princeton Univ., Princeton, NJ; [3]Psychology Department, Stanford Univ., Stanford, CA

Abstract: Reinstatement of neural patterns during memory retrieval is an increasingly popular method for studying how the brain supports episodic memory. But to what extent does neural reinstatement reflect the reinstatement of specific episodic memories as opposed to the processing of similar content? In this study we compare neural patterns when subjects listened to a description of an episode they previously experienced to patterns elicited when subjects listened to the same description without having prior exposure to the episode. The first group of subjects watched a movie and listened to a verbal description of the movie. The second group listened to the verbal description of the movie without ever seeing the movie. Importantly, the auditory description was perceptually identical for all subjects; the groups differed only in whether they had previous experience with the narrated content or not. Using searchlight analysis, we first compared the similarity of neural patterns between movie watching and listening to the verbal description, across subjects who did watch the movie. The searchlight analysis revealed scene-specific similarity between neural patterns elicited during movie-watching and during listening, i.e., neural reinstatement; these similarities were found throughout posterior-medial system cortical areas (posterior cingulate, angular gyrus, parahippocampal cortex). Next we examined neural similarity between a group of subjects who watched the movie and a group of subjects who listened to the description of the movie without ever watching it. Interestingly, neural patterns were similar between listening and watching throughout much of the same network, suggesting that memory of the movie was not required to elicit content-specific neural patterns. One region that showed different response properties was medial prefrontal cortex; in this region, neural patterns during listening were more similar to the movie patterns when participants had NOT seen the movie than when they had. These data indicate that content-specific neural patterns reinstated when listening to verbal description of a movie may also be elicited in the absence of specific episodic memories, and suggest that medial prefrontal cortex may support scene construction when listening to a novel narrative.

Disclosures: **A. Zadbood:** None. **Y. Leong:** None. **J. Chen:** None. **U. Hasson:** None.

Nanosymposium

18. Multivariate Approaches to Studying Medial Temporal and Prefrontal Contributions to Human Memory

Location: N227

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 18.08

Topic: F.01. Human Cognition and Behavior

Support: NSF GRFP, Office of Naval Research Grant N00014-15-1-0033

Title: Hippocampal and cortical organization of memories for items in context

Authors: *L. A. LIBBY[1], C. RANGANATH[2];
[1]Psychology, [2]Ctr. for Neurosci., UC Davis, Davis, CA

Abstract: Recollection of contextual details based on an item cue is known to engage medial temporal lobe (MTL) regions perirhinal cortex (PRC), parahippocampal cortex (PHC), and hippocampus. Models of MTL function propose that PRC and PHC support item and context memory, respectively, whereas hippocampus supports memory for bound item-context associations. However, it is unknown whether recollection-related activity in these regions can be dissociated in terms of the underlying organization of information coding. To address this question, in a functional magnetic resonance imaging (fMRI) study, we characterized how hippocampal and cortical regions organize item and context information during successful and unsuccessful recollection of item-context relations. Multiple exemplars of items from a set of categories were encoded in a set of context locations, and item and context memory were then assessed with a mixed item recognition-cued recall test. Trials were sorted according to item and context memory performance, and both univariate activation magnitude and multivariate information coding analyses were applied. Univariate analysis replicated previous findings that, compared to trials characterized by item familiarity, correct context retrieval was associated with greater activity across MTL regions. However, incorrect context judgments (context misattributions) were associated with greater univariate activity compared to correct context judgments in PHC only. In contrast to univariate effects, during correct context memory trials, the magnitude of multivariate evidence for context reinstatement in PHC was positively associated with context memory accuracy. Furthermore, context information uniquely modulated item representations in PRC. Finally, selective item-in-context coding was observed exclusively in the anterior hippocampus. Together, these results clarify the roles of PRC, PHC, and hippocampus in successful recollection, suggesting that similar univariate activation profiles may be orthogonal to underlying differences in the organization of episodic information. Future analyses will examine information coding in these regions during context misattribution.

Disclosures: L.A. Libby: None. **C. Ranganath:** None.

Nanosymposium

18. Multivariate Approaches to Studying Medial Temporal and Prefrontal Contributions to Human Memory

Location: N227

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 18.09

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant 2T32MH065214-11

Title: Differentiation of neural representations during processing of multiple information streams

Authors: *J. CHEN[1,2], M. CHOW[2], K. A. NORMAN[1,2], U. HASSON[1,2];
[1]Psychology, Princeton Neurosci. Inst., Princeton, NJ; [2]Psychology, Princeton Univ., Princeton, NJ

Abstract: When multiple independent sources of information are present in the environment, how does the brain separately track these information streams? To explore this question, we exposed subjects to two unrelated auditory narratives (~15 minutes each) during functional brain imaging. In one group, the narratives were played consecutively in a single session ("Intact" condition). In another group, the narratives were played in short segments in an interleaved fashion, switching between the two narratives approximately every 60 seconds ("Interleaved" condition). Multivoxel pattern similarity (correlation over voxels) was calculated between all possible pairs of narrative segments, and the difference of average within-narrative correlation vs. between-narrative correlation was computed ("context separation"). The analysis was performed in a searchlight across the brain, separately for the Intact and Interleaved groups. The searchlight revealed that, in default mode network (DMN) cortical regions, the two narrative contexts were strongly dissimilar in the Interleaved condition but less dissimilar in the Intact condition. Furthermore, hippocampal correlation with DMN cortical regions was greater for Interleaved than Intact, suggesting a greater reliance on hippocampal retrieval of prior information for the Interleaved group. The effects did not seem to be due simply to greater attentional focus/effort in the Interleaved condition, as later memory was matched between conditions. These results indicate that cortical representations of each information stream (context) were more differentiated when the two streams competed (the Interleaved condition), and suggest a mechanism by which the brain separates representations when tracking multiple information sources by recruiting disparate neuronal populations.

Disclosures: J. Chen: None. **M. Chow:** None. **K.A. Norman:** None. **U. Hasson:** None.

Nanosymposium

18. Multivariate Approaches to Studying Medial Temporal and Prefrontal Contributions to Human Memory

Location: N227

Time: Saturday, October 17, 2015, 1:00 PM - 3:30 PM

Presentation Number: 18.10

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R01 EY021755

Title: Attention promotes episodic encoding by stabilizing hippocampal representations

Authors: *M. ALY, N. B. TURK-BROWNE;
Princeton Univ., Princeton, NJ

Abstract: Attention not only modulates what we see, but also what we remember. Despite this connection in behavior, little is known about the mechanisms that link attention to memory formation in the brain. Using high-resolution fMRI, we investigated the hypothesis that attentional states are represented in the hippocampus, and that the quality of these representations during encoding influences whether attended information is later remembered. The study consisted of three phases. In Phase 1, participants performed an attention task in which, on every trial, they viewed an image of a room with a painting and then searched through a stream of other images for a painting from the same artist (art state) or a room with the same layout (room state). All trials of each attentional state were used to define an average pattern of activity within each hippocampal subfield that corresponded to the "template" representation for that state. In Phase 2, trial-unique images (rooms with art) were incidentally encoded while participants attended to either the art or room in different blocks. Memory for the cued aspect of each image was tested in Phase 3. We predicted that participants would be more likely to remember the attended information if, during encoding, their hippocampus was more strongly in an attentional state that prioritized that information. The data were consistent with our hypothesis: During encoding, trial-by-trial activity patterns in hippocampal subfield CA2/3 were more highly correlated with the task-relevant vs. task-irrelevant template representation when the attended items were subsequently remembered. In addition, individual differences in room memory were correlated with the average match between CA2/3 activity patterns and the room template representation during encoding. Finally, during successful vs. unsuccessful encoding, the attentional state of CA2/3 was more synchronized with that of retrosplenial cortex - a region important for episodic memory and visuospatial processing. Together, these results offer insight into the mechanisms by which attention transforms percepts into memories.

Disclosures: **M. Aly:** None. **N.B. Turk-Browne:** None.

Nanosymposium

019. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.01

Topic: F.01. Human Cognition and Behavior

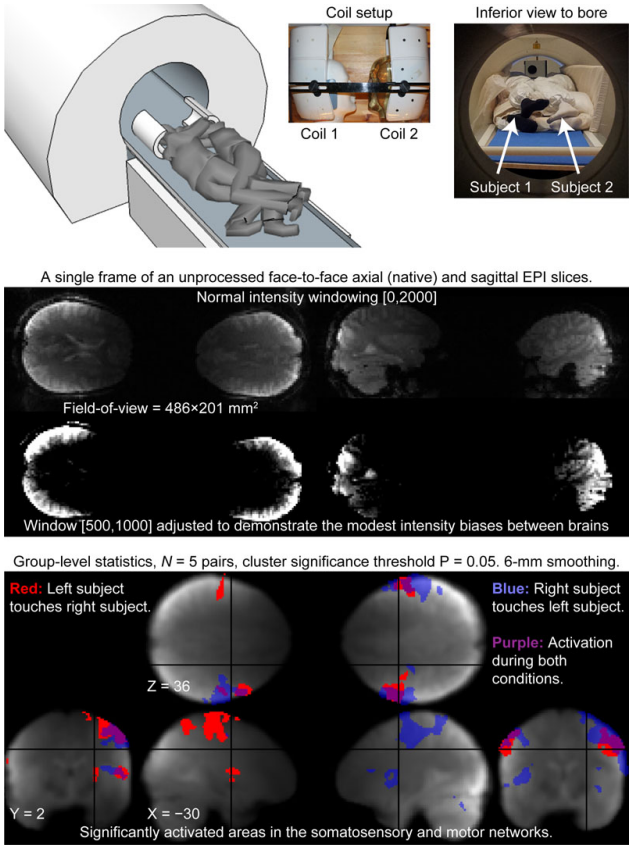
Support: ERC Advanced Grant #232946, ERC Starting Grant #313000, Academy of Finland #265917, Academy of Finland #218072, Instrumentarium Science Foundation, Swedish Cultural Foundation in Finland

Title: Imaging real-time tactile social interaction with two-person dual coil fMRI

Authors: ***V. RENVALL**[1,2,3], J. KAURAMÄKI[2,3], S. MALINEN[2,3], R. HARI[2,3], L. NUMMENMAA[2,3,4];
[1]Aalto Univ. Sch. of Sci., AALTO, Espoo, Finland; [2]Dept. of Neurosci. and Biomed. Engin., [3]Advanced Magnetic Imaging Ctr., Aalto Univ. Sch. of Sci., Espoo, Finland; [4]Turku PET Ctr. and Dept. of Psychology, Univ. of Turku, Turku, Finland

Abstract: Social interaction shapes our brains throughout life. Yet we know practically nothing about the neural basis of two-person interaction. The reasons have been mainly methodological, and only very recently (Lee, 2015) it has become possible to record fMRI from two persons interacting in the same magnet. We devised a setup, including our 8+8-channel two-brain receive coil array, to acquire fMRI data from two subjects simultaneously in a single 3-T scanner (Skyra). Here we present data from five pairs of subjects who were facing each other while lying on their sides (see Fig.). During fMRI recordings, the subjects touched lightly the lower lip of their imaging partner at about 2 Hz, in 30-s active and rest blocks according to auditory cues, or observed the touches. The sessions comprised 4 fMRI runs per dyad, each subject touching their partner during two runs and being touched by their partner in two. Imaging parameters included TR 3 s, TE 28 ms, α 80°, matrix 160×66, FOV 486×201 mm^2, slice thickness 3 mm + 0.3 mm slice gap, iPAT (GRAPPA) 2, BW 2404 Hz px^{-1}, and # of measurements 126 with fat saturation enabled; 49 slices were acquired using standard EPI sequence and reconstruction. Structural (MP-RAGE) brain data were acquired separately with a single-person 32-channel head coil. The data were preprocessed using a customized FSL-based pipeline to first separate the images of the two brains, then correct them for slice timing and motion, register, and finally reassemble back into two-brain volumes. FSL FEAT was used for statistical analysis of the main effects of touching and being touched. Our two-person fMRI setup provided feasible signal in the two-

brain volume, with some anterior signal attenuation due to coil geometry. Somatosensory and motor activations were found consistently in response to the touching and being touched, and auditory task cues evoked reliable auditory-cortex activation. We conclude that two-person fMRI is becoming a concrete tool for neuroscience studies of social interaction.



Disclosures: **V. Renvall:** None. **J. Kauramäki:** None. **S. Malinen:** None. **R. Hari:** None. **L. Nummenmaa:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.02

Topic: F.01. Human Cognition and Behavior

Support: EKFS

Title: Dynamics of neuromagnetic response to biological motion in adolescence

Authors: *M. PAVLOVA[1], C. BIDET-ILDEI[2], A. N. SOKOLOV[1];
[1]Univ. of Tübingen Med. Sch., Tübingen, Germany; [2]Univ. of Poitiers, Poitiers, France

Abstract: Brain imaging points to several brain regions engaged in the network subservingn visual processing of point-light body motion. However, temporal dynamics of this network remains largely unknown. Here we focus on the link between the visual sensitivity and neuromagnetic response to body motion. Typically developing adolescents detected a point-light walker embedded into a simultaneous scrambled walker mask. At early latencies of 180-244 ms, the visual sensitivity to biological motion negatively correlates with the root-mean-square (RMS) amplitude of the evoked neuromagnetic response over the right occipital, temporal and frontal cortices and over the left temporal cortex. At latencies of 276-340 ms, the visual sensitivity negatively links with the RMS amplitude over the right occipital and bilateral temporal cortices. At later latencies, there is still a tight inverse link between visual sensitivity and activation over the temporal cortices of both hemispheres. The outcome! indicates that already in adolescence, the right temporal cortex is a hub of the social brain circuitry. For the first time, the topographic patterns of MEG activation unfolding over time and linked to visual sensitivity reveal temporal dynamics of the entire cortical network underpinning body motion processing.

Disclosures: M. Pavlova: None. **C. Bidet-Ildei:** None. **A.N. Sokolov:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.03

Topic: F.01. Human Cognition and Behavior

Support: ERC StG 336305

Title: Modulation of early visual cortex activity by social features

Authors: *M. GAMER[1,2], J. PETH[2];
[1]Univ. of Wuerzburg, Wuerzburg, Germany; [2]Dept. of Systems Neurosci., Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Humans are social beings living in complex social structures, thus requiring substantial and continuous processing of social information. Previous research consistently revealed attentional preference for social features such as faces or verbal expressions in the environment. It is less clear, however, whether social signals are already capable of modulating

early activity in sensory cortices to drive attentional orienting. The current study used functional magnetic resonance imaging (fMRI) to examine regional increases of activity in striate and extrastriate visual cortex as a function of the presence of social features. For this aim, a large set of naturalistic photographic stimuli was prepared that included persons, faces or body parts in only one quadrant of the picture. Images were controlled for low-level physical properties such as contrast and brightness. While maintaining central fixation, 26 participants passively viewed these stimuli in the MR scanner. Subsequently, population receptive field mapping was used to delineate borders between striate and extrastriate visual areas and participants viewed the same set of stimuli again outside the MR scanner while acquiring eye tracking data. Fixation density maps obtained in the behavioral assessment indicated enhanced attentional allocation towards social features. Consistently, we observed increased activation of retinotopically organized early visual areas precisely corresponding to the quadrant that contained social information in the visual field. This pattern was not related to the distribution of physical saliency in terms of low-level image features. The current data indicate that social features in the visual field trigger enhanced responses in early visual cortex. Thus, the presence of complex social information is already encoded on the first stages of the visual processing hierarchy. This covert social attention might contribute to saccadic programming and thereby generate the frequently observed pattern of enhanced attention on faces and bodies in the visual field. It remains an interesting question for future research to elucidate potentially abnormal cortical representations of social scenes in psychiatric disorders with severe deficits in social functioning such as autism spectrum disorders.

Disclosures: **M. Gamer:** None. **J. Peth:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.04

Topic: F.01. Human Cognition and Behavior

Support: Templeton, Office of Naval Research

Title: Social prospection: a predictive coding model of mental state inference!

Authors: ***J. KOSTER-HALE**, F. CUSHMAN;
Psychology, Harvard Univ., Cambridge, MA

Abstract: Social reasoning requires making inferences about an unobservable causal structure: goals, beliefs, preferences, and personality traits. We have a sophisticated understanding of

which parts of the brain support social inference, but little insight into how these neural substrates function at a computational level. Hierarchical predictive coding (HPC) models posit that the brain generates continuous predictions of upcoming events, and then adjusts these predictions by computing an error signal that tracks deviations between predicted and observed events. This framework has been successfully applied in vision and neuroeconomics; here, we ask whether HPC can be extended to explain neural computations underlying social inference. We test this in the domain of action observation: others' actions license future inferences about both their preferences and future actions. Is the neural activity that subserves these inferences best explained by a HPC model? Participants watched agents first state a preference (e.g., "I prefer cats") and then select one item from a set (e.g., 2 cats, 2 dogs). We parametrically manipulate the predictability of the agent's action in two ways: 1) the *type* of item selected is congruent (e.g., a cat) or incongruent (e.g., a dog) with the stated preference. 2) the *specific* item is variably predictable based on the total number of options compatible with the stated preference (most predictable: 1 compatible and 3 incompatible items generates relative high certainty on the protagonist's next action; less predictable: 3 compatible and 1 incompatible item generates maximally a 1 in 3 chance of guessing what the agent will select). We find evidence supporting four key predictions of HPC in social cognition: 1) Different populations of neurons respond to violations of exception for low versus high level features; brain regions involved in action representation (e.g. right STS) respond to unexpected actions, while regions involved in preference representation (e.g. medial PFC) respond to unexpected preferences. 2) Neural activity varies parametrically with the relative expectedness of an event; the overall magnitude of the prediction error signal in STS inversely correlates with the probability that the agent selected the *specific* item that they did (e.g., correlates directly with the total probability mass on the unselected cats). 3) The response of these neural regions is offset in time, such that the error response in STS occurs before the error response in PFC. 4) Expectedness violation is context sensitive, such that the same event generates predictably different levels of neural activity, given only the stated background preference.

Disclosures: J. Koster-Hale: None. **F. Cushman:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.05

Topic: F.01. Human Cognition and Behavior

Support: Fondation Orange, Fondation de France

Title: Rest cerebral blood flow in the superior temporal sulcus (STS) correlates with social perception impairments in children with autism spectrum disorder (ASD)

Authors: A. SAITOVITCH[1], H. LEMAITRE[1], E. RECHTMAN[1], N. CHABANE[1], A. PHILIPPE[2], *Y. SAMSON[3], D. GRÉVENT[1], R. CALMON[1], N. BODDAERT[1], F. BRUNELLE[1], M. ZILBOVICIUS[1];
[1]INSERM unity 1000, Paris, France; [2]UMR 1163, Paris Descartes University, Inst. IMAGINE., Paris, France; [3]Salpetriere, Paris 75013, France

Abstract: Introduction: A lack of preference for relevant social features is one of the main clinical characteristics of ASD. During the last decade, the use of eye-tracking methodology has allowed an objective and quantitative characterization of social perception deficit in children with ASD. In addition, several brain imaging studies have suggested that abnormalities within the superior temporal sulcus (STS) could be related to social impairments in autism. In this study, we aimed to objectify social perception process in children with ASD using eye-tracking in order to investigate a putative correlation between social perception impairments and rest functional brain activity. Methods: For this purpose, arterial spin labelling (ASL) MRI was used to measure rest cerebral blood flow (CBF). Tobii T120 eye-tracker was used to measure number of fixations to the eyes of characters during passive visualization of social scenes. Sixteen young children with ASD (age = 5.0 ± 2.3; range = 2.3 to 10 years old), diagnosed by DSM-IVR/V and ADI-R participated in this study. Whole brain regression analyses were performed on the smoothed and normalized ASL images using number of fixations to the eyes as covariate of interest within the general linear model framework using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Results: Compared to 16 typically developing children (age = 7.7 ± 1.3 years old), children with ASD showed a significant reduction in number of fixations to the eyes during passive visualization of social scenes ($p < 0.01$). In children with autism, whole brain analyses showed a significant positive correlation between the number of fixations to the eyes, measure by eye-tracking, and cerebral blood flow at rest, measured by ASL-MRI, in the right superior temporal sulcus (STS) ($p < 0.001$ unc). Children with ASD who looked less to the eyes of characters during passive visualization of social scenes where those who had the lower rest CBF values in the right pSTS. Conclusion: These results show for the first time a correlation between a social behavior and a functional brain activity at rest, especially since the measurements were unrelated and performed separately. This correlation suggests that social behavior in children with ASD is associated with, and might be predicted by, the level of functional activity at rest within the STS.

Disclosures: **A. Saitovitch:** None. **H. Lemaitre:** None. **E. Rechtman:** None. **N. Chabane:** None. **A. Philippe:** None. **Y. Samson:** None. **D. Grévent:** None. **R. Calmon:** None. **N. Boddaert:** None. **F. Brunelle:** None. **M. Zilbovicius:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.06

Topic: F.01. Human Cognition and Behavior

Title: MEG source modeling during imitation, observation, and resting state in children on the autism spectrum

Authors: *M. DATKO[1], R. GOUGELET[2], M. METKE[3], T. DONOGHUE[2], M. KIRCHGESSNER[2], N. CASTRO[2], M. HUANG[4], J. PINEDA[2];
[1]Cognitive Sci., UC San Diego, San Diego, CA; [2]Cognitive Sci., [3]Neurosciences, [4]Radiology, UC San Diego, La Jolla, CA

Abstract: Background: Social and communicative impairments are among the core symptoms of autism and are associated with aberrant functioning of the human mirror neuron system (hMNS). Previous neurophysiological evidence supporting this observation comes from studies of EEG mu-rhythm suppression and fMRI BOLD signal activation related to the imitation and observation of biological motion. Magnetoencephalography (MEG) provides an ideal modality to investigate function and connectivity within the hMNS in autism, since it has superior source-localization compared to EEG along with higher temporal resolution compared to fMRI. This study used MEG to investigate hMNS function during tasks involving imitation and emotion recognition, and hMNS connectivity at rest. Methods: 10 participants with high-functioning autism (10-17 years of age, 1 female, average WASI IQ 97.7) were scanned with both MEG and fMRI. While being scanned with MEG, subjects were asked to imitate or passively observe videos and images of hands pressing buttons or of people making various facial expressions. Subjects also performed the Reading the Mind in the Eyes Task (RMET) (Baron-Cohen et al., 2001, J. Child. Psychol. Psychiatry). We used a source modeling technique optimized for MEG data (Huang et al. 2014, Neuroimage) to detect frequency amplitude changes related to hand and face imitation, as well as emotion recognition. We used the same source modeling technique on resting state MEG data in the same subjects, and compared those results to functional connectivity (FC) during resting state fMRI. Three separate FC analyses were performed, with three sets of regions of interest based on the regions showing the greatest task-related amplitude changes in the three MEG tasks. Results: During finger-movement imitation, as well as face imitation, changes in alpha amplitude were observed in ventral and dorsal premotor cortex. During RMET, amplitude changes associated with emotion discrimination were observed in medial prefrontal cortex, precuneus, and other areas previously associated with theory of mind. The comparison of fMRI and MEG data in a resting state revealed that amplitude in the alpha and beta MEG bands trended with low frequency BOLD fluctuations in the fMRI data in areas of

the hMNS. Conclusion: The novel use of MEG towards the investigation of hMNS function in autism corroborates previous findings of activation during imitation and observation from other modalities.

Disclosures: **M. Datko:** None. **R. Gougelet:** None. **M. Metke:** None. **T. Donoghue:** None. **M. Kirchgessner:** None. **N. Castro:** None. **M. Huang:** None. **J. Pineda:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.07

Topic: F.01. Human Cognition and Behavior

Support: Virginia Tech Center for Autism Research Student Grant Competition

Title: Effect of social disability on resting state brain networks in adults with autism or social anxiety

Authors: ***M. COFFMAN**[1], D. GRACANIN[1], J. LISINSKI[2], S. LACONTE[2], S. WHITE[1], J. A. RICHEY[1];
[1]Virginia Tech., Blacksburg, VA; [2]Carilion Res. Inst., Virginia Tech., Roanoke, VA

Abstract: Background: The default mode network (DMN) is a well-studied neural network related to social processing. Alterations in the DMN may reflect a shared mechanism for social deficits noted across clinical disorders, such as those seen in autism spectrum disorder (ASD; Weng et al., 2010; Uddin et al., 2013) and social anxiety disorder (SAD; Liao, et al., 2010). In ASD, aberrations in resting state networks are associated with core features such as social behaviors (Washington et al., 2014). However, there has been an underrepresentation of research on the mechanistic role the DMN may play in sustaining social deficits. Objectives: Our primary aim was to elucidate a potential common mechanism of social disability in ASD and SAD within the DMN. Specifically, we used a data fusion technique combining functional magnetic resonance imaging (fMRI) and diffusion tensor imagining (DTI) to examine functional and structural connectivity within the DMN. Secondary analyses examine the relationship between the DMN and social behavior. Hypotheses: We predicted that structural and functional connectivity within the DMN will show differential patterns in the clinical groups (ASD & SAD) compared to controls. It was further hypothesized that behavioral indices of social function will be related to DMN connectivity. Methods: 14 adults with ASD, 14 adults with SAD only, and 14 adults with no psychopathology (Controls) participated in this study. Participants were matched

on age (M=23.60) and Full Scale IQ (M=117.07). Diagnoses were confirmed with well-established semi-structured clinical interviews, including the Autism Diagnostic Observation Schedule (ADOS) and Anxiety Disorders Interview Schedule (ADIS). DTI and fMRI were collected on a 3T TIMTrio. The functional regions of the DMN were identified via ICA based on multivariate pattern analysis using FSL's MELODIC feature (Beckmann et al., 2005). Functional and diffusion weighted images will be processed through AFNI's FATCAT toolbox (Taylor & Saad, 2013). Social functioning was measured with the ADIS, ADOS, and the Social Responsiveness Scale (SRS). Results: Analyses in progress contrast structural and functional connectivity in the DMN between diagnostic groups, as well as contrasting the clinical groups and controls. Additional analyses will reveal relationships between social behavior and DMN connectivity. Conclusions: These results will offer elucidation of a shared pathway for social disability. Additionally, these results will highlight unique connective properties inherent to each clinical disorder. These findings have significant implications for treatment of social disabilities.

Disclosures: M. Coffman: None. **D. Gracanin:** None. **J. Lisinski:** None. **S. LaConte:** None. **S. White:** None. **J.A. Richey:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.08

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant DPI OD003312

Title: Neural bases of core and conceptual self: Implications for the representation of other persons and groups of people

Authors: *J. H. DRUCKER[1,2], L. W. BARSALOU[1], L. F. BARRETT[3,4];
[1]Emory Univ., Atlanta, GA; [2]RR&D Ctr. of Excellence, Atlanta VAMC, Decatur, GA; [3]Dept. of Psychiatry and the Martinos Ctr. for Biomed. Imaging, Harvard Med. School, Massachusetts Gen. Hosp., Boston, MA; [4]Psychology, Northeastern Univ., Boston, MA

Abstract: Self-representation is multifaceted. Building on prior research, the current experiment explores two such facets, *core self* and *conceptual self*, and how these constructs extend to neurocognitive representations of other persons and groups of people. Core self is a representation of oneself as an individual whose subjective experience is unified within a particular moment. It includes identification with one's body (body ownership), authorship for

one's actions (agency), and an embodied, egocentric point of view (first-person perspective). Conceptual self is a representation of oneself as an individual whose identity persists through time. It includes one's personality traits and physical characteristics, and the narrative of one's life constructed from accumulated autobiographical memories. An fMRI experiment (N = 19) was conducted to determine the neural correlates of core and conceptual representations for the self, other persons, and groups of people. On each trial, participants were presented for three seconds with an individual (the self, a relative, a friend, or an acquaintance), a group (adults or children), or a semantic prompt (physical or genetic). Participants were then presented for three seconds with a property (e.g., *tall*) and rated on a 3-point scale how well the property applied to the individual (e.g., how *tall* is the individual?), group (e.g., how *tall* are children?), or prompt (e.g., to what extent is *tall* a genetic property?). The first phase, in which the individual, group, or prompt was presented, was intended to elicit core representations. The second phase, in which the property was presented, was intended to elicit conceptual representations. The core self condition recruited brain areas associated with body ownership, agency, the first-person perspective, and visuospatial imagery. The conceptual self condition involved these as well, and further implicated brain areas previously associated with representing personality traits, semantic person knowledge, and executive control of memory retrieval, decision making, and theory-of-mind. Representations for other persons and groups of people rely on these and other systems to varying degrees, with a greater recruitment of medial parietal cortical areas involved in episodic memory retrieval. Some of the differences between self and other were modulated by the closeness of the personal relationship, particularly in ventral visual areas and the medial prefrontal cortex.

Disclosures: J.H. Drucker: None. **L.W. Barsalou:** None. **L.F. Barrett:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.09

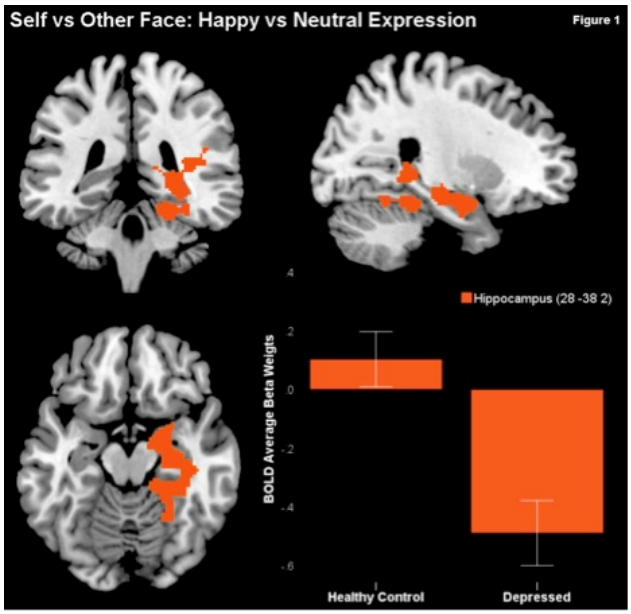
Topic: F.01. Human Cognition and Behavior

Support: 5K01MH092601

Title: FMRI evidence of altered implicit self-processing in adolescent depression

Authors: *M. B. HARMS[1], H. SCOTT[2], G. SMYDA[3], K. M. THOMAS[1], K. QUEVEDO[2]; [1]Univ. of Minnesota, Inst. of Child Develop., Minneapolis, MN; [2]Dept. of Psychiatry, Univ. of Minnesota, Minneapolis, MN; [3]Univ. of Pittsburgh, Sch. of Publ. Hlth., Pittsburgh, PA

Abstract: Negative self-processing is a key symptom of depression and there is substantial evidence linking depression to abnormal activity in brain regions supporting both explicit self-processing (midline cortical structures: MCS) and emotion processing (limbic regions). Prior research on self-processing is based on paradigms that require subjects to explicitly reflect on stimuli in relation to themselves and/or their emotions. Yet, many aspects of self-processing likely occur implicitly: i.e., below conscious awareness. The current study utilized a novel implicit measure of self-processing (The Emotional Self-Other Morph Task) that required recognition of the self face or of a non-familiar youth face to examine neural activations to happy, sad, and neutral faces. The faces were presented in blocks of pictures with high percentages of self features (self-face) or low percentages of self features/high percent stranger face (other-face) during fMRI. We scanned 38 healthy and 43 depressed adolescents. Hypotheses were: 1. healthy youth would show greater BOLD activation in limbic regions to emotional vs. neutral faces and greater activation in MCS to self vs. other faces. 2. In the self-face vs. other-face contrast, depressed youth would show less activation to happy vs. neutral faces in limbic regions, consistent with automatic negative self-processing biases and low positive emotionality in depression. Both of these hypotheses were confirmed at the whole-brain level. Follow-up analyses confirmed that these findings were due to differing activation between groups to the self-face, rather than to the other-face. Results are evidence of implicit emotional self-specific alterations in depression, in addition to previously described explicit self-processing alterations supported by MCS functional abnormalities. Our findings also provide new evidence for these altered patterns of brain activity during implicit self-processing in adolescence, a period characterized by heightened risk for depression and the challenge of forming an identity.



Disclosures: **M.B. Harms:** None. **H. Scott:** None. **G. Smyda:** None. **K.M. Thomas:** None. **K. Quevedo:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.10

Topic: F.01. Human Cognition and Behavior

Title: von Economo neurons and fork cells express a neurochemical signature linked to autonomic functioning

Authors: A. A. DIJKSTRA[1], L.-C. LIN[1], S. E. GAUS[1], *W. W. SEELEY[2,1];
[1]Neurol., Univ. of California, San Francisco, San Francisco, CA; [2]UCSF, Burlingame, CA

Abstract: The anterior cingulate and frontoinsular cortices are distinguished by two unique neuronal morphotypes, the von Economo neurons (VENs) and fork cells, which have been linked to conditions that undermine social-emotional functioning. The biological identity of these neurons remains mysterious, but insights could impact therapeutic efforts across a range of human diseases. In this study, we leveraged *in situ* hybridization data from the Allen Brain Atlas and identified VMAT2, GABRQ and ADRA1A expression in VENs, fork cells and a minority of neighboring Layer 5 neurons. We confirmed these results using immunohistochemistry or *in situ* hybridization. VMAT2 and GABRQ expression was observed in rhesus macaque VENs, fork cells and neighboring Layer 5 neurons but not in mouse cerebral cortex, underscoring the evolutionary significance of these neuronal morphotypes. Although VMAT2 serves to package monoamines into synaptic vesicles, in VENs and fork cells VMAT2 is expressed in the absence of monoamine synthesizing enzymes or reuptake transporters. Less conventionally, VMAT2 could package GABA into vesicles, but VENs and fork cells showed no expression of gluatamatic acid decarboxylase, the synthesizing enzyme for GABA, or GAT1, the GABA transporter. Together, these findings suggest an uncharacterized mode of neurochemical function. Human GABRQ and ADRA1A expression has been described in brainstem neurons involved in autonomic functioning. Overall, the biochemical signature found here suggests that VENs and fork cells are biochemically distinct from most other mammalian Layer 5 neurons and linked to autonomic functioning.

Disclosures: **A.A. Dijkstra:** None. **L. Lin:** None. **S.E. Gaus:** None. **W.W. Seeley:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.11

Topic: F.01. Human Cognition and Behavior

Support: NIMH (NAK: R01MH090134)

NIDA (RZG: DA034954; MAP: F32DA033088; SJM: 1K01DA037452-01A1)

Title: Reward wins - increased activation of the mesocorticostriatal salience network in human reactive aggression

Authors: *G. GAN[1], R. N. PRESTON-CAMPBELL[1], J. L. STEINBERG[2], S. D. LANE[3], T. MALONEY[1], M. A. PARVAZ[1], S. J. MOELLER[1], R. Z. GOLDSTEIN[1], N. ALIA-KLEIN[1]; [1]Psychiatry and Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Psychiatry, Virginia Commonwealth Univ., Richmond, VA; [3]3Psychiatry and Behavioral Sci., Univ. of Texas Hlth. Sci. Ctr., Houston, TX

Abstract: The propensity for reactive aggressive behavior that is typically triggered by provocation has been linked to hyperactivity of the brain's reward network. Here, we investigated if the opportunity to obtain a monetary reward is more salient than the opportunity to retaliate in clinically reactive aggressive (RA) compared with low aggressive individuals (LA). To do so, we measured behavioral and neural monetary reward-related and retaliatory responding using the functional MRI-adapted Point-Subtraction Aggression Paradigm (fMRI-PSAP). Nine male RA participants endorsed full or sub-clinical intermittent explosive disorder (IED) according to DSM-IV/IED-IR criteria and reported elevated Trait Anger on the State-Trait Anger Expression Inventory-2 ($p<.001$) relative to nine male LA individuals (matched on age, race, and education). All participants performed the fMRI-PSAP with the aim to earn money. A fictitious player infrequently subtracted money from the participant's earnings to provoke retaliatory behavior. On each trial, participants could choose to earn money (reward) or to subtract money from their opponent's earnings (retaliation) by pressing buttons. Behavioral and neural responses were compared between groups. Relative to LA participants, RA individuals worked more to earn money ($p=.015$, Figure 1A), but not to retaliate ($p>.7$). When engaging in monetary reward-driven behavior vs. retaliation, RA individuals exhibited increased activation in bilateral putamen and anterior insula compared with LA individuals (Figure 1B). Increased monetary reward-seeking behavior and reward-related activation in regions comprising the brain's mesocorticostriatal salience network in reactive aggressive individuals indicates that monetary reward is more salient in this population when presented with a choice between a rewarding versus a retaliatory option. These findings suggest that the use of positive

reinforcement might represent an efficacious intervention approach for the potential reduction of clinically significant reactive aggressive behavior.

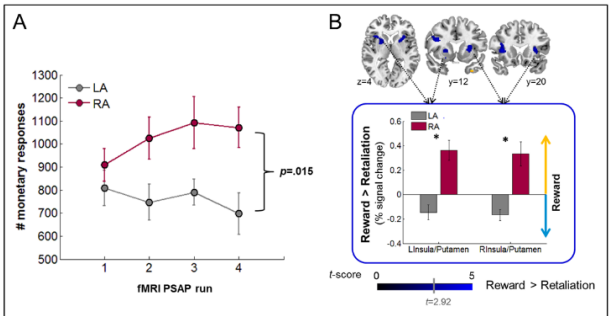


Figure 1: Compared with low aggressive individuals (LA, grey color), reactive aggressive individuals (RA, red color) worked more for obtaining a monetary reward across four fMRI-PSAP runs (A), and exhibited increased brain responses within bilateral putamen/insula for monetary reward vs. retaliation (B). ** significant at corrected cluster-level of p<.05 (>=86 connected voxels)*

Disclosures: G. Gan: None. **R.N. Preston-Campbell:** None. **J.L. Steinberg:** None. **S.D. Lane:** None. **T. Maloney:** None. **M.A. Parvaz:** None. **S.J. Moeller:** None. **R.Z. Goldstein:** None. **N. Alia-Klein:** None.

Nanosymposium

19. Social Cognition: Neural Processes and Disorders

Location: S405

Time: Saturday, October 17, 2015, 1:00 PM - 4:00 PM

Presentation Number: 19.12

Topic: F.01. Human Cognition and Behavior

Title: Brain regions influencing implicit violent attitudes

Authors: *I. CRISTOFORI[1,2], W. ZHONG[1,2], V. MANDOSKE[1], A. CHAU[1], F. KRUEGER[4,5], M. STRENZIOK[5], J. GRAFMAN[1,2,3];
[1]Rehabil. Inst. of Chicago, Chicago, IL; [2]Dept. of Physical Med. and Rehabil., [3]Dept. of Neurol., Northwestern Univ., Chicago, IL; [4]Mol. Neurosci. Dept., [5]Dept. of Psychology, George Mason Univ., Fairfax, VA

Abstract: Maladaptive aggression and violence can lead to interpersonal conflict and criminal behavior, which endangers the stability of the family and society and incurs substantial financial costs. Maladaptive aggression is associated with dysfunction in the ventromedial prefrontal cortex (vmPFC) and temporal cortex. Typically, such dysfunctional behaviors are measured by explicit self-report and history. Here, we investigated the neural basis of implicit attitudes toward aggression and violence using a modified Implicit Association Task (IAT). We tested a unique

sample of Vietnam War veterans who suffered penetrating brain injury (pTBI, n = 112) and healthy controls (HC, n = 33), who also served in combat in Vietnam but had no history of brain-injury or other neurological disorders. Our findings complemented existing evidence on the neural basis of aggression centered on the vmPFC, suggesting that the dorsolateral prefrontal cortex (dlPFC) and posterior inferior temporal cortex (ipTC) play a causal role in modulating implicit attitudes about violence. Furthermore, executive functions mediate the association between dlPFC and implicit attitudes towards violence and aggression. These results suggest that treatments aimed at increasing cognitive control using cognitive behavioral therapies that partially depend on the intact dlPFC could efficaciously treat aggressive and violent behaviors.

Disclosures: I. Cristofori: None. **W. Zhong:** None. **V. Mandoske:** None. **A. Chau:** None. **F. Krueger:** None. **M. Strenziok:** None. **J. Grafman:** None.

Nanosymposium

020. Reward and Uncertainty

Location: N228

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 20.01

Topic: F.02. Animal Cognition and Behavior

Support: NSF Grant #1460604

NIMH RO1 MH080066-01

Title: What do you do when you don't know what to do: Probing for informativeness on latent states during value-based decision making

Authors: *J. COCKBURN[1], M. J. FRANK[2];
[1]Cognitive, Linguistic and Psychological Sci., Caltech, Pasadena, CA; [2]Brown Univ., Providence, RI

Abstract: Learning and decision making are complicated by the fact that observed events (e.g., your flight departing on time) are often determined in part by unobserved processes (e.g., the weather conditions en route). The advantage of considering latent processes is evident when events are predictable if considered in concert with their latent influences, but appear random otherwise. In reward-based learning, recent studies have suggested that humans direct exploratory behaviors toward those actions that reduce uncertainty about their underlying values. However, little work has examined whether organisms actively select actions that would reduce uncertainty about the state of latent processes, even when these actions themselves are known to

carry little value. An optimal solution to the problem can be calculated for the setting that we study, but is computationally demanding. We propose a heuristic model that defines subjective utility in terms of both immediate expected value and the mutual information shared between action outcomes and latent states, where informativeness is increasingly weighted when latent states are particularly uncertain. Behavioral and electrophysiological (EEG) data show dissociable contributions of informativeness and reward value to choice, supporting predictions from the heuristic model.

Disclosures: J. Cockburn: None. **M.J. Frank:** None.

Nanosymposium

20. Reward and Uncertainty

Location: N228

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 20.02

Topic: F.02. Animal Cognition and Behavior

Support: American Federation for Aging research

Temple University CARAS Grant

Psi Chi Research Grant

NIH Grant AG0292592

Title: Age-related alterations in decision policy under conditions of uncertain strategy choices in mice

Authors: R. D. COLE[1], J. A. FRANCESCONI[1], A. YU[2], *V. V. PARIKH[1];
[1]Psychology & Neurosci., Temple Univ., Philadelphia, PA; [2]Cognitive Sci., Univ. of California San Diego, La Jolla, CA

Abstract: Prior literature has indicated a deterioration of decision-making capacity correlated with aging. In this study, we examined specifically how aging (in mice) affects the animal's ability to adaptively select decision strategies under conditions of stimulus uncertainty. Young (2 months) and aged (18 months) male C57BL/6J mice were trained on an operant task requiring both active responding (go-trials) as well as behavioral inhibition (no-go trials) under low- and high- uncertainty conditions to obtain a reward. Animals progressed through three phases of the task: low uncertainty (80% go trials), high uncertainty (50%/50% go/no go trials), and low uncertainty (20% go trials). This environmental manipulation encourages the animals to adapt

and adopt multiple behavioral strategies, in order to maintain optimal performance. Immediately after the last behavioral testing session, brains were removed to conduct immunohistochemical examination of c-fos expression in the frontostriatal networks, as these neural circuits have been show by prior work to be important for decision-making. Overall, mice in both age groups exhibited similar pattern of a go bias (higher false alarm rate when go trials are more frequent), as predicted by the Strategic Impatience Model proposed by Shenoy and Yu (2012). Interestingly, with a greater prevalence of no-go trials, aged mice showed higher hit latencies (1.94±0.10s vs. 1.25±0.11s in young mice; $p<0.01$)), as well as more misses (46.13±0.3.46% vs. 26.70 ±4.49%; $p<0.05$). Overall, under conditions of higher % of no-go trials, aged mice adopted a more conservative (inhibition) strategy that leads to fewer false alarms but also more misses. We found that neural activity in the right orbitofrontal and ventral prefrontal cortex declined in aged mice. Since these structures are a part of valuation network, and process information pertaining to impulsive choice and cost-benefit analysis, it is possible that that reduced activation of these regions may reflect or underlie a changed go/no-go decision threshold in aging. Collectively, our data suggest that both young and aged mice adapt their go/no-go responses to different settings of environmental statistics, but that aged mice are particularly affected when the % of no-go trials increases, such that they more drastically reduce go responses than young mice.

Disclosures: **R.D. Cole:** None. **J.A. Francesconi:** None. **A. Yu:** None. **V.V. Parikh:** None.

Nanosymposium

20. Reward and Uncertainty

Location: N228

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 20.03

Topic: F.02. Animal Cognition and Behavior

Support: McKnight Memory and Cognitive Disorder Award

Title: Population dynamics of reward and uncertainty in frontal and parietal cortex

Authors: N. C. FOLEY, *J. P. GOTTLIEB;
Neurosci., Columbia Univ. Med. Ctr., New York, NY

Abstract: In humans and non-human primates, attention and eye movements sample visual information. Decisions regarding oculomotor control depend on the lateral intraparietal area (LIP) and the frontal eye fields (FEF), two interconnected cortical areas where neurons prioritize targets for attention and gaze. However, it remains unclear how the brain computes this

selection. How do frontal and parietal neurons “know” which stimulus to sample? Behavioral and computational studies suggest that reward and uncertainty reduction play key roles in oculomotor selection, but it remains unknown how these factors are encoded in individual oculomotor cells. Here we test the hypothesis that signals of reward and uncertainty are transmitted to the oculomotor system from higher order frontal and parietal structures. Two candidate areas are the dorsolateral prefrontal cortex (dlPFC), specifically the pre-arcuate portion that projects to the FEF, and parietal area 7a, which connects with the dlPFC and LIP. To examine this idea we recorded neuronal ensemble activity in the dlPFC and area 7a using multi-electrode (“Utah”) arrays. Monkeys performed a task in which abstract visual cues indicated various reward distributions. In the first task, the reward distributions differed only in the probability of a high or low outcome; in the second task they differed both in the variance and magnitude of the possible rewards. The cues were presented at a peripheral location for 300 ms and, after a 600 ms delay, the monkeys made an instructed saccade to a randomly selected location. Because the monkeys did not freely choose their saccade, we could examine how the neurons encoded the statistics of the cue predictions independently of active decision strategies that may have altered the value of the cues. Population level analyses, including linear regression and logistic classifiers, decoded information about value and uncertainty from the dlPFC and 7a. During the delay period before the saccade, value and uncertainty encoding were robust in both areas; neural responses tended to increase with value and decrease with uncertainty. During and after the saccade, uncertainty encoding waned, while value encoding persisted and became higher in the dlPFC relative to 7a. The value response became particularly strong at the time of the reward, when it was stronger in the dlPFC relative to 7a. Representations in both PAC and 7a had strong oscillatory dynamics whose primary power was in low frequencies (~8hz) and which tended to be stronger in the dlPFC. The pre-arcuate cortex and area 7a are venues through which uncertainty and reward signals may be brought to bear on attention and eye movement control.

Disclosures: **N.C. Foley:** None. **J.P. Gottlieb:** None.

Nanosymposium

20. Reward and Uncertainty

Location: N228

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 20.04

Topic: F.02. Animal Cognition and Behavior

Title: Distinct mechanisms for behavioral control under uncertainty in the primate basal forebrain

Authors: *I. E. MONOSOV, N. LEDBETTER;
Anat. and Neurobio., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Uncertainty is thought to exert control over learning, choice, and emotion. But the neuronal mechanisms for these modulations of behavior by uncertainty are poorly understood. We show that the primate basal forebrain contains groups of neurons that signal information about uncertainty and reward value in distinct manners that may support different but complimentary roles of uncertainty in the control of behavior. One group of reward-sensitive neurons (Group 1) responded differentially to the presentation of single isoluminant visual objects associated with 100% and 0% chance of reward delivery. Interestingly, the same group of 'reward-value' sensitive neurons responded to the presentation of visual objects associated with predictions of probabilistic 'risky' rewards in a highly non-linear manner. For example, they responded to 100% and 50% reward predictions similarly. When the monkey made choices amongst certain- and uncertain cues, the same neurons again signaled the values of the offers in a non-linear manner before the choice was made. In contrast, a second group of neurons (Group 2) did not differentially respond to certain- and uncertain- options during choice behavior until the choice was made and the monkey anticipated the delivery of a risky reward. At this time, they displayed robust selectivity for uncertain expectation of the choice outcome (reward or no reward). These data show that the basal forebrain contains multiple neuronal mechanisms for the control of behavior under uncertainty. One mechanism may promote non-linear choice behavior to explore uncertainty. The second may participate in monitoring the delivery of uncertain outcomes to enhance learning in the uncertain context. How these mechanisms work together to facilitate appropriate behavior is the subject of our future investigations.

Disclosures: I.E. Monosov: None. **N. Ledbetter:** None.

Nanosymposium

20. Reward and Uncertainty

Location: N228

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 20.05

Topic: F.02. Animal Cognition and Behavior

Title: Neurons in posterior cingulate cortex encode information signals and regulate behavioral plasticity

Authors: *M. L. PLATT, J.-F. GARIÉPY, D. L. BARACK;
CCN, Duke Univ., Durham, NC

Abstract: The posterior cingulate cortex (PCC) forms the central hub of the default mode network. Brain imaging studies implicate PCC in a wide range of cognitive functions, including attention, prospective thinking, value computations, creativity, and curiosity. Neurophysiological studies in primates show that PCC neurons signal errors, reward omission, uncertainty, and novelty. Stimulation of PCC evokes strategy switching and inactivation of this area impairs learning. These findings may be unified by a core set of computations that harvest information from the environment to guide high-level behavioral strategies. One important question is whether these computations are independent of reward-related computations guiding learning and decision-making that have become increasingly well-understood over the last two decades. Here we directly test the hypothesis that PCC neurons encode information signals in the environment independently of reward and regulate future behavior based on this information. To do this, we designed a novel behavioral task that partially decorrelates expected reward and reward outcomes from expected information and information outcomes in a single task. In our task, two different fixed reward amounts were randomly assigned to two of six available targets on every trial. As the monkey samples targets, the amount of information about reward sequence decreases, while the expected reward of upcoming actions could decrease or increase, depending on rewards received to that point. Monkeys' behavior reflected both reward and information; response times were correlated with the size of experienced reward outcomes and the expected rewards of upcoming choices, as well as with gains in information from prior choices and the expected information from upcoming choices (multilinear regression, $p < 0.05$). We recorded the firing rates of 125 PCC neurons in two monkeys performing our task. PCC neurons preferentially encoded expected information over expected reward and information outcomes over reward outcomes. Furthermore, PCC neurons signaled the variability in the patterns of choices made by monkeys. Specifically, the strength of information outcome encoding predicted variability in the trial-by-trial order of targets selected. Moreover, different neurons preferentially signaled information outcomes by choice number in a trial. The discovery that PCC neurons encode information expectations and outcomes and predict behavioral variability suggests that this area, and by extension the default mode network, plays a key role in learning from and shaping strategic behavior on the basis of information.

Disclosures: **M.L. Platt:** None. **J. Gariépy:** None. **D.L. Barack:** None.

Nanosymposium

20. Reward and Uncertainty

Location: N228

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 20.06

Topic: F.02. Animal Cognition and Behavior

Support: Hilda and Preston Davis Foundation Postdoctoral Fellowship

NIDA DA19028

NIMH MH097990

DARPA W911NF-14-2-0043

Title: Competing neural representations of choice alternatives in orbitofrontal cortex during value-based decisions

Authors: *E. L. RICH, J. D. WALLIS;
Helen Wills Neurosci. Inst., UC Berkeley, Berkeley, CA

Abstract: When facing a preference decision, the brain should represent the value of available options and compare them to make a choice. The orbitofrontal cortex (OFC) is considered crucial for such value-based decisions, and strongly represents the value of items that are ultimately chosen. However, it's unclear how OFC compares alternatives in order to make these decisions. To address this, we trained two monkeys on a reward preference task involving pictures that predicted 4 reward values. We recorded ensembles of OFC neurons and local field potentials while animals either viewed a single reward-predictive picture or made choices between a pair of pictures. We then used patterns of neural activity associated with single pictures to decode the decision-making process that occurred when the animal was making a choice. During choices we found that the decoded category alternated between neural states associated with each option, as if the animal were considering each option in turn. These alternating representations followed idiosyncratic patterns from trial to trial. To determine whether these patterns reflected the decision process, we used the posterior probabilities of each category assignment as a measure of the strength of the representation of each picture. Stronger representations of the chosen picture predicted faster choice times, while stronger representations of the unchosen picture independently predicted slower choice times. In contrast, unavailable options had no predictive value. Eye movements gave further insight into the choice process. On "quick decision" trials, with only one saccade to the chosen picture, representations of that item were significantly stronger than representations of the unchosen picture. In contrast, in "deliberative decisions" the animal made multiple saccades to both options before choosing. In this case, and the unchosen representation competed more effectively with representations of the chosen item. Therefore, the relative representational strength of the two choice options correlated with how deliberately the subjects chose. This suggests that value-based decision-making evolves as a dynamic process in OFC, involving competing representations of choice alternatives. When one representation dominates in OFC, the animal's choice will be fast, but if two options have similar representational strength, the animal's choice will be slower and outward behavior more deliberative.

Disclosures: **E.L. Rich:** None. **J.D. Wallis:** None.

Nanosymposium

20. Reward and Uncertainty

Location: N228

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 20.07

Topic: F.02. Animal Cognition and Behavior

Support: R01 DA029330

T32 NS007224

Title: Metaplasticity as the neural substrates for choice under uncertainty

Authors: **S. FARASHAHI**[1], C. H. DONAHUE[2], H. SEO[3], D. LEE[3], *A. SOLTANI[1]; [1]Psychological & Brain Sci., Dartmouth Col., Hanover, NH; [2]Gladstone Inst. of Neurolog. Dis., San Francisco, CA; [3]Yale Univ. Sch. of Med., New Haven, CT

Abstract: Decision making often involves integration of reward outcomes over time, but this becomes considerably challenging if reward assignments on alternative options are probabilistic and change over time, as it is the case in natural environments. Reinforcement learning models suggest that the learning rates, which determine the time constant of reward integration, should be optimized to deal with variability or uncertainty of reward assignments in a given environment. However, it is unclear how computations necessary for finding the optimal learning rates can be performed by neuronal elements in the brain. Here, we propose that dopamine-dependent metaplasticity can offer a plausible neural substrate for tracking choice outcomes under reward uncertainty, and provide experimental evidence for our proposal. Firstly, we show that a model endowed with dopamine-dependent metaplasticity can robustly perform the probabilistic reversal learning (PRL) task by dynamically adjusting the learning rates solely based on reward feedback. In our model, synapses have multiple meta-levels associated with each of the two levels of synaptic strength (weak and strong). In addition, presence or absence of reward results in stochastic transitions between different meta-levels. This model predicted time-dependent, choice-specific learning rates that were different for rewarded and unrewarded trials, whereas fitting the model's choice behavior using RL models led to a small change in the learning rates across environments with various degrees of uncertainty. This result shows that often observed, constant learning rates might be due to shortcoming of models used for fitting rather than invariant learning rates. Secondly, to test the model's predictions, we analyzed behavioral data from monkeys performing the PRL task in two environments with different

degrees of reward uncertainty (Donahue CH & Lee D. “Dynamic routing of task-relevant signals for decision making in dorsolateral prefrontal cortex”. Nat Neuroscience (2015) vol. 18 (2) pp. 295-301). Consistent with the modeling results, fits based on the RL models suggested that monkeys applied equal learning rates in the two environments. However, by fitting the choice behavior using our model, we again obtained time-dependent, choice-specific learning rates. Finally, our model predicted certain sequences of choices better than RL models, especially when the rewarded target was changed after several trials. Overall, our results provide a link between metaplasticity and choice behavior under uncertainty, and explain rigidity of learning rates with respect to uncertainty and strategies observed previously.

Disclosures: S. Farashahi: None. **C.H. Donahue:** None. **H. Seo:** None. **D. Lee:** None. **A. Soltani:** None.

Nanosymposium

20. Reward and Uncertainty

Location: N228

Time: Saturday, October 17, 2015, 1:00 PM - 3:00 PM

Presentation Number: 20.08

Topic: F.02. Animal Cognition and Behavior

Support: CAS Hundred Talents Program

Shanghai Pujiang Program

Title: The attentional modulation of the activity of value-sensitive orbitofrontal neurons

Authors: *T. YANG, Y. XIE, C. CHEN, C. NIE;
Inst. of Neurosci., Shanghai, China

Abstract: The orbitofrontal cortex (OFC) plays an important role in associating reward value with visual stimuli. Neurons in the OFC are found to encode the value associated with visual stimuli but not other visual features, including shape, color, or spatial location. Here we investigate how visual attention may affect OFC neurons’ value encoding. We trained two monkeys to view simple shapes presented peripherally on a computer screen while holding their fixation at a central fixation point. The shapes were randomly selected from a pool of five, each of which was associated with 0, 1, 2, 4, and 8 drops of water, respectively. They were presented either alone or in pairs. In the latter case, one shape in the pair would be selected randomly by the computer and its associated reward would be delivered to the monkey in the end of the trial. In addition, in some trials, we manipulated the monkeys’ attention by changing the visual

saliency of one shape in the pair with a quick rotation of 100 ms. The rotated shape was randomly chosen and was not linked to the reward. The monkeys were trained to maintain their fixation throughout a trial. We first measured the monkeys' pupil size and confirmed that they learned the meaning of each shape. The pupil size dilation was positively correlated with the shapes' value after the shape onset. When a pair of shapes was presented, the pupil size dilation reflected the value of the shape that predicted a larger reward. We next recorded from the OFC neurons. The activity of a subset of neurons was modulated by shapes' value during the shape presentation period. When two different shapes were presented together, the firing rates of the OFC neurons reflected the value of the shape that predicted a larger reward more. Finally, the salience change produced a small but significant effect on the neurons' responses. For neurons that had higher firing rates for larger value stimuli measured under single stimulus conditions, their response to a pair of stimuli was also larger when the larger value stimulus in the pair was rotated than when the smaller value stimulus was rotated. The latency of the attentional modulation relative to the onset of the rotation was similar to the latency of their visual response, suggesting a bottom-up attention mechanism was in play. Our results provided evidence of attentional modulation of the activity of value-sensitive OFC neurons. They provide insights to understanding how attention may affect value-based decision making.

Disclosures: **T. Yang:** None. **Y. Xie:** None. **C. Chen:** None. **C. Nie:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.01

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant R01NS062829

DOD grant W81XWH-08-2-0148

NIH Grant K01MH089112

Title: Dynamic regulation of excitatory synapse development by a rac1-specific gef/gap complex

Authors: ***K. R. TOLIAS**, J. DUMAN, K. UM, J. CHENG, Y.-K. TU;
Dept. of Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Synapses are polarized sites of contact that mediate communication between neurons. Most excitatory synapses in the brain are located on actin-rich dendritic spines. Spines can rapidly remodel in response to environmental stimuli, and this structural plasticity is important for neural circuit formation, learning, and memory. Conversely, aberrant spine morphogenesis is associated with numerous neurological disorders, including intellectual disabilities and autism spectrum disorder. Thus, elucidating the mechanisms that regulate the formation and plasticity of spines and associated synapses will provide critical insights into brain function and disease. Rho GTPases direct the actin dynamics that drive the formation and remodeling of spines and synapses. While precise spatiotemporal regulation of Rho GTPases is necessary for their function, little is known about the mechanisms that enable Rho GTPase activators (GEFs) and inhibitors (GAPs) to act in concert to regulate Rho GTPase signaling. Recently, we identified a complex composed of a Rac-GEF (Tiam1) and a Rac-GAP (Bcr) that cooperate to regulate excitatory synapse development. Disruption of Bcr function within this complex increases Rac1 activity and spine remodeling, resulting in excessive synaptic growth that is rescued by Tiam1 inhibition. In contrast, Tiam1 loss results in decreased spino- and synaptogenesis and behavioral abnormalities in mice. Notably, receptors utilize the Tiam1-Bcr complex to control synaptogenesis. In response to EphB receptor activation, Tiam1 induces Rac1-dependent spine formation, whereas Bcr prevents Rac1-mediated receptor internalization, promoting spine growth over retraction. Likewise, we found that the adhesion-G-protein-coupled receptor BAI1 (ADGRB1) regulates spine and synapse development by recruiting Tiam1, Bcr and the polarity protein Par3 to synaptic sites where they mediate local Rac1 activation and actin remodeling. Together, these results suggest that a GEF/GAP complex containing Tiam1 and Bcr is required to maintain appropriate levels of Rac1 signaling necessary for proper excitatory synapse development.

Disclosures: **K.R. Tolias:** None. **J. Duman:** None. **K. Um:** None. **J. Cheng:** None. **Y. Tu:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.02

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NSERC

Title: Angiomotin (AMOT) is an important mediator of actin-dependent dendritic spine growth

Authors: *J. P. FAWCETT[1], M. WIGERIUS[2], D. QUINN[3], A. DIAB[2], A. KOLAR[3], S. KRUEGER[3];
[1]Montreal Neurol Inst., Halifax, NS, Canada; [2]Pharmacol., [3]Physiol. and Biophysics, Dalhousie, Halifax, NS, Canada

Abstract: Angiomotin (AMOT) is a scaffolding protein that has been shown to play a central role in the formation of cell-cell contacts. To date two AMOT isoforms have been described - an 80kDa isoform (p80) and a 130kDa isoform (p130). Both the p80 and p130 isoforms contain a coiled-coiled region that is necessary for the association of AMOT with the RhoGAP protein Rich1. The the p130 isoform contains a unique N-terminal region that binds f-actin. Currently, little is known about the role of AMOT in the nervous system. Here we show that both the p130 and p80 isoforms are present in the developing and adult CNS, with unique subcellular distributions in dissociated hippocampal neurons. While the p80 isoform is diffusely distributed in dissociated hippocampal neurons, the p130 isoform is enriched in dendritic spines consistent with its association with PSD-95 and MUPP-1. The N-terminal region of p130 is necessary to direct the protein into dendritic spines. Photobleaching experiments reveal that the mobility of the N-terminal region is similar to GFP-actin. When co-expressed with GFP-actin, the N-terminal fragment has no effect on actin mobility. Interestingly, full-length p130, when co-expressed with GFP-actin, is able to stabilize actin implicating the importance of the C-terminal region of p130 in regulating actin dynamics. Accordingly, silencing of p130 leads to multiple defects including changes in dendritic spine morphogenesis, synaptic function and Cdc42 activity. Together our results suggest that p130 AMOT functions to control dendritic spine morphogenesis by regulating Cdc42 activity and thus actin dynamics, providing evidence of a novel function for AMOT in the CNS.

Disclosures: J.P. Fawcett: None. **M. Wigerius:** None. **D. Quinn:** None. **A. Diab:** None. **A. Kolar:** None. **S. Krueger:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.03

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant MH082808

NIH Grant NS082266

Title: Rho regulators in synapse development and disease

Authors: *L. VAN AELST[1], Y. TAI[1], M. WANG[1], A. NAKANO-KOBAYASHI[2], N. NADIF KASRI[3];
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Dept. of Anat. and Developmental Biol., Kyoto Univ., Kyoto, Japan; [3]Dept. of Cognitive Neurosciences and Human Genet., Radboud Univ. Med. Ctr., Nijmegen, Netherlands

Abstract: Mutations in genes encoding Rho regulators have been found to underlie various forms of intellectual disability (ID). Oligophrenin-1 (OPHN1), which encodes a Rho-GAP, was the first identified Rho-linked ID gene. It was initially identified by the analysis of a balanced translocation t(X;12) observed in a female patient with mild ID. Subsequent studies revealed the presence of OPHN1 mutations in families with ID associated with cerebellar hypoplasia and ventriculomegaly. Most OPHN1 mutations identified to date have been shown, or predicted, to result in OPHN1 loss-of-function; however, the pathophysiological role of OPHN1 remains poorly understood. By temporally and spatially manipulating OPHN1 gene expression, we found that during early development postsynaptic OPHN1 plays a key role in activity-dependent maturation and plasticity of excitatory synapses, indicating the involvement of OPHN1 in normal activity-driven glutamatergic synapse development. More recently, we obtained evidence that OPHN1 plays also a critical role in mediating mGluR-LTD in CA1 hippocampal neurons. mGluR-LTD induction elicits rapid dendritic OPHN1 synthesis, which is dependent on mGluR1 activation. This response is essential for mGluR-LTD, as acute blockade of OPHN1 synthesis impedes LTD. mGluR-induced OPHN1 mediates LTD and associated persistent decreases in surface AMPARs via interactions with Endophilin-A2/3. Importantly, this role of OPHN1 is separable from its effects on basal synaptic strength, which require both OPHN1's Rho-GAP activity and interaction with Homer1b/c. The former contributes to the stabilization of synaptic AMPARs, while the later facilitates receptor recycling and thereby maintenance of a mobile pool of surface AMPARs. Thus, our data unveil a multifunctional role for OPHN1 at CA1 synapses. Independent of its role in activity driven glutamatergic synapse development, regulated OPHN1 synthesis plays a role in mGluR-dependent LTD. As such, our findings provide insight into the cellular basis by which mutations in OPHN1 could contribute to the behavioral and cognitive deficits in OPHN1 patients.

Disclosures: L. Van Aelst: None. **Y. Tai:** None. **M. Wang:** None. **A. Nakano-Kobayashi:** None. **N. Nadif Kasri:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.04

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant NS62821

NIH Grant NS28182

Title: From molecular recognition to synaptic connectivity: IgSF cell surface proteins controlling neural wiring in *Drosophila*

Authors: *E. OZKAN[1], Y. J. PARK[1], R. A. CARRILLO[2], K. P. MENON[2], K. C. GARCIA[3], K. ZINN[2];
[1]Biochem. & Mol. Biol., Univ. of Chicago, Chicago, IL; [2]Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA; [3]Dept. of Mol. and Cell. Physiol., Stanford Univ., Stanford, CA

Abstract: The specific wiring of the nervous system is essential for its function. Defects in wiring mechanisms can lead to several neurodevelopmental diseases and incorrect perception of sensory cues. According to the *Chemoaffinity Hypothesis*, cell surface receptors identify neurons and guide their connectivity, through protein-protein interactions. While many such "molecular tags" have now been identified directing processes such as axonal guidance and synapse specification, it is unlikely that the complex connectivity of the animal brain can be explained by the limited number of molecules known to guide it. We have addressed this fundamental question by high-throughput interaction screening of cell surface receptors and secreted ligands of the three largest extracellular protein families in *Drosophila melanogaster*, and identified novel protein families with neurodevelopmental functions. In this study, we focused on two protein families belonging to the Immunoglobulin superfamily (IgSF), the Dprs and the Dpr-interacting proteins (DIPs), with 21 and 9 members respectively. We and others have now shown that these proteins are expressed throughout the nervous system, and in specific patterns that identify neurons, and function in synapse specification and neuronal survival in the optic lobe and in neuromuscular junctions. We have also studied the molecular principles of recognition between Dprs and DIPs using biochemical and biophysical techniques. Using an avidity-driven extracellular protein-binding assay, we revealed the "Dpr-ome" – all interactions between Dprs and DIPs. The network of interactions revealed that both Dprs and DIPs are cross-reactive; i.e. they interact with multiple partners in overlapping and complex patterns. The Dpr-DIP interface can support thirty-six unique Dpr-DIP interactions. Our crystal structure and the supporting affinity measurements of Dpr6 bound to DIP-alpha show a hydrophobic interface driven by shape complementarity, and not by electrostatics. Overall, we believe that (1) shape complementarity might be more suitable to a highly cross-reactive interface, such as the Dpr-DIP interface, and (2) cross-reactivity is a valuable strategy to address the problem of a limited number of molecular interactions defining a very large number of cellular interactions.

Disclosures: **E. Ozkan:** None. **Y.J. Park:** None. **R.A. Carrillo:** None. **K.P. Menon:** None. **K.C. Garcia:** None. **K. Zinn:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.05

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIDA Funding

Title: Microglial colonization and interactions with synapses in the developing reward circuitry

Authors: ***I. A. HAWES**, L. DEBIASE, A. BONCI;
Natl. Inst. On Drug Abuse, Baltimore, MD

Abstract: Microglia are abundant within brain regions that process information about reward and subtle perturbations in maturation of the reward circuitry may be linked to susceptibility to developing substance dependence. However, the properties of microglia within the developing reward circuitry are poorly defined and it is not known whether these cells participate in synaptic pruning and circuit maturation. We used transgenic mice that express EGFP within microglia to quantify the density, morphology, and phagocytic capacity, of these cells in three key regions of the reward circuitry: the ventral tegmental area (VTA), the nucleus accumbens (NAc), and the medial prefrontal cortex (mPFC). Microglial density peaked during early postnatal periods in all three regions and then declined sharply to adult levels. However, in the NAc, microglial density peaked at postnatal day (P) 10-12, while in the VTA and mPFC microglial density peaked at P14-16, suggesting that achievement of adult microglial distribution in different brain regions follows a distinct time course. In the visual system, phagocytosis of synapses is most pronounced in microglial cells with a sparsely-branched, amoeboid morphology. Morphology of microglial cells within the reward circuitry became significantly more complex as development progressed, with prominent branching evident in all investigated brain regions by P12. This rapid anatomical maturation suggests that microglial participation in synaptic pruning within the reward circuitry may parallel that observed in the visual system and peak within the first postnatal week of life. However, preliminary analysis of microglial phagocytotic capacity through immunostaining for CD68, a lysosomal marker, indicates that microglial CD68 content is equal across time points in all assessed brain regions. Together these observations raise the possibility that maturation of microglial morphology and tissue distribution may be regulated independently from phagocytotic activity. Future studies will define the full time course of microglial-mediated synaptic pruning

within distinct regions of the reward circuitry and determine whether disruption of these processes affects responses to exposure to drugs of abuse.

Disclosures: **I.A. Hawes:** A. Employment/Salary (full or part-time); National Institute on Drug Abuse. **L. DeBiase:** None. **A. Bonci:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.06

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: Jerome Lejeune Foundation

Title: Lack of Mecp2 in the developing embryonic cortex delays the acquirement of mature neuronal identity

Authors: ***F. BEDOGNI**[1], C. COBOLLI GIGLI[1], L. SCARAMUZZA[1], R. ROSSI[2], C. KILSTRUP-NIELSEN[3], N. LANDSBERGER[1];
[1]San Raffaele Res. Inst., Milan, Italy; [2]Inst. Nazionale Genetica Molecolare, Milan, Italy; [3]Univ. of Insubria, Varese, Italy

Abstract: MeCP2 is a transcriptional modulator involved in the onset of different brain pathologies when mutated in humans; between these Rett syndrome (RTT) is the disease by far most frequently associated with such mutations. RTT is a neurological disorder that mainly affects girls (1/10.000 live born female) and is characterized by autistic features, seizures, ataxia and stereotypical hand movements. Recent evidences (Bedogni, 2015) demonstrated that MeCP2 could play an important role during embryonic stages of development as early as at E15.5. We in fact detected transcriptional deregulations suggestive of a delay (or possibly a stall) in the acquisition of full mature neuronal identity. Interestingly, much of the transcriptional effects persisted at later time points (E18 and P8), suggestive that such defects could persist throughout life. Possibly due to such transcriptional defects, MeCP2 null neurons respond less, *in vitro*, to stimuli such as glutamate or current injection, which could be in agreement with the fact that at such early stages of maturation Mecp2 null neurons exhibit reduced neuritis length and nuclear size, as well as a delay in the expression of proper markers of cortical layer identity. Such defects could thus be considered the earliest features affecting Mecp2 null cortexes, leading to the delay in proper network formation and strongly concurring to the later exacerbation of the overall neurological phenotype displayed by Mecp2 null animals in adulthood.

Disclosures: **F. Bedogni:** None. **C. cobolli Gigli:** None. **L. scaramuzza:** None. **R. rossi:** None. **C. kilstrup-Nielsen:** None. **N. landsberger:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.07

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant NS077907

Nancy Lurie Marks postdoctoral grant

Title: Activity dependent corticostriatal development and its implication in Autism spectrum disorders

Authors: ***R. PEIXOTO**, W. WANG, D. CRONEY, Y. KOZOROVITSKIY, B. SABATINI; Harvard Med. Sch., Cambridge, MA

Abstract: Autism spectrum disorders (ASDs) are characterized by a core set of symptoms including communication deficits, impaired reciprocal social interactions and repetitive stereotyped behaviors. ASD symptoms often emerge during the toddler stage following an apparent normal infancy and resulting in the regression of previously learned abilities. This late onset and selective degradation of cognitive features suggest that some forms of ASD may arise from impaired neurodevelopmental processes affecting specific neuronal circuits during particular stages of development. Recent studies suggest that abnormal development of caudate and associative cortical regions are associated with ASDs. However, a detailed functional characterization of corticostriatal development and its relevant regulatory mechanisms is still lacking. Using a combination of optogenetic, chemicogenetic and electrophysiological approaches we found that the majority of corticostriatal synaptogenesis in mice occurs during a narrow postnatal developmental period characterized by a correlated increase in cortical and striatal activity and the emergence of bursting firing patterns in SPNs. Early corticostriatal connectivity is highly dependent and modulated by acute and chronic changes in cortical activity suggesting that imbalances in cortical function affect SPN and basal ganglia circuit development. In addition, we found that mouse models of ASD with cortical hyperexcitability exhibit increased corticostriatal connectivity. Taken together these results indicate that corticostriatal development is highly influenced by cortical activity and point to a potential common pathophysiological mechanism underlying several forms of ASD.

Disclosures: **R. Peixoto:** None. **W. Wang:** None. **D. Croney:** None. **Y. Kozorovitskiy:** None. **B. Sabatini:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.08

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant NS065183

Title: Par polarity proteins in dendritic spine morphogenesis and plasticity

Authors: ***H. ZHANG**, Q. WU, V. L. DIBONA, L. P. BERNARD;
Neurosci. and Cell Biol., Robert Wood Johnson Med. School, Rutgers Univ., Piscataway, NJ

Abstract: Neurons are probably the most polarized/compartmentalized cell type in the human body. Their polarity establishment starts with axon/dendrite specification. Further compartmentalization occurs during the formation of dendritic spines, which receive most of the excitatory synaptic inputs in the brain. This raises the exciting possibility that proteins regulating global cell polarization are involved in the localized polarity during dendritic spine formation. Indeed our studies show that the Par (Partitioning-defective) polarity complex, which includes Par3, Par6 and atypical PKC (aPKC), plays a key role in spine morphogenesis. Par3 functions through the Rac exchange factor TIAM1 to locally regulate the activity of the small GTPase Rac; while Par6 and aPKC function through p190 RhoGAP and the RhoA GTPase. Our recent studies show that another polarity protein Par1 is involved in dendritic spine morphogenesis downstream of NMDA receptors. Par1 functions through phosphorylating the synaptic scaffolding protein PSD-95 on Ser561. We further found that phosphorylation of this site regulates a conformational switch that is important for bidirectional spine structural plasticity. Together, our studies reveal important roles for Par polarity proteins in dendritic spine morphogenesis and plasticity. Ongoing studies are aimed at elucidating how the interplay between different Par proteins regulates synaptic plasticity.

Disclosures: **H. Zhang:** None. **Q. Wu:** None. **V.L. DiBona:** None. **L.P. Bernard:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.09

Topic: A.05. Synaptogenesis and Activity-Dependent Development

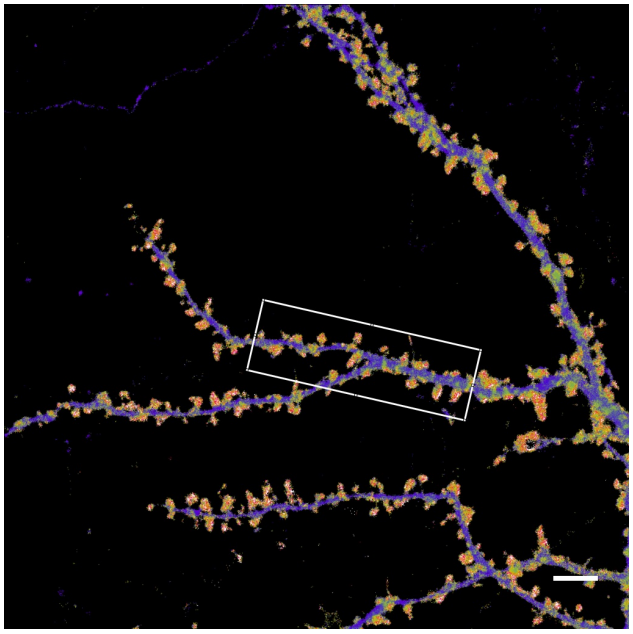
Support: R01MH104632

R01GM083889

Title: Activity-dependent localization of monomeric G-actin to spines during synapse formation and plasticity

Authors: *W. LEI, E. VITRIOL, Y. RUI, K. MYERS, J. ZHENG;
Departments of Cell Biol. & Neurol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: The actin cytoskeleton is enriched in dendritic spines and its dynamic remodeling underlies the development and modification of the postsynaptic structure during plasticity. Actin filaments (F-actin) are polymerized from and disassemble into globular actin monomers (G-actin). A wide range of accessory proteins are known to regulate the assembly and disassembly of F-actin, as well as to organize actin filaments into distinct networks for different cellular functions. G-actin is generally thought to exist as a single diffusible pool throughout the cell to passively support actin assembly. In this study, we present evidence that a pool of monomeric G-actin is preferentially enriched in dendritic spines of hippocampal neurons in cell culture and in organotypic slices. Importantly, this spine enrichment of G-actin can be regulated by synaptic activity as LTP induction can markedly increase the spine pool of G-actin that appears to correlate with spine enlargement. The spine enrichment of monomeric G-actin is further supported by G-actin mutants that cannot be polymerized into filament. Interestingly, these non-polymerizable G-actin mutants also undergo activity dependent localization to spines, suggesting an intriguing mechanism underlying spatiotemporal regulation of G-actin distribution. Overexpression of the non-polymerizable G-actin was found to result in the impairment of spine development and structural changes associated with synaptic plasticity. Finally, we show that G-actin enrichment in spines depends on several actin monomer-binding proteins. Together, these findings highlight a novel actin mechanism by which spatiotemporal targeting and delivery of G-actin into spines regulate the actin remodeling needed for spine formation and modification during synaptic plasticity.



Disclosures: **W. Lei:** None. **E. Vitriol:** None. **Y. Rui:** None. **K. Myers:** None. **J. Zheng:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.10

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Title: Development of Glutamatergic and GABAergic synapses on principal neurons in the rat neocortex

Authors: *S. NASKAR[1], E. BALZANI[2], V. TUCCI[2], L. CANCEDDA[2];
[2]Neurosci. and Brain Technologies, [1]Inst. Italiano Di Tecnologia (IIT), Genova, Italy

Abstract: Development of cortical microcircuits is a complex process wherein newborn neurons extend their axons in search of inputs from targets in the vicinity - a process also known as synaptogenesis. This is important for both excitatory and inhibitory newborn neurons, as it helps them to become functional units of the cortical circuit and establish a correct balance between excitation and inhibition, disruptions in the maintenance of which results in neurodevelopmental disorders. Morphological and functional studies in the rodent hippocampus, midbrain and hypothalamus have revealed that GABAergic synapses develop before Glutamatergic synapses.

Only a handful of studies on the GABA-Glutamate sequence of synaptogenesis exists in the developing neocortex, and they provide contrasting results. In an attempt to provide detailed functional evidences of the GABA-Glutamate sequence of synaptogenesis on principal neurons in the developing rodent neocortex, we performed electrophysiological, morphological and behavioral studies. We found that Glutamatergic miniature postsynaptic currents (mPSCs), which are an indicator of Glutamatergic synaptogenesis, appear earlier than GABAergic mPSCs in Layer 2/3 of the neocortex. Interestingly, frequencies of both Glutamatergic and GABAergic mPSCs show an 'abrupt' increase at postnatal day 9 (P9). This abrupt increase in Glutamatergic and GABAergic synaptogenesis is modulated by Serotonin because systemic Serotonin reuptake inhibition with Selective Serotonin Reuptake Inhibitors (SSRIs) accelerates the development of Glutamatergic and GABAergic synaptogenesis in Layer 2/3 of the neocortex. Interestingly, in Layer 5 of the cortex the frequencies of both Glutamatergic and GABAergic mPSCs increase in a linear fashion and no abrupt changes in the frequencies of Glutamatergic and GABAergic mPSCs are observed. Currently, we are assessing the morphology of all recorded cells. In order to investigate the sequential development of sensory and motor behaviors, we performed behavioral experiments using the SHIRPA test in young rat pups aged between postnatal day 2 and 10. We observed that by P7, a period in development when thalamocortical afferents are in position in Layer 4 of the neocortex, most sensorimotor tasks were performed successfully by pups. Currently, we are assessing the integration of sensory information by huddling behavior in pups. Taken together, our results suggests that Glutamatergic synapses are formed prior to GABAergic synapses in the neocortex and that, in Layer 2/3, synaptogenesis increases abruptly between postnatal day 8 and 9, with Serotonin modulating this abrupt increase.

Disclosures: **S. Naskar:** None. **E. Balzani:** None. **V. Tucci:** None. **L. Cancedda:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.11

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: GM092914

MH071674

S10RR025524

Title: Activation of Rac by the guanine nucleotide exchange factor (GEF) Asef2 regulates dendritic spine formation through a spinophilin-dependent targeting mechanism

Authors: C. M. ROBINSON, J. C. EVANS, M. SHI, *D. J. WEBB;
Biol. Sci., Vanderbilt Univ., Nashville, TN

Abstract: Dendritic spines are small, actin-rich protrusions that comprise the postsynaptic terminals of excitatory synapses. Rho family GTPases, which include Rac, Rho, and Cdc42, are key regulators of dendritic spine formation through their ability to control actin dynamics. However, the upstream and downstream signals that modulate Rho GTPases in spine formation are not well understood. In this study, we show that the Rho family GEF Asef2 promotes dendritic spine formation through activation of Rac. Knockdown of Asef2 with shRNAs causes a decrease in the number of spines and synapses, whereas expression of GFP-tagged Asef2 results in an increase in spine and synapse density. The Asef2-mediated effect on spines and synapses is abolished by expression of Asef2 GEF-activity-deficient mutants or by knockdown of Rac, suggesting that Asef2-Rac signaling is critical for dendritic spine formation. Because the F-actin binding protein spinophilin localizes to dendritic spines and associates with Asef2, we hypothesized that spinophilin has a role in Asef2-mediated spine formation. Indeed, Asef2 is recruited to dendritic spines by spinophilin. In addition, knockdown of spinophilin negates the Asef2-mediated effect on spine and synapse formation, suggesting that the recruitment of Asef2 to spines by spinophilin is critical for spine formation. Collectively, our data demonstrate that spinophilin-Asef2-Rac signaling is an important, new mechanism for regulating dendritic spine and synapse formation. Interestingly, alterations in the Asef2 gene have been linked to autism and to the co-occurrence of alcohol dependence and depression, which are disorders associated with dendritic spine defects, suggesting that the Asef2 signaling pathway is crucial for maintaining normal cognitive and behavioral functions.

Disclosures: **C.M. Robinson:** None. **J.C. Evans:** None. **M. Shi:** None. **D.J. Webb:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.12

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant NS069844

Title: The kinesin motor unc-104/KIF1A promotes synaptogenesis by restraining the Wallenda/DLK MAP kinase signaling cascade

Authors: ***J. LI**[1], Y. ZHANG[2], P. SOPPINA[1], R. HUME[1], T. RASSE[2], C. COLLINS[1]; [1]MCDB, Univ. of Michigan, Ann Arbor, MI; [2]Res. Group Synaptic Plasticity, Hertie Inst. for Clin. Brain Res., Univ. of Tübingen, Tübingen, Germany

Abstract: A functional synapse requires the synthesis and localization of synaptic vesicles, concomitant with the assembly and positioning of cytomatrix components of the pre-synaptic active zone, however the cellular events that regulate this process are still poorly understood. Previous studies have suggested an important role for the unc-104/KIF1A motor in the transport of synaptic vesicle precursors and active zone components to the synapse. It is therefore surprising that synaptic defects in *unc-104* mutants can be rescued independently of the global defects in axonal transport. Mutations in the MAPKKK Wallenda (Wnd)/DLK and downstream signaling components JNK and Fos rescue the active zone assembly impairment, synaptic vesicles loss and electrophysiological defects of multiple hypomorphic mutations in *unc-104*. Our findings, using the *Drosophila* neuromuscular junction (NMJ) as a model synapse, indicate that the synaptic assembly defects in *unc-104* mutants are largely due to over-active Wnd/DLK signaling: loss of *unc-104* function leads to activation of a transcriptional reporter for Wnd/DLK signaling, nerve terminal overgrowth, and enhanced axonal regeneration, all of which depend on Wnd/DLK pathway function. Wnd protein is misregulated in *unc-104* mutants, and ectopic activation of Wnd signaling in motoneurons causes synaptic assembly and neurotransmission defects that mimic loss of *unc-104*. These findings highlight an important role for Wnd in regulating synaptogenesis, as well as an intriguing relationship with a kinesin motor. This role is independent (and likely upstream) of other unc-104 synaptogenetic cargos, liprin-α and Rab3. Rather than directly influencing unc-104's transport functions, the Wnd signaling pathway plays a regulatory role downstream of unc-104 in synaptogenesis by controlling the protein level of components of synaptic vesicles and pre-synaptic active zones. The regulation of Wnd by unc-104 reveals a mechanism for globally coordinating the synthesis of synaptic proteins with their transport. Taken together with previous findings that Wnd/DLK promotes the regenerated growth of injured axons and unc-104 promotes synapse formation, we propose that the Wnd signaling pathway under the control of unc-104 is generally utilized during development and plasticity to coordinate a switch between states of axons: axons that are growing but not forming synapses (when Wnd signaling is on and unc-104 is inactive), versus axons that are primed to form synaptic contacts (when Wnd signaling is off and unc-104 is active).

Disclosures: J. Li: None. **Y. Zhang:** None. **P. Soppina:** None. **R. Hume:** None. **T. Rasse:** None. **C. Collins:** None.

Nanosymposium

104. Synaptogenesis and Activity-Dependent Development

Location: N426A

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 104.13

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant K99NS085035

NIH Grant R21NS076950

Title: Molecular mechanisms of electrical synapse formation

Authors: *A. MILLER, A. WHITEBIRCH, A. SHAH, C. MOENS;
Div. of Basic Sci., Fred Hutchinson Cancer Res. Ctr., Seattle, WA

Abstract: Camillo Golgi and Santiago Ramón y Cajal famously argued over whether the nervous system was one big syncytium or instead a network of independent units. While Cajal won the day and it is clear that neurons are separate units, communication between neurons can occur directly at electrical synapses. Electrical synapses are created by gap junction (GJ) channels between neurons and allow direct cytoplasmic communication. While we know electrical synapses are important for nervous system function, we know little about the molecular mechanisms that build neuronal GJs. We have utilized the zebrafish Mauthner (M) circuit to identify mutations that affect electrical synaptogenesis and identified two classes of mutants: 1) the Disconnect (Dis) class, which disrupts synapse formation, and 2) the Amped (Amp) class, which cause ectopic synapses to form. We found that the Dis3 mutation disrupts a homologue of connexin36 (cx36), the main, mammalian neuronal GJ forming gene. During GJ formation, both the pre- and postsynaptic neurons contribute hemichannels composed of hexamers of Cx protein to form GJs. Despite this apparent simplicity, GJs can contain multiple different Cx proteins, which can affect their functional properties. Through genome gazing we found that zebrafish have four orthologous cx36-like genes, cx34a (Dis3), cx34b, cx35a, and cx35b, but their roles in synaptogenesis are unclear. We developed a CRISPR-based *in vivo* screen and found that only cx34a and cx35a were required for M synapse formation. We further found that Cx34a is required exclusively postsynaptically, while Cx35a is required exclusively presynaptically, for synaptogenesis. Our CRISPR screen also identified a scaffolding molecule that is required exclusively postsynaptically for synapse formation. Together we conclude that vertebrate electrical synapses can be molecularly asymmetric in GJ composition, but also at the level of intracellular scaffolding. These asymmetries suggest a molecular mechanism for generating signaling unidirectionality across the synapses and further suggest that we are just scratching the surface of electrical synapse complexity. Moreover, this work represents the first steps into understanding the molecular mechanisms of how electrical synapses form and allows Golgi to rest a bit easier.

Disclosures: **A. Miller:** None. **A. Whitebirch:** None. **A. Shah:** None. **C. Moens:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.01

Topic: B.08. Synaptic Plasticity

Support: EMBL

Title: Microglia contribute to autism-related functional connectivity and behavioral deficits

Authors: *C. T. GROSS;
EMBL, Monterotondo (RM), Italy

Abstract: Microglia are cells of the myeloid lineage that infiltrate the brain during development and play a role both in the maturation of brain circuits and in its response to inflammation and injury. During early development microglia phagocytosis is important for removing whole neurons, while later in development it appears to have a role in selectively eliminating synapses. We and others have shown that mutations that block neuron-microglia signaling are able to interfere with this phagocytic function and result in deficits in brain wiring. Specifically, we have shown that mice lacking the neuron-microglia signaling chemokine Cx3cl1 show an overabundance of weak synaptic contacts, presumably due to a deficit in synaptic elimination and maturation. We found that these deficits were associated with widespread weak functional brain connectivity and deficient social and repetitive behavior, all hallmarks of autism. These findings propose for the first time a specific neurophysiological deficit for weak functional connectivity and open the possibility that deficits in microglia function could contribute to key features of autism.

Disclosures: **C.T. Gross:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.02

Topic: B.08. Synaptic Plasticity

Support: NIH;NINDS GRANT R01NS084298

grant from CHDI

Title: A pathogenic interaction between complement and microglia drives early loss of synapses in Huntington's disease

Authors: D. WILTON[1], M. HELLER[1], A. FROUIN[1], A. DAGGETT[2], W. YANG[2], *B. A. STEVENS[3];
[1]Boston Children's Hosp., Boston, MA; [2]UCLA, Los Angeles, CA; [3]Childrens Hosp. Kirby Ctr., Childrens Hosp., Boston, MA

Abstract: Synapse loss is a hallmark of many neurodegenerative diseases including Huntington's disease HD (Graveland et al., 1995; Ferrante et al., 1991; Mucke et al., 2012). HD pathology involves reduced synaptic transmission in the basal ganglion and loss of synaptic proteins. Despite synaptic dysfunction being one of the earliest events in HD pathology, the mechanisms driving synapse loss remain unknown. During development, synapse loss as a result of pruning is a normal and highly regulated process required for the correct wiring of the brain. Our laboratory along with others have shown that microglia play a key role in regulating this process (Schafer et al., 2012; Paolicelli et al., 2011). In the developing mouse visual system, microglia phagocytose synapses that are undergoing pruning in a manner that is dependent on complement (C1q, C3 and CR3) and neuronal activity (Stevens et al., 2007; Schafer et al 2012;). Our data suggest a model in which less active synapses are selectively labeled with complement and then engulfed by microglia that express complement receptors (CR3/Cd11b). In Huntington's disease, microglial activation is an early event in HD pathology and upregulation of complement components has been detected in post-mortem tissue. We hypothesize that the developmental mechanism of microglia-mediated synaptic pruning is aberrantly reactivated early in Huntington's disease (HD) pathology and mediates early synapse loss and dysfunction. In support of this hypothesis, preliminary data from two HD models (BACHD, zQ175) show that phagocytic microglia are enriched in disease affected regions (striatum and motor cortex) and engulf cortico-striatal synapses prior to the appearance of motor and cognitive deficits. Super-resolution microscopy reveals that complement proteins localize to vulnerable cortico-striatal synapses during periods of active synapse loss and treatment with a novel C1q blocking antibody is able to reduce synapse loss in these HD models. Together, these results suggest that aberrant interactions between the complement system and microglia may drive early loss of cortico-striatal synapses and contribute to behavioral deficits and neurodegenerative pathology in HD.

Disclosures: **D. Wilton:** None. **M. Heller:** None. **A. Frouin:** None. **A. Daggett:** None. **W. Yang:** None. **B.A. Stevens:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.03

Topic: B.08. Synaptic Plasticity

Support: NIH Grant RO1 EY019277

NIH Grant F31 NS086241-01A1

Title: Norepinephrine mediates changes in microglial dynamics during sleep and wake states

Authors: *G. O. SIPE, A. K. MAJEWSKA;
Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: Microglia are the brain's resident immune cells and play critical roles in functions such as defense against infection, disease and injury as well as network development, synaptic plasticity and adult neurogenesis. The majority of studies investigating microglial process dynamics in health and disease have been carried out in anesthetized animals, which typically exhibit a slow-wave sleep-like state. Given that slow-wave sleep is critical for synaptic development, network maintenance, and post-injury recovery, and microglia are implicated in facilitating all these processes, we wondered whether microglia may have different roles in the brain depending on arousal state. While the biological basis for sleep's effect on the brain is not well understood, we hypothesized that microglial implement their dynamic homeostatic and immune functions preferentially during sleep states. In order to test this hypothesis, we determined microglial motility in anesthetized and awake states. We used the CX3CR1-GFP mouse line to quantify *in vivo* basal microglial motility and found that microglia have significantly reduced motility in awake animals, resulting in decreased formation of pseudopodia and consequently tissue surveillance. We then investigated whether noradrenergic signaling, known to contribute to changes in arousal, contributes to the decreased microglial motility during wake states. By pharmacological stimulating beta-2 noradrenergic receptors, which are enriched in microglia, we observed decreased motility in anesthetized animals demonstrating that noradrenergic stimulation is sufficient to inhibit microglial motility. Recent evidence has implicated microglia as being active participants in ocular dominance plasticity, a role that likely depends upon their process motility. To begin to test whether microglial roles in ocular dominance plasticity require sleep state-like process motility, we monocularly deprived animals for 4 days to induce an ocular dominance shift in binocular visual cortex, while simultaneously injecting the beta-2 agonist salmeterol every 12 hours. We observed that animals continuously

injected with beta-2 agonists did not have an ocular dominance shift, suggesting that chronic inhibition of microglial motility prevents the structural remodeling of neuronal networks. Our results suggest that microglial functions may depend on periods of sleep and that disruptions of sleep may lead to disrupted tissue homeostasis and/or poor post-injury outcomes.

Disclosures: **G.O. Sipe:** None. **A.K. Majewska:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.04

Topic: B.08. Synaptic Plasticity

Support: K01DK100616

Title: Obesity promotes synaptic stripping by increasing microglial sensitivity to neuronal chemoattractants

Authors: *A. M. STRANAHAN;
Neurosci. and Regenerative Med., Med. Col. of Georgia, Augusta, GA

Abstract: Obesity is associated with chronic inflammation and cytokines in the obese systemic environment infiltrate the brain parenchyma. Exposure to inflammatory cytokines activates microglia, the primary immune cell population in the brain, and hippocampal inflammation may mediate increased vulnerability to age-related cognitive impairment in obesity. Microglial activation and synaptic deficits are present in models of obesity, but interrelationships between these processes remain poorly understood. We isolated primary microglia from mice maintained on high- or low-fat diets (HFD, LFD) to determine whether obesity promotes internalization of neuronal synapses, or 'synaptic stripping.' Initial studies evaluated microglial internalization of subcellular fractions labeled with a pH-sensitive fluorophore (pHrodo). Comparison of pHrodo-labeled synaptosomes, nuclei, or mitochondria revealed that microglia from HFD mice exhibit significantly greater uptake of synaptosomes, relative to LFD microglia. Uptake of other fractions was similar in cells from HFD or LFD mice. These findings were consistent with increased overlap between microglial processes and hippocampal synaptic puncta in tissue from HFD mice. Microglia are highly motile, and static analyses do not address mechanisms for colocalization with synapses in obesity. To generate a more dynamic measure, we performed time-lapse imaging in the presence of nucleosides, growth factors, and cytokines that promote attraction between microglia and neurons. Primary microglia from HFD or LFD mice were

stimulated with ATP, M-CSF, or Complement 3 (C3) followed by visualization of actin redistribution. Microglia from HFD mice showed greater membrane ruffling and process outgrowth in the presence of C3, and increased actin redistribution relative to LFD microglia. Because obesity also increased C3 receptor (C3R) expression, we subsequently applied synaptosomes to microglia from HFD or LFD mice in the presence of a C3R inhibitor. Inhibiting C3R blocked the effect of obesity, suggesting that microglia in the obese brain exhibit more aggressive synaptic stripping and greater sensitivity to eat-me signals. While more studies will be necessary to determine whether synaptic phagocytosis contributes to hippocampal dysfunction in obesity, the data are consistent with reports of increased rates of dementia among obese individuals. Understanding how obesity-induced inflammatory signaling influences the brain could lead to new treatments that attenuate risk in vulnerable populations.

Disclosures: A.M. Stranahan: None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.05

Topic: B.08. Synaptic Plasticity

Support: Smith Family Foundation

Dana Foundation

John Merck Scholars Program

NIH R01-NS-07100801

Title: Innate immune molecules protect synapses from excess microglia-mediated pruning during CNS development

Authors: *E. K. LEHRMAN[1,2], D. K. WILTON[1], S. T. CHANG[1], A. FROUIN[1], C. A. WELSH[1,2], H. UMEMORI[1], B. STEVENS[1,2];
[1]Neurobio., Boston Children's Hosp., Boston, MA; [2]Program in Neurosci., Harvard Med. Sch., Boston, MA

Abstract: Microglia, the brain's resident immune cells and phagocytes, are emerging as critical regulators of developing synaptic circuits in the healthy brain. Recent studies from our lab and others indicate that microglia engulf synapses in the developing brain; however, how microglia

know which specific synapses to target for removal remains a major open question. We found that microglia are one of the major cellular effectors mediating developmental synaptic refinement, and that their activity-dependent engulfment of presynaptic inputs in the dorsal lateral geniculate nucleus of the thalamus (dLGN) may underlie the removal of weak or overlapping inputs necessary to establish mature synaptic circuits (Schafer et al., 2012). We identified C1q, C3, and microglial C3 receptor, CR3, as required for promoting microglial phagocytosis of retinogeniculate inputs and normal synaptic refinement (Bialas and Stevens, 2013, Schafer et al., 2012, Stevens et al., 2007). As these molecules are classic innate immune signals known for directing macrophages to phagocytose apoptotic cells or debris, our findings suggest that microglia-mediated pruning may be analogous to the removal of non-self material by phagocytes in the immune system. To prevent bystander damage during an immune response, the immune system employs protective signals to inhibit inappropriate phagocytosis of healthy self cells. We hypothesize that these protective signals are also required in the CNS to prevent inappropriate microglial engulfment of necessary connections during synaptic refinement. In support of this, we have identified an immune protective signal that is enriched in the dLGN during peak pruning and required to prevent excess microglial engulfment of synaptic inputs. Its receptor is primarily expressed by microglia in the dLGN during peak pruning and downregulated by microglia in adulthood. Mice lacking the protective signal exhibit increased microglial engulfment of retinogeniculate inputs during peak pruning as well as overpruning of eye-specific territories in the developing dLGN. Moreover, this increased engulfment may lead to reduced synapse numbers in adulthood, with a specific loss of retinogeniculate synapses. These data are the first to demonstrate that “breaks” on microglial phagocytosis are required to protect necessary connections from inappropriate removal. Microglia-mediated synaptic refinement thus appears to depend on a careful balance of positive and negative regulators of phagocytosis, and understanding the consequences of disrupting this balance may provide insight into disorders characterized by immune dysregulation and circuit abnormalities.

Disclosures: **E.K. Lehrman:** None. **D.K. Wilton:** None. **S.T. Chang:** None. **A. Frouin:** None. **C.A. Welsh:** None. **H. Umemori:** None. **B. Stevens:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.06

Topic: B.08. Synaptic Plasticity

Support: NIH R01-NS060125

Title: Interleukin-1β alters cortical connectivity through dynamic changes in IL-1β receptor localization and MHCI signaling

Authors: *A. MCALLISTER, M. ESTES;
Ctr. for Neurosci., UC Davis, Davis, CA

Abstract: There is growing evidence for a critical role for neuroimmune interactions in brain development and both genetic associations and environmental risk factors implicate immune molecules in neurodevelopmental disorders. Recent genetic data from multiple large cohorts of individuals with autism spectrum disorder (ASD) and schizophrenia (SZ) demonstrate associations with genes encoding immune molecules, including several cytokines and their receptors as well as genes within the major histocompatibility complex (MHC). Among the cytokines, the interleukin (IL)-1 family is enriched in genetic mutations associated with ASD and SZ. In addition to genetic associations, there is increasingly compelling evidence for environmental risk factors that alter immune responses, especially maternal infection during the late first trimester, for both disorders. During brain development, immune molecules are present at synapses where they regulate synapse formation and function. In the CNS, IL-1 receptor complex co-receptors, IL1RAPL1 and IL-1RAcP, function as central synaptic organizers through trans-synaptic interactions with PTPδ. We recently discovered that IL-1β, acting through this receptor complex, bi-directionally regulates cortical connectivity in a dose-dependent manner. IL-1β levels are also altered in the brain of postnatal offspring in a mouse model of maternal infection (MIA), suggesting that IL-1β signaling might mediate the effects of MIA in altering connectivity and leading to SZ and ASD-like behaviors. Indeed, both IL-1β and MIA appear to decrease synapse density through altering the synaptic localization of IL1RAPL1 and IL-1RAcP. These elevated levels of IL-1β also increase MHCI expression on neurons and MEF2 signaling, which are required for IL-1β to decrease synapse density. We are currently studying the relationship between these two immune pathways in synaptogenesis during development and in disease, which may be a central mechanism underlying aberrant cortical connectivity in SZ and ASD.

Disclosures: A. McAllister: None. **M. Estes:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.07

Topic: B.08. Synaptic Plasticity

Support: NIH grant 1F30AG046044-01A1

Title: MHCI promotes developmental synapse elimination and aging-related synapse loss at the vertebrate neuromuscular junction

Authors: *L. M. BOULANGER[1], M. M. TETRUASHVILY[2], M. MCDONALD[3];
[1]Mol. Biol. and Princeton Neurosci. Inst., [2]Mol. Biol., Princeton Univ., Princeton, NJ; [3]UCSD, San Diego, CA

Abstract: The neuromuscular junction (NMJ) is the sole site of communication between motor neurons and muscle fibers. With aging, this motor neuron-muscle link is disrupted, leaving some muscle fibers completely disconnected from nervous system control. Muscle denervation is a major cause of loss of independence and increased morbidity and mortality in the elderly. Retraction of motor neuron axons from muscle motor end plates is a feature of normal development that also occurs with aging. During development, each muscle fiber is initially contacted by multiple motor neurons. By the end of the second postnatal week, in mice, most motor neuron axon branches have retracted, leaving mature muscle fibers singly-innervated. We find that developmental synapse elimination at the NMJ is promoted by specific immune proteins, members of the major histocompatibility complex class I (MHCI). Multiple members of the large MHCI gene family are expressed at the NMJ when synapse elimination is occurring, and developmental synapse elimination at the NMJ is persistently impaired in two different lines of MHCI-deficient mutant mice: $\beta 2m^{-/-}TAP^{-/-}$ mice, which lack stable cell-surface expression of most MHCI proteins, and $K^{b-/-}D^{b-/-}$ mice, which lack the classical MHCIs *H-2K* and *H-2D*. Furthermore, synapse elimination is modestly but significantly accelerated in mice that overexpress the classical MHCI *H-2D* under the control of the neuron-specific enolase promoter (*NSE-D^b* mice). Thus classical MHCIs promote synapse elimination at the developing NMJ, and modifying MHCI expression can bidirectionally regulate synapse elimination: decreasing MHCI expression disrupts synapse elimination, while increasing MHCI levels accelerates synapse elimination. MHCI mRNA levels increase in aging MNs that are vulnerable to aging-related denervation, but MHCI expression is relatively low in MNs that are resistant to aging-related denervation (e.g., the extraocular muscles). We find that aging-related muscle denervation is reduced in MHCI-deficient mice. These results suggest that aberrant re-activation of MHCI-dependent synapse elimination mechanisms might contribute to denervation of aging muscle. They also raise the possibility that reducing MHCI expression in aging motor neurons could protect against aging-related muscle denervation.

Disclosures: L.M. Boulanger: None. **M.M. Tetruashvily:** None. **M. McDonald:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.08

Topic: B.08. Synaptic Plasticity

Support: NIH Grant Number NINDS R01NS059867

Title: The innate-immune receptor PGRP-LC controls presynaptic homeostatic plasticity

Authors: *N. HARRIS[1], D. BRASIER[2], D. K. DICKMAN[3], G. W. DAVIS[1];
[1]UCSF, San Francisco, CA; [2]Carnegie Mellon Univ., Pittsburgh, PA; [3]USC, Los Angeles, CA

Abstract: It is now appreciated that the brain is immunologically active. Highly conserved innate immune signaling responds to pathogen invasion, injury and promotes structural refinement of neural circuitry. However, it remains generally unknown whether innate immune signaling has a function during the day-to-day regulation of neural function in the absence of pathogens and irrespective of cellular damage or developmental change. We have identified an innate immune receptor, a member of the peptidoglycan pattern recognition receptor family (PGRP-LC), that is required for the induction and sustained expression of homeostatic synaptic plasticity. This receptor functions presynaptically, controlling the homeostatic modulation of the readily releasable pool of synaptic vesicles following inhibition of postsynaptic glutamate receptor function. Thus, PGRP-LC is a candidate receptor for retrograde, trans-synaptic signaling, a novel activity for innate immune signaling and the first known function of a PGRP-type receptor in the nervous system of any organism.

Disclosures: **N. Harris:** None. **D. Brasier:** None. **D.K. Dickman:** None. **G.W. Davis:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.09

Topic: B.08. Synaptic Plasticity

Support: P50

Title: Alterations in adolescent stress cascades in genetic and environmental mouse models of major mental illness and the implications on adult behavioral deficits

Authors: *L. N. HAYES, K. AN, S. BARODIA, J. MOORE, S.-H. KIM, H. JAARO-PELED, D. FUKUDOME, T. FAUST, M. NIWA, A. SAWA;
Psychiatry, Johns Hopkins Univ., Baltimore, MD

Abstract: Adult-onset major mental illnesses, such as psychotic and mood disorders, are caused by multiple genetic and environmental factors, but a common pathophysiological mechanism in the developmental trajectory may exist. Our central hypothesis is that changes in stress cascades from adolescence are connected to aberrant synaptic pruning, which in turn leads to behavioral abnormalities in adulthood. We provided data from two distinct models both exhibiting behavioral abnormalities relevant to psychotic disorders only after adolescence. First, maternal immune activation (MIA) elicited by polyinosinic:polycytidylic acid at embryonic day 9 displayed increased glucocorticoids and blunted immune response particularly in microglia in young adulthood. Second, the CAMKII::DN-DISC1 Tg mice, in which the dominant negative DISC1 transgene is expressed under the CaMKII promoter, showed increased oxidative stress, glucocorticoids, and cytokines in young adulthood. In addition, the DISC1 model displayed a reduction in spine density between P42-P49. Furthermore, administration of a compound FRAX486 during the critical period in adolescence ameliorated the spine changes and behavioral deficits (e.g., forced swim test) in adulthood. Data of possible spine changes in MIA will also be discussed.

Disclosures: L.N. Hayes: None. **K. An:** None. **S. Barodia:** None. **J. Moore:** None. **S. Kim:** None. **H. Jaaro-Peled:** None. **D. Fukudome:** None. **T. Faust:** None. **M. Niwa:** None. **A. Sawa:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.10

Topic: B.08. Synaptic Plasticity

Support: NIH Grant MH092351

NIH Grant NS091546

Title: Shared and distinct functions for bloc-1 subunits in the modulation of presynaptic vesicle pools and homeostatic plasticity

Authors: *D. K. DICKMAN, W. MA, J. PALUCH, W. GUO, S. TREVIDI;
Neurobio., USC, Los Angeles, CA

Abstract: The nervous system is endowed with potent and adaptive mechanisms that ensure robust and reliable functionality of synapses, referred to as synaptic homeostasis. Recent evidence indicates that defects in synaptic homeostasis may contribute to the etiology of complex neurological and psychiatric diseases. Presynaptic homeostatic plasticity (PHP) has been observed in organisms ranging from *Drosophila* to humans, where inhibition of postsynaptic receptors leads to a compensatory increase in presynaptic release that restores normal transmission. However, the mechanisms underlying PHP remain enigmatic. Using forward genetic approaches in *Drosophila*, we have previously identified mutations in two genes, the schizophrenia susceptibility gene dysbindin and snapin, to be required for PHP. Dysbindin and Snapin are components of the Biogenesis of Lysosome-related Organelles Complex 1 (BLOC-1), a complex consisting of Dysbindin, Snapin, and six other protein subunits. Biochemical evidence suggests that all eight subunits function as a unit, although this hypothesis has not been rigorously tested using genetic approaches. Further, the role of the BLOC-1 in general, and in the nervous system in particular, is unclear. To determine the function of the BLOC-1, we have generated null mutations in *Drosophila* of a central component, pallidin. We find that like Dysbindin and Snapin, Pallidin traffics to synaptic terminals and is not necessary for synapse morphology at the neuromuscular junction. However, while basal synaptic transmission appears unperturbed, BLOC-1 components are necessary to sustain the full synaptic vesicle pool under high frequency stimulation. Imaging and ultrastructural analyses indicate that endosomal intermediates are disrupted during high activity in the absence of BLOC-1 components, leading to a striking buildup of tubular endosomal structures. We also find that while Dysbindin is necessary for PHP through the modulation of the readily releasable synaptic vesicle pool, Pallidin is dispensable for this process. We present a model in which the entire BLOC-1 complex is necessary to maintain the recycling synaptic vesicle pool under conditions of high activity by facilitating the traffic of vesicles through synaptic endosomal intermediates. However, only a distinct subset of the BLOC-1, including Dysbindin and Snapin, are necessary for the homeostatic modulation of presynaptic release through a specific increase in the readily releasable pool. Together, this reveals shared and distinct functions of BLOC-1 subunits in activity- and plasticity-dependent trafficking of synaptic vesicles.

Disclosures: D.K. Dickman: None. **W. Ma:** None. **J. Paluch:** None. **W. Guo:** None. **S. Trevidi:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.11

Topic: B.08. Synaptic Plasticity

Support: NIH Grant MH100066

NIH Grant MH043784

NIH Grant MH051234

Title: The role of nuclear factor-κB in cortical immune activation in schizophrenia

Authors: *D. W. VOLK, J. R. EDELSON, K. M. ROMAN, A. E. MOROCO, D. A. LEWIS; Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Convergent lines of evidence indicate a key role of immune- and inflammation-related abnormalities in the pathophysiology of schizophrenia, including higher mRNA levels for multiple cytokines and for the viral restriction factor interferon-induced transmembrane protein (IFITM) in the prefrontal cortex (PFC). The transcription factor nuclear factor-κB (NF-κB) directly regulates the expression of the same cytokines and IFITM variants that are overexpressed in schizophrenia, and we recently reported higher mRNA levels for two NF-κB family members (i.e. NF-κB1 and NF-κB2) in the PFC in schizophrenia. Furthermore, NF-κB transcriptional activity is initiated through multiple canonical and non-canonical pathways that involve a diverse collection of receptors, DNA binding inhibitors, and disinhibiting kinases. In addition, evidence of immune disturbances has also been reported for bipolar disorder (BP) and major depressive disorder (MDD). Consequently, we determined whether other NF-κB family members and components of canonical and non-canonical pathways that activate NF-κB are similarly over-expressed in schizophrenia, BP, and MDD using quantitative PCR in PFC area 9 from 62 schizophrenia subjects individually matched to healthy subjects for sex and age and also from 19 triads of BP, MDD and healthy subjects. In schizophrenia subjects, we found higher mRNA levels for 1) other NF-κB family members, including RelA and c-Rel but not RelB, 2) multiple receptors that initiate NF-κB signaling (e.g., TLR4, IL-1R, LTβR, CD40, RANK), 3) inhibitors that bind to, interfere with, and are themselves induced by NF-κB (e.g., IκBα, IκBβ, but not IκBε) and 4) kinases that phosphorylate and allow IκBs to be degraded (e.g., IKKα, IKKβ, IKKγ). Transcript levels for NF-κB2 and c-Rel, but not other NF-κB-related markers, were higher in BP, while mRNA levels of NF-κB-related markers were not altered in MDD. The convergent findings of higher mRNA levels of 1) multiple NF-κB family members, 2) canonical and non-canonical pathway markers that initiate NF-κB signaling, and 3) immune markers that are reported to be induced by NF-κB (i.e. IκBs, cytokines, and IFITM) suggest that NF-κB transcriptional activity is elevated in schizophrenia. Given the central role of NF-κB as a transcriptional regulator of immune activation, higher NF-κB activity may represent a molecular

hub that promotes greater transcription of a wide array of immune-related markers in the PFC in schizophrenia but not in mood disorders. Taken together, these studies support further investigation into the potential role of NF-κB-related markers as therapeutic targets in schizophrenia.

Disclosures: **D.W. Volk:** None. **J.R. Edelson:** None. **K.M. Roman:** None. **A.E. Moroco:** None. **D.A. Lewis:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Autifony-consultant, Bristol-Myers Squibb-investigator initiated research support, Concert Pharmaceuticals-consultant, Sunovion-consultant, Pfizer-investigator initiated research support.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.12

Topic: B.08. Synaptic Plasticity

Support: Hartwell foundation

NIH T32-AI007496

NIH NS081026

SFARI

RSRT

Title: Anti-microbial immune mediators promote social behavior by maintaining proper neuronal connectivity

Authors: ***A. J. FILIANO**[1], Y. XU[3], N. J. TUSTISON[2], R. MARSH[1], I. SMIRNOV[1], S. P. GADANI[1], V. LITVAK[3], J. KIPNIS[1];
[1]Neurosci., [2]Radiology and Med. Imaging, Univ. of Virginia, Charlottesville, VA; [3]Microbiology and Physiological Systems, Univ. of Massachusetts, Worcester, MA

Abstract: Immune dysfunction is observed in numerous neurological conditions that feature social deficits as a core symptom, such as autism spectrum disorder (ASD). Whether immune dysfunction directly contributes to the pathogenesis of ASD or is a product of an alternative

etiology is unknown. To test this, we manipulated mouse peripheral and central immune systems, both genetically and pharmacologically, and measured behavior and neuronal connectivity. Immune deficiency caused social deficits and aberrant hyper-connectivity in many fronto-cortical nodes. These social deficits and the aberrant hyper-connectivity were rescued by restoring the immune system integrity. We further determined the soluble mediators that are released from the peripheral immune cells and are affecting both central immunity (microglia) and neurons. Interestingly, these mediators are all involved in anti-microbial and anti-viral immune responses. We analyzed the transcriptomes of multiple organisms and determined a link between social behavior and immune gene signatures. Our data suggest that some immune genes may be essential to a co-evolutionary arms race between the necessity for organisms to be social and the greater propensity to spread pathogens as organisms aggregate.

Disclosures: **A.J. Filiano:** None. **Y. Xu:** None. **N.J. Tustison:** None. **R. Marsh:** None. **I. Smirnov:** None. **S.P. Gadani:** None. **V. Litvak:** None. **J. Kipnis:** None.

Nanosymposium

105. Role of Immune System Molecules in Synaptic Plasticity

Location: S404

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 105.13

Topic: B.08. Synaptic Plasticity

Support: NIH grant EY02858

NIH grant MH07166

The Mathers Charitable Foundation

The Ruth K. Broad Biomedical Research Foundation

The Rosenberg Family Foundation

Title: Enhancing learning and memory via the presynaptic action of PirB receptor

Authors: *M. DJURISIC[1], M. SHAMLOO[2], C. SHATZ[1];
[1]Dept Biol Sci., Bio-X, Stanford Univ., Stanford, CA; [2]Dept. of Neurosurg., Stanford Univ., Stanford, CA

Abstract: The hippocampus plays a crucial role in learning and memory consolidation throughout life. Mechanisms of synaptic plasticity such as long-term potentiation (LTP) and

long-term depression (LTD) are thought to be cellular correlates of learning and memory. Thus, manipulations that enhance plasticity are of interest as a means of enhancing cognition. The innate immune receptor Paired Immunoglobulin-like Receptor B (PirB) is expressed in forebrain pyramidal neurons including hippocampus. PirB is also a receptor for Beta amyloid; congruently, genetic deletion of PirB in mouse models of Alzheimer's disease protects against memory loss. Here, we examine PirB's role in hippocampal synaptic plasticity, learning and memory. Either germ-line (PirB-/-) or conditional excision (cKO) of PirB in excitatory neurons of CA3 and CA1 regions of hippocampus, result in LTD at CA3-CA1 synapses that is deficient using the standard low-frequency induction protocol; paradoxically, a modest LTP is observed. In WT, LTD expression at CA3-CA1 synapses is accompanied by a decrease in probability of release (Pr), a mechanism known to be cannabinoid receptor type 1 (CB1R)-dependent. However, this decrease in Pr is not observed in PirB-/- or cKO mice, a finding that can explain the deficient LTD in these mice. Consistent with this shift in Hebbian synaptic plasticity favoring LTP, PirB-/- mice perform better on hippocampus-dependent learning and memory tasks. For example, in fear conditioning, PirB-/- mice acquire the task approximately twice as fast as WT; on the subsequent cued and contextual recall of fear conditioning, PirB-/- mice spent 2-3X more time freezing than WT. Together, results suggest that PirB is part of a signaling network that regulates Hebbian synaptic plasticity by modulating presynaptic parameters such as release probability. Therapeutically, pharmacological blockade of PirB could result in cognitive enhancement, and might be useful for treating memory impairment in Alzheimer's disease.

Disclosures: **M. Djurisic:** None. **M. Shamloo:** None. **C. Shatz:** None.

Nanosymposium

106. Tauopathy and Dementia

Location: S403

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 106.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The effect of pathogenic transgene suppression on synapse dynamics during tauopathy

Authors: ***J. S. JACKSON**[1], J. D. JOHNSON[1,2], Z. AHMED[1], S. MEFTAH[1], M. L. HUTTON[1], J. T. ISAAC[1], M. C. ASHBY[2], M. J. O'NEILL[1];
[1]Lilly UK, Windlesham, United Kingdom; [2]Univ. of Bristol, Bristol, United Kingdom

Abstract: The pathological accumulation of tau is associated with a number of diseases including Alzheimer's Disease (AD). A severe loss of synapses occurs at the early clinical stages and has been correlated with cognitive deficits in AD patients; however the time course of this

synapse loss and how the turnover of synapses is affected are relatively unknown. Here we use *in vivo* two-photon microscopy to assess the temporal dynamics of axonal boutons and dendritic spines in a transgenic mouse model of human tauopathy, rTg4510, which expresses the P301L tau mutation downstream of a tetracycline-operon-responsive element. Adeno-associated virus expressing GFP was injected into the layer 2/3 of the cerebral cortex to enable the visualisation of neurons and a cranial window was implanted for long-term imaging of the somatosensory cortex. GFP-labelled neurons were imaged weekly between five and twelve months of age. This time period spans the onset of pathology through to severe cortical neurodegeneration in this model. The gross morphology of axons and dendrites and the dynamics of their synaptic structures were assessed in wild-type and transgenic mice of different ages as pathology progresses. In addition, a third group of animals received doxycycline to determine the effects of suppressing the pathogenic P301L transgene on synaptic structures and neurite morphology. Weekly imaging of a period of over six months enabled the dynamics of synapses to be determined at a temporal resolution which has not previously been reported in wild-type animals or in a tauopathy model. Gross morphological changes such as the presence of dystrophic neurites were visible as the pathology progressed. These dystrophic neurites were found to have a distinctive morphological phenotype prior to degeneration. Alongside this, synapse loss and changes in the stability of synapses were also present. These synaptic and morphological changes and the effects of transgene suppression will inform subsequent drug discovery studies to identify novel therapies to stabilize synapse loss in AD and other tauopathies.

Disclosures: **J.S. Jackson:** A. Employment/Salary (full or part-time); Eli Lilly. **J.D. Johnson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Eli Lilly. **Z. Ahmed:** A. Employment/Salary (full or part-time); Eli Lilly. **S. Meftah:** A. Employment/Salary (full or part-time); Eli Lilly. **M.L. Hutton:** A. Employment/Salary (full or part-time); Eli Lilly. **J.T. Isaac:** A. Employment/Salary (full or part-time); Eli Lilly. **M.C. Ashby:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Eli Lilly. **M.J. O'Neill:** A. Employment/Salary (full or part-time); Eli Lilly.

Nanosymposium

106. Tauopathy and Dementia

Location: S403

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 106.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Functional and biochemical characterization of the link between the aggregation of Tau and its toxicity in a novel gene transfer-based rat model of tauopathy

Authors: *M. D'ORANGE[1], A.-P. BEMELMANS[1], G. AUREGAN[1], C. JOSÉPHINE[1], M. GUILLERMIER[1], N. DUFOUR[1], M.-C. GAILLARD[1], M. GUERIF[2], *D. CHERAMY[2], E. DIGUET[2], M. COLIN[3,4,5], L. BUÉE[3,4,5], E. BROUILLET[1], P. HANTRAYE[1], K. CAMBON[1]; [1]CEA, MIRCen, UMR9199 CEA/CNRS/Université Paris Sud, Fontenay Aux Roses, France; [2]Inst. de Recherches Servier, DRD-RDNPS, Croissy sur Seine, France; [3]Inserm, UMR-S 1172, Lille, France; [4]Univ. Lille 2, Faculté de Médecine, IMPRT, JPARC, Lille, France; [5]CMRR, CHR, Lille, France

Abstract: Although Alzheimer's disease (AD) has been well characterized from an anatomo-pathological point of view, its causes remain elusive and an effective disease-modifying therapy is still awaited. While the contribution of Tau to AD neurodegeneration is certain, the relative contribution of soluble oligomers and neurofibrillary tangles (NFTs) to the trigger and progression of the pathology remains largely unknown. NFT numbers have been correlated with cognitive decline and synaptic loss, but they may only reflect the final products of neuroprotective processes against toxic oligomeric Tau. Our aim was to generate a fast-developing model of tauopathy, independently of the beta-amyloid component of AD, to study the role of soluble and aggregated Tau species in the pathological processes leading to dementia. To that purpose, adeno-associated viral vectors (AAV) encoding the human 1N4R Tau isoform were injected in the hippocampus of adult rats. Overexpression of either the wild-type (WT) or the P301L mutant protein induced Tau hyperphosphorylation and its missorting to the somato-dendritic compartment, characteristics of early stages of tauopathy. In addition, we designed a new AAV vector allowing co-expression of WT Tau and a pro-aggregant peptide in a 1:1 stoichiometric ratio. At one month post-injection, while overexpression of WT Tau alone did not lead to its aggregation into fibrils, its co-expression with the pro-aggregant peptide led to the formation of AT100-positive somatic inclusions composed of full-length WT Tau. Animals injected with the P301L mutant-Tau construct presented a slower kinetic of aggregation, starting at 1 month post-injection with neuritic aggregates, and converting into somatic lesions at 3 months post-injection. Preliminary results suggest that the different Tau constructs do not present the same capacities to trigger neurotoxic effects. This could be related to differences in the kinetic of aggregation. Behavioral analysis at 2 months post-injection will help us decipher which species of Tau are responsible for the cognitive deficits. This model, the first in rats to show fast aggregation of the wild-type form of Tau, will be useful to study the pathological pathways linking the aggregation of Tau to neuronal distress and could lead to the identification of new therapeutic targets. It could also facilitate the development of biomarkers by dosage in the CSF and plasma, or using *in vivo* PET imaging.

Disclosures: **M. D'Orange:** None. **A. Bemelmans:** None. **G. Auregan:** None. **C. Joséphine:** None. **M. Guillermier:** None. **N. Dufour:** None. **M. Gaillard:** None. **M. Guerif:** None. **D. Cheramy:** None. **E. Diguet:** None. **M. Colin:** None. **L. Buée:** None. **E. Brouillet:** None. **P. Hantraye:** None. **K. Cambon:** None.

Nanosymposium

106. Tauopathy and Dementia

Location: S403

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 106.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 AG032611

NIH Grant R01 NS077239

NIH Grant R01 AG020197

Title: Specific and epitope-dependent detection of tau aggregates in transgenic tauopathy mice *in vivo*

Authors: *S. KRISHNASWAMY[1], Y. LIN[1], W. J. RAJAMOHAMEDSAIT[1], H. B. RAJAMOHAMEDSAIT[1], E. M. SIGURDSSON[2];
[1]Neurosci. and Physiol., [2]Neurosci. and Physiology, and Psychiatry, New York Univ. Sch. of Med., New York, NY

Abstract: Recently, we reported that peripheral injection of a single-chain variable antibody fragment (scFv) against the tau protein resulted in a strong *in vivo* brain signal in tg tauopathy mice using an *In vivo* Imaging System but not in wt or amyloid-β plaque mice (Krishnaswamy S et al, J Neurosci, 34, 2014). Similar specificity but a weaker signal was observed with 6B2G12, the parent tau monoclonal antibody (mAb). Importantly, signal intensity correlated well with the degree of tau pathology and probe colocalization with intraneuronal tau aggregates. Both were associated with markers of endosomes, autophagosomes and lysosomes, suggesting their interaction in these degradation pathways. Here we compared signal intensity of various mAbs against different tau epitopes in the same tg tauopathy mice (P301L, htau), that received a single intravenous (i.v.) injection of different mAbs. Two doses were compared (50 vs. 250 μg), sometimes in the same animals. At least a week interval was between injections to allow the brain signal to subside to baseline background values. As expected, the larger dose gave several fold higher brain signal for all the mAbs, suggesting that their brain uptake is not saturated at the

lower dose. Generally, 6B2G12 (K_D=10^{-9}-10^{-10} M) led to 2-3 fold stronger signal than: 1) a lower affinity (4E6G7, K_D=10^{-7} M) but more phospho-selective mAb against the same 396,404 epitope; 2) a high affinity (5G2A3, K_D=10^{-9} M) mAb against Asp421 truncated tau, and; 3) a low affinity mAb against conformational tau (2D2, K_D not yet determined). These differences likely reflect both the relative prominence of these tau epitopes in these mice and the affinities of the mAbs. All showed specificity for tau pathology, resulting in a much stronger brain signal in tauopathy mice compared to a very weak brain signal in Aβ plaque- (Tg-SwDI) or wt mice. Limited signal was also detected with control IgG. Importantly, the signal correlated well with the degree of tau pathology and the i.v. injected mAbs partially colocalized with stained neuronal tau aggregates (PHF1, MC1 and tau-5) and markers of endosomes, autophagosomes and lysosomes (EEA1, LC3, P62 and Rab7) as we had observed previously with 6B2G12. Overall, these findings suggest that tau mAbs against different epitopes can be used to assess epitope prominence *in vivo* in mouse models but their affinities are likely to matter as well. Smaller antibody fragments of such imaging probes with even better brain penetration resulting in a stronger brain signal have great potential as clinical imaging ligands.

Disclosures: S. Krishnaswamy: None. **Y. Lin:** None. **W.J. Rajamohamedsait:** None. **H.B. Rajamohamedsait:** None. **E.M. Sigurdsson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; H. Lundbeck A/S. F. Consulting Fees (e.g., advisory boards); H. Lundbeck A/S.

Nanosymposium

106. Tauopathy and Dementia

Location: S403

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 106.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: AAV-delivered human tau propagation and pathology in wild-type and tau knock-out mice

Authors: *S. WEGMANN, M. J. KIRK, R. E. BENNETT, S. NICHOLLS, K. TORO, A. C. S. AMARAL, Z. FAN, L. SAQRAN, S. L. DEVOS, S. TAKEDA, E. HUDRY, B. T. HYMAN; Neurol., Mass Gen. Hosp. / Harvard Med. Sch., Charlestown, MA

Abstract: In different tauopathies, the progressive deposition of tau protein into neurofibrillary tangles (NFTs) suggests a spread of misfolded tau through the neural system. In Alzheimer's disease (AD), pathological tau aggregation occurs in a distinct pattern in connected areas,

suggesting a trans-synaptic propagation of tau through the neural system: tangles form first in the entorhinal cortex from where they spreads through the limbic system, cortical areas, and finally throughout the brain. NFT pathology and spreading can be mimicked in genetic mouse models expressing, for example, human tau carrying the FTDP-17 mutation P301L. To generate a more versatile and adaptable model of tau expression, we use AAV-mediated eGFP-2a-tau expression in mice. This approach benefits from the individual expression of tag-less P301L tau in combination with eGFP labeling of transduced tau expressing neurons. Stereotactic injections of AAV eGFP-2a-P301Ltau into distinct brain areas of different aged mice of different genetic backgrounds facilitated the comparison of tau vulnerability across different neuron populations. Postmortem FACS sorting of GFP-positive transduced neurons allowed the biochemical characterization of tau expressing neurons. Using immunofluorescence labeling of human tau in post-mortem brain sections, we were also able to identify neurons that contained human tau but no GFP, thus received human tau from neighboring or synaptically connected neurons. Such tau propagation between neurons was observed for both wild-type and P301L tau, both in wild-type as well as in tau knock-out mice. These finding suggested a cellular role of tau transmission other than prion-like templated misfolding. We believe that our eGFP-2a-tau AAVs, which can be used *in vitro* and *in vivo*, are great tools to reveal new details of tau biology and tau diseases.

Disclosures: **S. Wegmann:** None. **M.J. Kirk:** None. **R.E. Bennett:** None. **S. Nicholls:** None. **K. Toro:** None. **A.C.S. Amaral:** None. **Z. Fan:** None. **L. Saqran:** None. **S.L. Devos:** None. **S. Takeda:** None. **E. Hudry:** None. **B.T. Hyman:** None.

Nanosymposium

106. Tauopathy and Dementia

Location: S403

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 106.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: ARUK-ESG2014-3

UoB-MRC Centenary Award

Title: Stability of neuronal network function in tauopathy-associated dementia

Authors: *J. WITTON[1], A. D. RANDALL[2,1], M. C. ASHBY[1];
[1]Univ. of Bristol, Bristol, United Kingdom; [2]Univ. of Exeter, Exeter, United Kingdom

Abstract: The formation and deposition of aggregates of tau protein in the brain is characteristic of dementias such as Alzheimer's disease. How tau-associated neuropathology disrupts cellular activity and function however, remains unclear. In this study, using repeated *in vivo* two-photon imaging, we longitudinally assess changes in cortical neuronal population activity as pathology develops in a transgenic mouse model of tauopathy-associated dementia (rTg4510 line). rTg4510 mice overexpress a mutant form of human tau protein, and develop forebrain neurofibrillary tangles, neurodegeneration, and associated cognitive impairments in an age-dependent manner. To assess the effect of this progressive pathology on neuronal network function, neurons in superficial (layer II/III) vibrissal sensory cortex in rTg4510 and wild-type littermate mice were infected with adeno-associated virus driving expression of the genetically encoded Ca^{2+} indicator GCaMP6. The skull dorsal to the infection site was replaced with a glass cranial window to allow optical access for *in vivo* imaging. Activity evoked by deflection of a single whisker was localised to the barrel field in contralateral primary somatosensory cortex using intrinsic optical imaging and widefield fluorescence imaging of GCaMP6. Spontaneous and sensory stimulation-evoked Ca^{2+} transients from groups of individual neurons in these regions were then repeatedly imaged in GCaMP6 expressing neurons in lightly anaesthetised, head-fixed mice using two-photon microscopy. Imaging sessions were performed at regular intervals between 5-to-7 months, an age range that spans the emergence and establishment of cortical degeneration in these mice. Analysis of the short-term (within session) and longer-term (week-to-week) dynamics of neuronal activity at the regional, population and individual cell levels are used to establish the effect of tau-based pathology on the stability of cortical representation of sensory activation.

Disclosures: J. Witton: None. **A.D. Randall:** None. **M.C. Ashby:** None.

Nanosymposium

106. Tauopathy and Dementia

Location: S403

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 106.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The Strategic Research Program for Brain Sciences of the Ministry of Education, Culture, Sports, Science and Technology of Japan

CREST/JST

Title: Quality loss of FUS and SFPQ alters the ratio of Tau isoforms, which recapitulates FTLD accompanied with aberrant adult neurogenesis

Authors: *S. ISHIGAKI[1], Y. FUJIOKA[1], D. HONDA[1], S. YOKOI[1], H. OKADO[2], H. WATANABE[1], M. KATSUNO[1], G. SOBUE[1];
[1]Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan; [2]Tokyo Metropolitan Inst. of Med. Sci., Tokyo, Japan

Abstract: Fused in sarcoma (FUS) is genetically and clinicopathologically linked to amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). We found that the intranuclear interaction between FUS and splicing factor, proline- and glutamine-rich (SFPQ) was weakened by disease-associated FUS mutants, and disrupted in both familial and sporadic ALS/FTLD brains. Both FUS and SFPQ regulate alternative splicing of Mapt gene at exon10 which generates two pathogenic isoforms of neural microtubule-associated protein tau (Tau) protein. Silencing of FUS or SFPQ resulted in the increased ratio of 4-repeat Tau (RD4)/ 3-repeat Tau (RD3). Mice with hippocampus specific FUS-knockdown and SFPQ-knockdown exhibited abnormal behaviors mimicking FTLD-like behavioral impairments, as well as reduced adult neurogenesis. The aberrant behaviors and reduced adult neurogenesis were rescued by co-silencing of RD4. Thus, our findings suggest a novel pathophysiological link between FUS and Tau in ALS/FTLD through the regulation of RD4/RD3 isoforms accompanied with altered adult neurogenesis.

Disclosures: S. Ishigaki: None. **Y. Fujioka:** None. **D. Honda:** None. **S. Yokoi:** None. **H. Okado:** None. **H. Watanabe:** None. **M. Katsuno:** None. **G. Sobue:** None.

Nanosymposium

106. Tauopathy and Dementia

Location: S403

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 106.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01NS074874

Title: Cognitive dysfunction correlates with Tau pathology and neuronal loss in the entorhinal cortex-hippocampal circuit in aged EC-Tau mice

Authors: *H. FU, S. A. HUSSAINI, M. HERMAN, S. EMRANI, L. LIU, C. PROFACI, H. FIGEROA, K. DUFF;
Taub Inst. for Res. on Alzheimer's Dis. and the Aging Brain, Columbia Univ. Med. Ctr., New York, NY

Abstract: Neurofibrillary tangles (NFTs) composed of hyperphosphorylated microtubule-associated protein tau (MAPT) are the best correlation with dementia stages of patients with Alzheimer's disease (AD). The NFTs start in the entorhinal cortex (EC) and spread into limbic and association cortices in a precise and defined manner as AD evolves. We have generated a transgenic mouse model (line EC-Tau) in which human Tau is differentially expressed in the EC and pre-/para- subiculum. At younger ages (< 14 mo) tau accumulates in cell bodies in the EC and is distributed through the performant path. At later ages (20-24 mo), tau distribution is more widespread, and it includes cells in the dentate gyrus (DG) and CA1. We have now examined very old mice (28-36 mo) and have found that human Tau protein spreads more extensively through the cortex including to the perirhinal cortex (PRC). The temporal and spatial distribution of Tau pathology in the whole mouse brain is currently being investigated using the iDISCO brain clearance method. Mature tauopathy in the EC correlates with neuronal cell loss. At ~24 months of age, there is significant loss of NeuN-positive neurons in EC-layer II (EC-II) of EC-Tau mice compared to control mice ($P < 0.05$). At ~34 months of age, neuronal loss is more extensive with significantly less neurons being observed in EC-II, EC-III/IV, and pre-/para-subiculum of EC-Tau mice compared to control mice (P 0.05). At 30+ months of age, however, EC-tau mice showed significant spatial and non-spatial learning and memory deficits compared to control mice ($P < 0.05$). Spatial disorientation and confusion in familiar surroundings is an early symptom commonly seen in patients with AD. The medial entorhinal cortex (MEC) is severely affected in AD. The MEC contains grid cells which are involved in spatial orientation so we examined neuronal activity in grid cells in the MEC of the EC-tau mice using *in vivo* microelectrode array recording. Neuronal activity was shown to be altered in 30+ mo old EC-Tau mice compared to control mice. Overall, EC-tau mice demonstrate progressive tauopathy that impacts neurodegeneration, physiology and cognition of relevance to the early stages of human AD. Keywords: Tau pathology, Alzheimer's disease, entorhinal cortex, grid cells, neuronal loss, cognitive deficits, transgenic mouse model

Disclosures: **H. Fu:** None. **S.A. Hussaini:** None. **M. Herman:** None. **S. Emrani:** None. **L. Liu:** None. **C. Profaci:** None. **H. Figeroa:** None. **K. Duff:** None.

Nanosymposium

106. Tauopathy and Dementia

Location: S403

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 106.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: ROCK inhibitors for modulation of tau phosphorylation: An opportunity to target Alzheimer's disease pathology and enhance memory

Authors: *M. TURK[1,2,3,4], A. SINIARD[2,3,4], M. DEBOTH[2,3,4], T. WANG[2], T. DUNCKLEY[2], P. PIRROTTE[2], S. ODDO[1], **M. HUENTELMAN**[1,2,3,4];
[1]Arizona State Univ., Phoenix, AZ; [2]Translational Genomics Res. Inst., Phoenix, AZ; [3]Arizona Alzheimer's Consortium, Phoenix, AZ; [4]Evelyn F McKnight Brain Inst. at the Univ. of Arizona, Tucson, AZ

Abstract: Rho-associated, coiled-coil-containing protein kinase 1 (ROCK) is an enzyme that plays important roles in neuronal cells including mediating actin organization and dendritic spine morphogenesis. The ROCK inhibitor (ROCK-i) Fasudil has been shown to increase learning and working memory in aged rats, but another ROCK-i, Y27632, was shown to impair learning and memory. We are interested in exploring how these, and other ROCK-i, may be acting mechanistically to result in very different outcomes in treated animals. Thirteen different ROCK-I were used to treat human neuroglioma cells overexpressing 4-repeat tau (H4-tau) across a 96-hour time course. The IC-10 dosage, at which 10% of H4-tau cells are no longer viable after 120 hours of drug treatment, was used drug-containing media was refreshed every 24 hours. The ratio of Serine 396 phosphorylated tau (p-tau) to total tau was measured using ELISA at each of 8 time points. The measurement of this ratio was chosen as our *in vitro* bench mark for the action of the ROCK inhibitors. Tau protein is a putative anti-Alzheimer's disease therapeutic target and we have shown previously that Fasudil can inhibit tau phosphorylation in addition to its effect on learning and memory. All drug treatments were compared against the corresponding time point for vehicle-treated cells. Fasudil was the only commercial drug to significantly decrease the p-tau to total tau ratio ($p=0.0004$). Of note, Y27632 did not decrease this ratio ($p=0.218$). Several of the novel ROCK-i did significantly decrease the p-tau to total tau ratio; of these, T343 had the greatest statistical significance ($p=0.003$). T299, another newly designed ROCK-i, displayed no change in the p-tau to total tau ratio despite its similarity to T343 in ROCK1 and ROCK2 inhibition. The results of these four drugs were replicated in H4-tau cells using a higher IC-50 dosage. While results of treatment with Fasudil, Y27632, and T343 at IC-50 doses were significant and in the same direction of the IC-10 dose effect ($p=0.01$; 0.08; 0.003), T299 at the IC-50 dosage in contrast significantly increased the p-tau total tau ratio ($p=0.0009$). Phosphorylation of tau at Serine 396 decreases tau mobility and the ability of tau to bind microtubules, possibly contributing to the tauopathy of Alzheimer's disease. Further research is necessary to parse out whether the effects of Fasudil on learning and memory are mediated through changes in p-tau to total tau expression, or through other on- or off-target effects. We have begun work in this area by collecting and sequencing RNA from H4-tau cells treated by one of each of the four drugs at IC-50 dosage across a 36-hour time course.

Disclosures: **M. Turk:** None. **A. Siniard:** None. **M. DeBoth:** None. **T. Wang:** None. **T. Dunckley:** None. **P. Pirrotte:** None. **S. Oddo:** None. **M. Huentelman:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.01

Topic: C.03. Parkinson's Disease

Support: M.J.Fox Foundation, Research Grant, 2014

Title: The role of activating transcription factor 4 (ATF4) in nigral degeneration induced by human alpha-synuclein cytotoxicity

Authors: *O. S. GORBATYUK[1,2], V. G. SERGEYEV[1,3], J. C. GULLY[1], M. S. GORBATYUK[1], S. ZOLOTUKHIN[4], H. MENDEZ-GOMEZ[5];
[1]Dept. of Vision Siences, Univ. of Alabama At Birmingham, Birmingham, AL; [2]Ctr. for Neurodegeneration and Exptl. Therapy, Univ. of Alabama at Birmingham, Birmingham, AL; [3]Udmurt State Univ., Izhevsk, Russian Federation; [4]Pediatrics, [5]Mol. Genet. & Microbiology, Univ. of Florida, Gainesville, FL

Abstract: Activating transcription factor 4 (ATF4) is a member of the pancreatic ER kinase (PKR)-like ER kinase (PERK) signaling pathway that directly binds ER-stress target genes and plays a crucial role in both adaptation to stress and activation of apoptosis. Previous publications demonstrated conflicting evidences pointing to the role of ATF4 in the pathogenesis of Parkinson's disease. In current study we designed experiments manipulating components of PERK signaling pathway to determine the role of ATF4 in mediating the ER-stress response to human α-synuclein (α-syn) overexpression in the substantia nigra pars compacta (SNc). We used a combination of transgenic mice and rAAV-mediated gene transfer to tease out the exact roles of ATF4 in α-syn mouse model of Parkinson-like neurodegeneration. We revealed that restriction of ATF4 overexpression achieved by ATF4+/- transgenic mice diminished α-syn induced loss of nigral DA cells. Moreover, rAAV mediated ATF4 overexpression was toxic and this effect was provided in part through downstream mediator, pro-apoptotic CHOP. This was confirmed by experiments with overexpression of ATF4 in CHOP+/- and CHOP-/- mice demonstrated significantly diminished loss of nigral TH-positive neurons. However, loss of nigral neurons in these knockout models was still significant compared to C57BL6 mice injected with control virus. This observation suggests that besides activation of pro-apoptotic CHOP downstream targets there is(are) another not-identified yet pro-death pathway(s), mediated by ATF4. This was also confirmed in above CHOP knockout models and experiments with rAAV mediated α-syn overexpression in mice with double knockout of both ATF4 and CHOP. Our data

allow to suggest that manipulation with expression of both ATF4 and CHOP proteins can have therapeutic potential.

Disclosures: O.S. Gorbatyuk: None. **V.G. Sergeyev:** None. **J.C. Gully:** None. **M.S. Gorbatyuk:** None. **S. Zolotukhin:** None. **H. Mendez-Gomez:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.02

Topic: C.03. Parkinson's Disease

Support: Fondazione con il Sud (2011-PD-13)

Title: Early cognitive and neuronal dysfunction preceding neurodegeneration in a mouse model of alpha-synucleinopathy

Authors: *A. IEMOLO[1], N. GIORDANO[1,2], A. BJÖRKLUND[3], P. CALABRESI[4,5], B. PICCONI[5], E. DE LEONIBUS[1,2];
[1]Dept. of Neuropsychopharm., Inst. of Genet. and Biophysics, Napoli, Italy; [2]Telethon Inst. of Genet. and Med., Pozzuoli, Italy; [3]Dept. of Exptl. Med. Sci., Wallenberg Neurosci. Ctr., Lund, Sweden; [4]Dept. of Medicine, Neurol. Unit, Univ. degli Studi di Perugia, Perugia, Italy; [5]Fondazione Santa Lucia, IRCSS, Rome, Italy

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting more than 1 % of people over the age of 65. The neuropathological hallmarks of PD are loss of dopaminergic (DA) neurons in the substantia nigra (SN) and formation of intraneuronal protein inclusions termed Lewy bodies, composed mainly of α-synuclein (α-Syn) protein. At a late stage of PD, abnormally accumulating α-Syn is considered responsible for DA neuronal death, motor deficits and dementia. Early cognitive impairment (ECI) can precede dementia and motor disturbance in PD and represent an unmet medical need for the early diagnosis and treatment of cognitive dysfunction. In this study, we explored the mechanisms through which α-Syn accumulation leads to the development of ECI and its transition to dementia. Recently developed animal models of PD show that adeno-associated viral vector (AAV)-mediated overexpression of α-Syn in the midbrain of adult rats induces a progressive loss of nigral DA neurons and motor impairment. We therefore introduced an AAV overexpressing human α-Syn protein into young adult CD1 male mice by bilateral stereotaxic injection targeting either the SN or the hippocampus (HP). Control animals were injected with AAV-GFP. Four weeks after injection,

mice were subjected to a series of behavioral tests and brain tissues were processed for detecting neurodegeneration. A separate group of animals was subjected to ex-vivo electrophysiological recordings in the dorsal striatum (Intracellular Patch Clamp) and in the CA1 subfield of the HP (Extracellular Field Potentials). Mice that received a bilateral intra-SN inoculation of the AAV-α-Syn, showed selective motor skill and coordination learning impairment. On the other hand, mice injected in the HP showed selective deficits both in object memory span and in a contextual fear conditioning paradigm. Despite the impaired behavior observed, there was no DA neuronal loss within the SN. These changes were correlated with altered learning-dependent synaptic plasticity in striatal medium-sized spiny neurons. Also, electrophysiological recordings of field potentials in CA1, showed a significant impairment of LTP in AAV- α-Syn overexpressing mice. Twenty four weeks after AAV overexpression we found a generalized sensorimotor and cognitive impairment in the SN of mice overexpressing α-Syn. These findings provide *in vivo* evidence that α-Syn overexpression leads to cognitive impairment and associated changes in neuronal plasticity preceding neurodegeneration and dementia, suggesting the interesting hypothesis that ECI and dementia are due to different neuronal disease mechanisms.

Disclosures: **A. Iemolo:** None. **N. Giordano:** None. **A. Björklund:** None. **P. Calabresi:** None. **B. Picconi:** None. **E. De Leonibus:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.03

Topic: C.03. Parkinson’s Disease

Support: Michael J.Fox Foundation

Title: Impairment of PARK14-dependent Calcium signaling is a novel determinant of idiopathic Parkinson's disease

Authors: ***V. M. BOLOTINA**[1], Q. ZHOU[1], A. YEN[1], G. RYMARCZYK[1], H. ASAI[2], C. TRENGROVE[2], N. AZIZ[1], M. T. KIRBER[1], T. IKEZU[2], B. L. WOLOZIN[2];
[1]Med., [2]Pharmacol. and Exptl. Therapeut., Boston Univ. Sch. of Med., Boston, MA

Abstract: The etiology of idiopathic Parkinson’s disease (PD) remains enigmatic despite success in identification of numerous genes (PARKs) that underlie familial PD. To find new keys to this still incurable neurodegenerative disorder we focused on the poorly understood PARK14 disease locus (identified as the *Pla2g6* gene) and the store-operated Ca^{2+} signaling pathway. Analysis of

the cells from idiopathic PD patients revealed a significant deficiency in the store-operated PLA2g6-dependent Ca^{2+} signaling, which we could mimic in a new B6.Cg-*Pla2g6*$^{\Delta Ex2\text{-}Vbol}$ (PLA2g6 Ex2^{KO}) mouse model. Here we demonstrate that idiopathic, genetic or molecular impairment of PLA2g6-dependent store-operated Ca^{2+} entry (SOCE) and depletion of ER Ca^{2+} stores can trigger autophagic dysfunction, and cause progressive loss of dopaminergic (DA) neurons in substantia nigra pars compacta (SNc) and age-dependent L-DOPA-sensitive motor dysfunction. Discovery of this previously unknown sequence of pathological events that could initiate and/or promote idiopathic PD, and the ability to mimic this pathology in a novel genetic mouse model opens new opportunities for cure for this devastating neurodegenerative disease.

Disclosures: V.M. Bolotina: None. **Q. Zhou:** None. **A. Yen:** None. **G. Rymarczyk:** None. **H. Asai:** None. **C. Trengrove:** None. **N. Aziz:** None. **M.T. Kirber:** None. **T. Ikezu:** None. **B.L. Wolozin:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.04

Topic: C.03. Parkinson’s Disease

Support: Whitehall Foundation

NIH AG043970

Title: Aging-dependent SIRT1-mediated deacetylation of Foxa2 regulates mitochondrial oxidative stress and dopaminergic neuron degeneration

Authors: *H. SHI[1], S. H. PARK[1], R. HOOD[3], N. MILLER[1], Z. XIE[2], C. K. MESHUL[3], D. J. SURMEIER[2], Y. C. MA[1];
[1]Lurie Children's Hosp. of Chicago Res. Ctr., [2]Dept. of Physiol., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [3]Portland VA Med. Ctr., Oregon Hlth. Sci. Univ., Portland, OR

Abstract: Aging has been established as the most important risk factor for Parkinson’s disease (PD), but the underlying mechanism leading to dopaminergic neuron degeneration is not known. Here we report an aging-dependent pathway involving SIRT1 and its deacetylation of dopaminergic neuron-specific transcription factor Foxa2 in regulating mitochondrial oxidative stress and dopaminergic neuron degeneration. We observed that dopaminergic neuron-specific knockout of SIRT1 exacerbated dopaminergic neuron degeneration in a mouse model of PD in

aging-dependent manner, with significantly increased dopaminergic neuron loss in aged SIRT1 knockout PD mice. This is due to elevated mitochondrial oxidative stress level in SIRT1 knockout mice as measured by a redox-sensitive variant of green fluorescent protein. We also mapped novel SIRT1 deacetylation target site on Foxa2 and generated acetyl-Foxa2 specific antibodies. Using RNA-seq and chromatin-immunoprecipitation (ChIP), we identified a gene expression program controlled by Foxa2 and SIRT1 to protect against aging-dependent mitochondrial oxidative stress. In SIRT1 knockout mice, reduced deacetylation of Foxa2 leads to the change of its nuclear-cytoplasmic localization, compromised gene expression and increased mitochondrial oxidative stress. Remarkably, the deacetylation of Foxa2 by SIRT1 is dramatically changed in aged mice and human Parkinson's disease patients, suggesting a critical role for this aging-dependent SIRT1-mediated deacetylation pathway in regulating mitochondrial oxidative stress and dopaminergic neuron degeneration in Parkinson's disease.

Disclosures: H. Shi: None. **S.H. Park:** None. **R. Hood:** None. **N. Miller:** None. **Z. Xie:** None. **C.K. Meshul:** None. **D.J. Surmeier:** None. **Y.C. Ma:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.05

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS072604

NIH Grant NS087449

MJFF

Title: Neuronal and glial implications of LRRK2 dysfunction

Authors: *M. J. LAVOIE[1], J. SCHAPANSKY[1], H. MELROSE[2], J. NARDOZZI[1];
[1]Brigham & Women's Hosp. & Harvard Med. Sch., Boston, MA; [2]Mayo Clin., Jacksonville, FL

Abstract: Autosomal dominant mutations in the multi-domain kinase LRRK2 are the most common genetic cause of Parkinson's disease (PD) and are associated with classic Lewy body pathology associated with the sporadic form of the disorder. The pathogenic missense mutations are believed to impart a gain-of-function at the level of LRRK2 kinase activity, but the functional role of LRRK2 in the cell remains unclear and the impact of disease linked mutations are not well understood. Furthermore, a remaining challenge in the field is connecting LRRK2

dysfunction to the observed synucleinopathy at a mechanistic level. Our data in various monocyte systems indicate that the immunologic stimulation of cells results in the recruitment of LRRK2 to autophagolysome membranes, its dimerization, and the facilitation of macroautophagy. These biochemical responses of the LRRK2 proteins can be recapitulated by direct stimulation of autophagy with rapamycin. Autophagic flux is reduced following the silencing of endogenous LRRK2 expression or the use of LRRK2 kinase inhibitors, demonstrating the direct contribution of LRRK2 kinase activity to the up-regulation of autophagic flux. Furthermore, modulation of LRRK2 expression or kinase activity can dramatically affect the clearance of aggregate-protein proteins. Using a G2019S knockin mouse model, we also observed significant alterations in glial reactivity in response to tissue injury, consistent with prior work supporting a physiological role for LRRK2 in non-neuronal cells. Independent work has also extended these findings into neuronal systems to understand the consequences of LRRK2 kinase inhibition and pathogenic mutation on alpha-synuclein homeostasis. We conducted an analysis of primary neuronal cultures harvested from wild-type and G2019S knockin mice, and our data reveal a complex relationship between LRRK2 activity and alpha-synuclein metabolism in the cell and suggest a novel model for LRRK2 dysfunction and disrupted proteostasis in PD.

Disclosures: **M.J. LaVoie:** None. **J. Schapansky:** None. **H. Melrose:** None. **J. Nardozzi:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.06

Topic: C.03. Parkinson’s Disease

Support: NIH R03NS087338

MSCRF 2014-MSCRFE-0587

Title: The PARK10 gene USP24 is a negative regulator of autophagy

Authors: ***M. M. LIPINSKI**[1], J. PETER[1], C. SARKAR[1], O. AWAD[2], R. A. FELDMAN[2]; [1]Anesthesiol., [2]Microbiology and Immunol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Autophagy, a lysosome-dependent catabolic pathway involved in turnover of intracellular proteins, protein aggregates and organelles plays an essential neuroprotective

function during brain aging. Defects in autophagy are causatively linked to neurodegenerative diseases, including Parkinson's disease (PD), and its up-regulation has been proposed as a potential prevention and treatment strategy. To reach this goal, it will be important to understand how autophagy is dysregulated in both familiar and idiopathic PD and identify molecular targets for its safe modulation. In a high-throughput functional screen of a human genome-wide siRNA library we identified ubiquitin specific peptidase 24 (USP24) as a negative regulator of autophagy. USP24 is a poorly-characterized gene located on chromosome 1 in the PARK10 locus associated with late-onset PD. Consistent with a specific function for USP24 in PD, non-synonymous single nucleotide polymorphisms (SNPs) in the coding region of this gene affect predisposition to PD in diverse populations. Our data demonstrate that USP24 protein levels are increased in the substantia nigra of a subpopulation of non-familial PD patients, suggesting potential involvement also in idiopathic PD. In human cell lines and in human iPS cell derived neurons USP24 knock-down led to up-regulation in levels of cellular autophagy, as assessed by translocation of the GFP-LC3 autophagy reporter from cytosolic to autophagosomal localization and by increase in the autophagosome associated LC3-II. Levels of autophagy induced by USP24 knock-down were further enhanced by lysosomal inhibitors, indicating that USP24 inhibition increased autophagy flux upstream of the lysosomes. Knock-down of USP24 also caused accumulation of the type III PI3 kinase product, PtdIns3P, as assessed by quantification of the FYVE-dsRed reporter. Consistently, induction of autophagy by loss of USP24 function was attenuated in the presence of the type III PI3 kinase inhibitors, spautin 1 or 3MA. On the other hand, knock-down of USP24 failed to affect mTOR activity, as indicated by lack of change in the phosphorylation of mTORC1 targets, ribosomal protein S6 and S6 kinase. Importantly, induction of autophagy following USP24 knock-down was not associated with loss of cell viability. Instead, it lead to decreased accumulation of PD mutant α-synuclein A53T. Together, our data indicate that USP24 is a novel negative regulator of autophagy flux in PD, acting upstream of the type III PI3 kinase but downstream or independent of mTOR.

Disclosures: **M.M. Lipinski:** None. **J. Peter:** None. **C. Sarkar:** None. **O. Awad:** None. **R.A. Feldman:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.07

Topic: C.03. Parkinson's Disease

Support: Van Andel Research Institute

EPFL

Swiss National Science Foundation (Grant No. 310030_144063)

Title: Enhancing GTPase activity attenuates the neurodegenerative effects of G2019S LRRK2 in a rat model of Parkinson's disease

Authors: *E. TSIKA[1], D. J. MOORE[3,2];
[1]EPFL, Renens, Switzerland; [2]EPFL, Lausanne, Switzerland; [3]Ctr. for Neurodegenerative Sci., Van Andel Res. Inst., Grand Rapids, MI

Abstract: Mutations in the leucine-rich repeat kinase 2 (LRRK2, PARK8) gene cause late-onset, autosomal dominant Parkinson's disease (PD) and represent the most common cause of familial PD. LRRK2 can function as a GTPase and kinase *in vitro* and disease-associated mutations can either enhance kinase activity (i.e. G2019S) or decrease GTPase activity (i.e. R1441C, Y1699C). Despite their differential effects on enzymatic activity, LRRK2 mutations commonly promote neuronal toxicity in primary cultures, and at least for the common G2019S mutation toxicity appears to be dependent on kinase activity. The contribution of GTPase activity to mutant LRRK2-induced neuronal toxicity is poorly understood. We have previously developed an adenoviral-mediated gene transfer model in adult rats where the expression of human G2019S LRRK2, but not wild-type (WT) LRRK2, induces the progressive degeneration of nigrostriatal pathway dopaminergic neurons. We have recently demonstrated in this model that the neurotoxic effects of G2019S LRRK2 are dependent on kinase activity by the simultaneous introduction of a kinase-inactive mutation (D1994N) into LRRK2. In this study, we sought to similarly evaluate the contribution of GTPase activity to G2019S LRRK2-induced neurodegeneration. We recently identified a hypothesis-testing mutation, R1398L, located in the catalytic Switch II region of the GTPase domain which markedly enhances the GTP hydrolysis activity of LRRK2 thereby favoring the GDP-bound "inactive" conformation. We created adenoviral vectors expressing human WT, G2019S and G2019S/R1398L LRRK2 or GFP from a neuronal-specific synapsin-1 promoter. Adult rats were subjected to unilateral intrastriatal injections of adenoviral vectors at six distinct locations and assessed at 42 days post-injection. LRRK2 variants or GFP were expressed equivalently throughout the ipsilateral striatum and to some extent within the substantia nigra pars compacta following retrograde axonal transport. G2019S LRRK2 induced the degeneration of nigral dopaminergic neurons and striatal neurite degeneration relative to WT LRRK2 or GFP. Importantly, the GTPase-enhanced variant, G2019S/R1398L, failed to induce similar neuropathological phenotypes to G2019S LRRK2 in rats. These data suggest that genetic enhancement of GTPase activity is sufficient to completely attenuate the neurotoxic actions of G2019S LRRK2. Our proof-of-concept studies support modulation of GTPase activity as a potentially viable therapeutic strategy for the inhibition of mutant LRRK2-induced neurodegeneration in PD.

Disclosures: E. Tsika: None. **D.J. Moore:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.08

Topic: C.03. Parkinson's Disease

Title: Cell Culture Model to understand the mechanism of association between Parkinson's disease and Melanoma

Authors: *A. BOSE[1], G. PETSKO[2];
[1]Neurosci., [2]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting the world affecting 7 to 10 million people. PD is characterized by loss of melanin-positive dopaminergic neurons in the substantia nigra (SN). Melanoma is a malignant tumor of the melanin producing cells of the skin. Epidemiological studies have shown that PD patients have a lower risk of developing most cancers except melanoma. The occurrence of melanoma in PD or vice versa is substantially higher than expected, with an odds ratio of up to 6-fold (Olsen et al., 2006, Bertoni et al., 2010). We have used human melanoma cell lines (SK-MEL-2), fibroblast cell lines (CCD-1070SK), breast cancer (MCF-7) and colorectal adenocarcinoma (Caco-2) cells for our study. We show by cell viability (XTT) assays that overexpression of the WT α-synuclein and the A53T α-synuclein and subsequent treatment with Paraquat which is an environmental toxin causes significant increase in cell death in the SK-MEL-2 cell lines expressing WT α-synuclein, and mutant (A53T) synuclein as compared to the CCD-1070SK and MCF-7 and Caco-2 cells. Cell death is higher in the cells expressing the A53T mutant than in the cells expressing WT synuclein. We also show by western blotting that levels of α- synuclein and melanin are higher in the cells expressing the A53Tα-synuclein. By immunocytochemistry we show that α-synuclein and MART-1 co-localize in the SK-MEL-2 cells suggesting that there may be common signaling pathways that play a role in PD and melanoma which could explain the comorbidity between the two diseases. These cellular models will be a very useful tool to study the underlying mechanisms of association between PD and melanoma

Disclosures: A. Bose: None. **G. Petsko:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.09

Topic: C.03. Parkinson's Disease

Title: Membrane stress-associated aldehyde triggers exosome-mediated transcellular α-Synuclein pathology by impairing lysosomal function

Authors: *S. ZHANG[1], E. EITAN[2], M. P. MATTSON[2];
[2]Natl. Inst. on Aging, [1]NIH, Baltimore, MD

Abstract: Parkinson's disease (PD) is characterized by degeneration of neurons in the brainstem, substantia nigra and cerebral cortex resulting in autonomic and motor dysfunction, and cognitive impairment. Intraneuronal accumulation of alpha-synuclein is believed necessary and sufficient to cause neuronal degeneration in PD. Recent findings suggest that alpha-synuclein pathology can be propagated transneuronally, but the underlying molecular mechanisms are unknown. The aldehyde 4-hydroxynonenal (HNE), which is known to be generated by membrane-associated oxidative stress, is found in Lewy bodies in PD. Here we show that HNE binds to endogenous alpha-synuclein at pathophysiologically relevant concentrations in primary rat cortical neurons. Prolonged incubation with HNE causes alpha-synuclein accumulation of aggregated alpha-synuclein phosphorylated at serine 129, and perinuclear accumulation of ubiquitinated proteins. HNE-treated neurons exhibit cleaved-caspase 3 and Thioflavin S staining. The aggregation of alpha-synuclein and accelerated neurodegeneration in HNE-treated neurons is attributed to impaired chaperone-mediated autophagy and lysosomal function at an early stage, and subsequent macro-autophagic deficiency. Intriguingly, HNE also triggers the release of alpha-synuclein oligomer-containing exosomes from cortical neurons, and those exosomes are internalized by and toxic to previously healthy neurons. In contrast, exosomes released from neurons not exposed to HNE contain relatively low amounts of alpha-synuclein oligomers and are not neurotoxic. Additional findings suggest that alpha-synuclein associated with exosomes released from HNE-treated neurons can serve as a seed for the propagation of misfolded proteins with beta-sheet structure in recipient neurons. Our findings suggest that an aldehyde generated by membrane-associated oxidative stress can interfere with alpha-synuclein degradation in lysosomes, thus promoting the intraneuronal accumulation of αalpha-synuclein oligomers, many of which are then released from the cells in exosomes which can then transfer cytotoxic alpha-synuclein oligomers to other neurons.

Disclosures: S. Zhang: None. **E. Eitan:** None. **M.P. Mattson:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.10

Topic: C.03. Parkinson's Disease

Title: Striatal mitochondria DNA quantity tips the balance between mitochondrial fission and fusion: Implications for L-DOPA Induced Dyskinesia

Authors: *E. B. WARREN[1], C. KONRADI[1,2,3];
[1]Pharmacol., [2]Psychiatry, [3]Kennedy Ctr. for Res. on Human Develop., Vanderbilt Univ., Nashville, TN

Abstract: Current pharmacotherapy for Parkinson's Disease (PD) replaces depleted dopamine (DA) with a DA precursor, L-DOPA. While initially beneficial, this treatment eventually causes L-DOPA Induced Dyskinesia (LID), characterized by excessive and uncontrolled movements. Ninety percent of PD patients treated with L-DOPA develop LID within ten years, some more rapidly than others. In previous studies comparing the putamina of "dyskinetic" and "nondyskinetic" PD patients, our lab discovered that mitochondrial DNA (mtDNA) was significantly decreased in the dyskinetic group. Evidence suggests that LID is caused by maladaptive changes in striatal neurons, which are likely exacerbated by abnormalities in metabolic pathways. While mtDNA encodes subunits of the mitochondrial respiratory chain, the relationship between mtDNA quantity and neuronal function remains unclear. We hypothesized that because deficits in mitochondrial fission and fusion can impact mtDNA quantity, decreased mtDNA levels may have a reciprocal effect on mitochondrial dynamics. Alterations in the balance between mitochondrial fusion and fission can both negatively impact cell function and viability, and may translate to molecular changes analogous to those seen in models of LID. Here, we treated primary striatal cultures from mouse and rat with ethidium bromide to decrease mtDNA levels. We also expressed an shRNA against the mtDNA polymerase to decrease mtDNA levels in a neuroblastoma cell line. By examining expression levels of genes associated with mitochondrial fission and fusion (Dnm1l, Fis1, Mfn1, Mfn2, and Opa1) and determining mitochondrial morphology with imaging, we found a close relationship between mtDNA levels and mitochondrial morphology. Small decreases in mtDNA promote a pro-fusion response, whereas decreasing mtDNA beyond a certain threshold results in a pro-fission response. Subsequent studies will attempt to identify the tipping point between these two responses, as well as pinpoint any species-related differences. Overall these results suggest that decreased mtDNA may potentiate the development of LID by destabilizing the mitochondrial network and consequently the intracellular environment.

Disclosures: **E.B. Warren:** None. **C. Konradi:** None.

Nanosymposium

107. Cell Dysfunction and Degeneration in Parkinson's Disease

Location: N230

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 107.11

Topic: C.03. Parkinson’s Disease

Support: William Dow Lovett Endowment

Title: Microrna regulation by dj-1 in Parkinson's disease

Authors: ***S. E. OH**, H. J. PARK, E. S. PARK, E. JUNN, M. M. MOURADIAN;
Ctr. for Neurodegenerative and Neuroimmunologic Diseases, Dept of Neurol., Rutgers-Robert Wood Johnson Med. Sch., Piscataway, NJ

Abstract: DJ-1 (PARK7) mutations are linked to recessively inherited Parkinson’s disease (PD), and its dysregulation is implicated in sporadic PD as well as in other neurodegenerative disorders such as Alzheimer's and Huntington's diseases. DJ-1 is a highly conserved, multifunctional protein that is cytoprotective in neurons and may be necessary for astrocyte-mediated neuroprotection against oxidative stress. In addition to quenching reactive oxygen species through the oxidation of its cysteine residues, DJ-1 binds to transcription factors and mRNAs that are involved in the antioxidant response, effectively regulating both transcription and translation in response to oxidative stress. Yet, the impact of DJ-1 in regulating non-coding RNAs, including microRNAs (miRNAs) that play a prominent role in the transcriptome and protein expression, has yet to be studied. Here, we employed Affymetrix GeneChip Human Gene 2.0 ST RNA expression microarray to screen for microRNAs modulated by DJ-1. Efficient DJ-1 knock-down in human neuroblastoma SH-SY5Y cells was achieved by using pooled multiple silencing RNAs (siRNAs) against DJ-1. Among sixteen microRNA species that were found to be differentially expressed by greater than 1.5-fold as a result of DJ-1 depletion, we identified microRNA-221 (miR-221) to be down-regulated to the greatest extent. miR-221, which is one of the most abundant miRNAs in the human brain, reportedly facilitates cell proliferation and self-renewal, as well as promotes neurite outgrowth and neuronal differentiation. RT-qPCR analyses confirmed that while knock-down of DJ-1 decreases the level of miR-221, the re-introduction of wild-type DJ-1, but not its pathogenic mutants L166P or M26I, can restore miR-221 expression. Notably, over-expression of mature miR-221 via transfection with its precursor pre-miR-221 construct is cytoprotective against MPP+-induced cell death. Conversely, the inhibition of endogenous miR-221 via transfection with anti-miR-221 construct (complementary to mature

miR-221) sensitizes cells to MPP+. Additionally, miR-221 down-regulates pro-apoptotic molecules such as Bcl-2-like protein 11 (BCL2L11/Bim/Bam) to normal levels even when cells are exposed to significant oxidative stress. These findings suggest that miR-221 contributes to DJ-1 mediated neuroprotection through inhibiting apoptotic mechanisms, and PD associated DJ-1 mutants lose the ability to regulate this microRNA and its protective effects.

Disclosures: S.E. Oh: None. **H.J. Park:** None. **E.S. Park:** None. **E. Junn:** None. **M.M. Mouradian:** None.

Nanosymposium

108. Molecular Mechanisms Associated with Ischemia

Location: S401

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 108.01

Topic: C.08. Ischemia

Support: AHA 13SDG13970009

NIH #S10RR027535

NIH grant U54NS083932

NIH grant S21MD000101

NIH grant R01NS066027

Title: Region specific expression of ASIC subunits in the brain determines differential contribution of ASIC2 to neuronal injury

Authors: J. WU[1,3], N. JIANG[1,4], T. YANG[5], Y.-Q. JIANG[1,6], Y. ZHOU[1], B. WANG[2], Y. HU[3], Y.-H. JI[4], R. SIMON[5], Z.-G. XIONG[5], *X. ZHA[1];
[1]Physiol. and Cell Biol., [2]Mathematics and Statistics, Univ. of South Alabama, Mobile, AL; [3]Shanghai Inst. of Pharmaceut. Industry, Shanghai, China; [4]Life Sci., Shanghai Univ., Shanghai, China; [5]Neurobio., Morehouse Sch. of Med., Atlanta, GA; [6]Urology, The Third Hosp. of Hebei Med. Univ., HeBei, China

Abstract: Acid-sensing ion channels (ASICs) are one key mediator of acidosis-induced neuronal injury. Little is known about the relative abundance of different ASIC subunits in the brain. In this study, we semi-quantitatively determined the molar ratio of different ASIC subunits in mouse brain. ASIC1a subunits outnumber the sum of ASIC2a and 2b. There was a region-

specific variation in ASIC2a and 2b expression, with cerebellum and striatum expressed predominantly 2b and 2a, respectively. Regarding differential trafficking, in acutely dissected brain tissue, ASIC1a and 2a but little 2b reached the cell surface. Consistent with the biochemical results, ASIC2 deletion attenuated neuronal injury in multiple brain regions. These data suggest that the main functional ASICs in brain are ASIC1a homomers and ASIC1a/2a heteromers at a 2:1 stoichiometry, and ASIC2 plays an indispensable role to acid signaling in the brain.

Disclosures: J. Wu: None. **N. Jiang:** None. **T. Yang:** None. **Y. Jiang:** None. **Y. Zhou:** None. **B. Wang:** None. **Y. Hu:** None. **Y. Ji:** None. **R. Simon:** None. **Z. Xiong:** None. **X. Zha:** None.

Nanosymposium

108. Molecular Mechanisms Associated with Ischemia

Location: S401

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 108.02

Topic: C.08. Ischemia

Support: NIH grant RO1-NS37570

Title: Molecular mechanisms of T cell damage following stroke

Authors: *A. RAYASAM[1], B. CLARKSON[2], T. KIM[3], A. LINDSTEDT[4], J. KIJAK[4], R. VEMUGANTI[3], M. SANDOR[4], Z. FABRY[4];
[1]Univ. of Wisconsin - Madison, Madison, WI; [2]Neurol., The Mayo Clin., Rochester, MN; [3]Neurosurg., [4]Univ. of Wisconsin-Madison, Madison, WI

Abstract: Stroke is the third leading cause of death in the United States and affects 15 million people worldwide annually. Understanding the exact mechanisms of tissue damage and the contribution of infiltrating immune cells to detrimental inflammation in acute stroke will lead to novel therapies. Several studies have identified lymphocytes, particularly CD4 T cells, as key mediators of the detrimental effects caused by cerebral ischemia/ reperfusion injury (CI/RI), in an experimental animal model for stroke. Published data from our lab indicates that IL-21 is a key CD4+ T cell-derived innate inflammatory factor that contributes to increased early ischemic tissue injury and infarct volume. We presented data that blocking IL-21 prior to or 1 hour following transient Middle Cerebral Artery Occlusion (tMCAO) decreased ischemic lesion formation and the lack of IL-21 protected mice from tissue damage in the CNS. Finally, we detected CD4+ IL-21+ T cells in the CSF filled subarachnoid and perivascular spaces

surrounding and penetrating infarcted tissue in post mortem brain tissue from human patients with acute stroke. Elucidating the molecular mechanisms for how T cell produced IL-21 acts can reveal novel therapeutic targets for limiting reperfusion damage post stroke. Preliminary data from our lab and others suggests that endothelial CXCL13 is up-regulated following tMCAO. Furthermore recent studies have identified new populations of circulating IL-21-producing CXCR5+ (ligand for CXCL13)ICOS+IL-21+ T follicular helper cells (Tfh) are associated with human diseases. Despite this, there is a lack of knowledge about the contribution of circulating Tfh cells to pathogenesis of stroke. Based on these publications and our preliminary data, we hypothesize that following tMCAO, endothelial CXCL13 is up-regulated and preferentially recruits CXCR5+ICOS+IL-21 producing Tfh cells to increase reperfusion induced damage. The target of these IL-21 producing T cells is also unknown. Our preliminary data suggest that IL-21 damages neurons surrounding the infarcted core to increase reperfusion-induced damage. During oxygen glucose deprivation (OGD) conditions, IL-21R is most highly up-regulated on neurons compared to other cells of Central Nervous System. Moreover, addition of IL-21 to neurons *in vitro* increases neuronal cell death by autophagy. Finally, IL-21R is expressed on penumbral neurons following tMCAO. Based on our published and preliminary data, we propose that IL-21 is a novel critical mediator of ischemic injuries in the brain and that IL-21-targeting therapies might be beneficial in stroke.

Disclosures: **A. Rayasam:** None. **B. Clarkson:** None. **T. Kim:** None. **A. Lindstedt:** None. **J. Kijak:** None. **R. Vemuganti:** None. **M. Sandor:** None. **Z. Fabry:** None.

Nanosymposium

108. Molecular Mechanisms Associated with Ischemia

Location: S401

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 108.03

Topic: C.08. Ischemia

Support: Cooper Medical School of Rowan Univ Student Research Support

Title: Effect of hypoxia on lactate dehydrogenase (ldh) gene expression in human glioblastoma cells

Authors: G. CHAVIANO, T. N. FERRARO, *R. J. BUONO;
Biomed. Sci., Cooper Med. Sch. of Rowan Univ., Camden, NJ

Abstract: We hypothesize that the lactate dehydrogenase genes A and B (LDHA and LDHB) can be used as prototypes to understand hypoxic gene induction and hypoxic gene repression and

reactivation upon re-perfusion. The hypoxia inducible factor (HIF) is a transcription factor protein that binds to DNA promoters and drives expression of specific genes such as LDHA when oxygen tensions are low. In contrast, the molecular mechanisms driving hypoxic gene repression and reactivation after re-perfusion are not understood. This study utilizes human glioblastoma (GBM) cells to study the molecular mechanism controlling hypoxic repression and reactivation of LDHB. GBM cell line U118-MG was obtained from the American Tissue Culture Collection (ATCC) and cultured as per ATCC protocols. The cells were subjected to normoxic (pO2 = 20.9% circulating culture chamber air) or hypoxic (pO2 = 0) conditions for 3 and 22 hours. Immunofluorescence and image analysis were used to determine the percent of cells in each condition that expressed LDHA or LDHB. Results demonstrate that under normoxic conditions GBM cells expressed more LDHB protein compared to LDHA protein (17.6% cells vs 7.2% cells, p=0.05). After 22 hours exposure to hypoxia, GBM cells increase expression of LDHA protein to significantly higher levels compared to LDHB (82% cells vs 22.6% cells, p=0.049) and compared to LDHA expression under normoxia (7.2% in normoxia vs 82% in hypoxia, p=0.002). There was no statistically significant difference in LDHB expression after 22 hours exposure to hypoxia (17.6% in normoxia vs 22.6% in hypoxia, p=0.74) likely due to the long half-life of this protein (~48hours). These experiments demonstrate a model system to elucidate mechanisms controlling hypoxic gene repression and gene reactivation after re-perfusion. Ongoing experiments include increasing hypoxia time points out to 72 hours, measuring LDHA and LDHB mRNA by real time PCR in GBM cultures, and making LDHB promoter reporter constructs for transfection experiments. Promoter regions potentially regulating hypoxic repression and reactivation have been identified by in silico comparison of LDHB promoter sequences in human and non-human primates. Promoter deletion constructs and cell transfection experiments will functionally identify the LDHB promoter region that is responsive to oxygen tension. This region can be used to isolate binding proteins related to LDH-B gene regulation based on oxygen tension. The discovery of this transcription factor could serve to decrease the aggressiveness of tumor cells as well as lead to treatment strategies to prevent re-perfusion injury in neural tissues after hypoxia.

Disclosures: **G. Chaviano:** None. **T.N. Ferraro:** None. **R.J. Buono:** None.

Nanosymposium

108. Molecular Mechanisms Associated with Ischemia

Location: S401

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 108.04

Topic: C.08. Ischemia

Support: NIH Grant R01 HL116995

Title: Rab7 regulates endothelial tight junction protein trafficking and paracellular permeability of the blood-brain barrier after ischemic stroke

Authors: *D. AGALLIU[1,2], M. HSU[2], A. ARAC[3], D. KNOWLAND[4], A. EDINGER[2]; [1]Neurol., Columbia Univ. Med. Ctr., New York, NY; [2]Developmental and Cell Biol., Univ. of California, Irvine, Irvine, CA; [3]Neurol., UCLA, Los Angeles, CA; [4]Neurosci., UCSD, San Diego, CA

Abstract: Brain endothelial cells form a paracellular and transcellular barrier to blood-borne solutes via tight junctions (TJs) and scarce endocytotic vesicles. The blood-brain barrier (BBB) plays a pivotal role in the healthy and diseased CNS. BBB damage after ischemic stroke contributes to increased mortality; yet the roles of paracellular versus transcellular mechanisms in this process are not well-understood. We have previously shown by intravital two-photon microscopy, using a transgenic strain in which endothelial TJs are labeled with eGFP, that stepwise impairment of transcellular followed by paracellular barrier mechanisms accounts for BBB deficits in stroke. Moreover, Caveolin-1 deficient mice, which have reduced endothelial transcellular permeability, display a normal increase in paracellular permeability after transient MCAO, suggesting that these two mechanisms are independent. Here, we address the role of TJ remodeling in regulation of endothelial paracellular permeability following stroke. The small GTPase Rab7 plays an essential role in regulation of trafficking inside the cell as proteins move from the late endosome to the lysosome for degradation. We have generated mice deficient for Rab7 in endothelial cells (Rab7ECKO) and have examined changes in BBB permeability, neuronal survival and neurological deficits at 48h after t-MCAO. We find that Rab7EC-deficient mice have reduced paracellular permeability following stroke, as assessed by leakage of biocytin-TMR tracer. This correlates with preservation of TJ structural integrity and reduced degradation of TJ protein at 48h after t-MCAO in Rab7ECKO mice as compared to wild-type littermates. Conversely, leakage of serum IgG via receptor-mediated transcytosis occurs normally in these mutants. Moreover, Rab7EC-deficient mice have a reduced neuronal death in both the sensory and motor cortex and have a moderate protection against stroke as assessed by several neurological tasks. These findings suggest that Rab7 regulates TJ protein trafficking and degradation at the late phase of stroke, which is responsible for the enhancement of paracellular permeability of the barrier. Moreover, inhibition of Rab7 activation in endothelial cells may protect CNS damage after ischemic stroke.

Disclosures: D. Agalliu: None. **M. Hsu:** None. **A. Arac:** None. **D. Knowland:** None. **A. Edinger:** None.

Nanosymposium

108. Molecular Mechanisms Associated with Ischemia

Location: S401

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 108.05

Topic: C.08. Ischemia

Support: MY 04/10

Title: Differential effects of erythropoietin on brain endothelial cells and astrocytes in primary culture during anoxia

Authors: *Z. REDZIC, H. AL-SARRAF, S. MALATIALI, M. AL-AWADI;
Physiol., Fac. of Med., Safat, Kuwait

Abstract: It has been shown that erythropoietin (EPO) exerted overall neuroprotective effects *in vivo* [1] but also injurious effects on brain cells *in vitro*. To further elucidate mechanisms of EPO's action in the brain, this study was aimed to explore mechanisms of EPO's action on astrocytes and brain endothelial cells (BECs) *in vitro* during anoxia. Rat astrocytes and BECs were cultured [2] and exposed either to anoxia (<0.3% O2, 5% H2, 5% CO2 in N2) or to control conditions (5% CO2 in air) for 2-48h. Cytokines in the cell culture media were estimated by ELISA; cell viability, apoptosis and necrosis were estimated by flow cytometry. Expression of EPO or EPOR were silenced in cultured cells using siRNAs; efficiency of silencing was confirmed by RT-PCR and/or ELISA. A one-way ANOVA with post hoc analysis was used with $p<0.05$ being considered as significant; group sizes were 4-10 samples/group. Anoxia (2-48h) exerted neither significant reduction in viability nor significant increase in apoptosis of BECs; it caused a significant, time-dependent reduction in the viability of astrocytes, which was accompanied by a significant increase in apoptosis. Addition of rat recombinant EPO did not exert significant effects on BECs' viability during 2h anoxia, but significantly reduced viability and increased apoptosis after 24h and 48h. These detrimental effects were completely ($p<0.001$) and marginally but significantly ($p<0,05$) attenuated when expression of EPOR and EPO genes were silenced in BECs, respectively. Exposure of BECs to 24h anoxia in the medium that contained both EPO and vascular endothelial growth factor (VEGF) significantly reduced cell viability ($p<0.01$) and increased early apoptosis ($p<0.01$), an effect that was attenuated by Jak2 kinase inhibition. Simultaneous addition of EPO and angiopoietin 1 (Ang1) exerted significant ($p<0.05$) protective effects on BECs, an effect that was attenuated when EPOR gene expression was silenced. Addition of EPO exerted clear protective effects on astrocytes during 2-6h anoxia, while it exerted detrimental effects after 24-48h. These detrimental effects were largely ($p<0.01$) attenuated when expression of EPO gene was silenced or when Jak2 kinase was inhibited. Addition of VEGF with EPO to the medium during 24h and 48h anoxia reversed detrimental effects of EPO, an effect that was attenuated when EPO gene expression was silenced. In conclusion, this study revealed that EPO could exert differential effects on BECs and astrocytes

during anoxia; whether these effects were protective or injurious largely depended on simultaneous signaling by VEGF and Ang1. 1. Bull Exp Biol Med. 2014;156:642-4. 2. Methods Mol Biol 2012; 814:415-430.

Disclosures: **Z. Redzic:** None. **H. Al-Sarraf:** None. **S. Malatiali:** None. **M. Al-Awadi:** None.

Nanosymposium

108. Molecular Mechanisms Associated with Ischemia

Location: S401

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 108.06

Topic: C.08. Ischemia

Support: NIH P30GM103400

National Natural Science Foundation of China 81200928

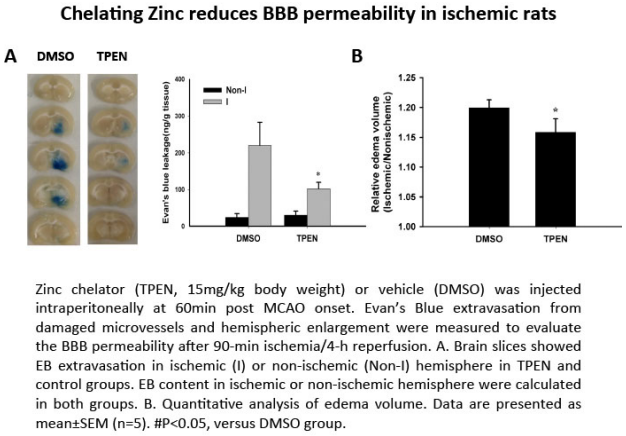
Beijing Nova Program Z141107001814045

Title: Zinc critically contributes to cerebral ischemia-induced blood-brain barrier disruption by activating MMPs and inducing loss of tight junction proteins in cerebral microvessels

Authors: Z. QI[1], J. LIANG[2], R. PAN[1], W. DONG[2], W. SHI[2], *K. J. LIU[1];
[1]Dept. of Pharmaceut. Sci., Col. of Pharmacy, Univ. of New Mexico, Albuquerque, NM;
[2]Cerebrovascular Dis. Res. Institute, Xuanwu hospital of Capital Med. Univ., Beijing, China

Abstract: Zinc ions are stored in synaptic vesicles and cerebral ischemia triggers their release from the terminals of neurons. Intracellular zinc accumulation has been shown to play an important role in neuronal death following ischemia. However, little is known about the role of zinc in ischemia-induced blood-brain barrier (BBB) disruption. In this study, we investigated whether zinc contributes to ischemia-induced acute BBB disruption and the possible mechanisms using both cellular and animal stroke models. Exogenous added zinc dramatically increased BBB permeability and loss of occludin and claudin-5 in the endothelial monolayer under oxygen glucose deprivation conditions. Significantly, a dramatically elevated level of zinc was detected in cerebral microvessels isolated from ischemic rats. Treatment with a specific zinc chelator N,N,N′,N′-tetrakis(2-pyridylmethyl) ethylenediamine (TPEN), even at 60min post ischemia onset, not only reduced zinc accumulation in the microvessels, but also attenuated Evan's Blue extravasation and reduced edema volume in the ischemic rats. Furthermore, removing zinc completely reversed matrix metalloproteinases activation and prevented ischemia-induced loss of occludin and claudin-5 in the microvessels. These findings suggest that zinc critically contributes

to BBB interruption following cerebral ischemia/reperfusion, implicating zinc as a crucial target for reducing acute BBB injury in ischemic stroke.



Zinc chelator (TPEN, 15mg/kg body weight) or vehicle (DMSO) was injected intraperitoneally at 60min post MCAO onset. Evan's Blue extravasation from damaged microvessels and hemispheric enlargement were measured to evaluate the BBB permeability after 90-min ischemia/4-h reperfusion. A. Brain slices showed EB extravasation in ischemic (I) or non-ischemic (Non-I) hemisphere in TPEN and control groups. EB content in ischemic or non-ischemic hemisphere were calculated in both groups. B. Quantitative analysis of edema volume. Data are presented as mean±SEM (n=5). #P<0.05, versus DMSO group.

Disclosures: Z. Qi: None. **J. Liang:** None. **R. Pan:** None. **W. Dong:** None. **W. Shi:** None. **K.J. Liu:** None.

Nanosymposium

108. Molecular Mechanisms Associated with Ischemia

Location: S401

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 108.07

Topic: C.08. Ischemia

Title: Brain region specific regulation of mechano-growth factor (MGF) expression after hypoxia brain injury

Authors: *M. M. SZYMANSKA, T. M. RACKOHN, W. W. ASHLEY, Jr.;
Neurolog. Surgery, Loyola Univ. Med. Ctr., Maywood, IL

Abstract: Cerebral vasospasm (CV) and related ischemic injury is a major contributor to death and disability after aneurysmal subarachnoid hemorrhage (aSAH) due to induction of hypoxia-like brain damage. Our goal is understanding the molecular mechanisms of action of a potential therapeutic target that could be used to prevent CV-induced brain damage, mechano-growth factor (MGF),a splice variant of insulin-like growth factor 1(IGF-1),which has shown to be neuroprotective after stroke in a gerbil model of ischemic injury. In these studies specifically, we aimed to characterize hypoxia induced changes in the MGF mRNA and protein expression in different brain regions commonly affected by aSAH and CV. The brain regions analyzed were

motor cortex, hippocampus, stratum and hypothalamus. We treated adult Wistar rats with either 6, 8, 10 or 12 % hypoxia for 4 h or normoxia (21 % oxygen level) conditions for the same duration of time in an isobaric hypoxia chamber and we sacrificed the animals either at 2, 4, 24, 72 hours or 7 days post treatment. Brain regions were micro-dissected and total RNA and protein were isolated using PureZOL reagent or RIPA buffer, respectively. MGF mRNA levels were measured using quantitative real time RT-PCR method and protein levels were analyzed using western blot. In addition to MGF, we analyzed expression of genes implicated to be involved in MGF mediated neuroprotective pathway. These included heme oxygenase 1 (HO-1) and biliverdin reductase A (BVA). In order to measure relationship of MGF expression to cell death, caspase 3 and 8 mRNA were also analyzed. Our data indicated that hypoxia induced brain specific changes in MGF mRNA and protein expression in a dose and time responsive manner. In addition, expression of genes involved in HO-1 pathway were also differentially regulated depending on the brain region analyzed. Lastly, these changes potentially correlated with alterations in the effects of hypoxia-induced cell damage. These data indicate that hypoxia has differential effects on MGF regulation depending on a brain region analyzed. Further studies need to be performed in order to understand potential molecular mechanisms associated with MGF effects in these brain regions and the potential use of MGF as a therapeutic agent for prevention of hypoxia and CV induced brain damage.

Disclosures: **M.M. Szymanska:** None. **T.M. Rackohn:** None. **W.W. Ashley:** None.

Nanosymposium

108. Molecular Mechanisms Associated with Ischemia

Location: S401

Time: Sunday, October 18, 2015, 8:00 AM - 10:00 AM

Presentation Number: 108.08

Topic: C.08. Ischemia

Title: Mitochondrial dynamics during global cerebral ischemia/reperfusion injury

Authors: *T. H. SANDERSON[1], M. BUKOWSKI[2], R. KUMAR[1], L. CALO[2];
[1]Emergency Med., [2]Wayne State Univ., Detroit, MI

Abstract: Global brain ischemia/reperfusion induces neuronal damage in vulnerable brain regions. A key event leading to neuronal death is mitochondrial cytochrome c release which we have demonstrated is accompanied by release of mitochondrial Opa1, a key mitochondrial fusion protein. In this study, we analyzed the potential perturbations in the mitochondrial fusion/fission process during ischemia/reperfusion. We first evaluated whether Opa1 release from the mitochondria was associated with cristae junction remodeling and Opa1 complex breakdown.

TEM images demonstrate cristae architecture is lost following global brain ischemia and this correlates to Opa1 and cytochrome c release from the mitochondria. Furthermore, BN-PAGE and Western blot of Opa1 complexes following global brain ischemia reveal loss of Opa1 oligomeric complexes (6 and 24 hours following ischemia, n=5, $p<0.05$). We next sought to determine how mitochondrial dynamics was affected. Simulated ischemia (OGD) of neurons transfected with mito-localized GFP and MR-DEVD to detect caspase activation revealed a dual phase fragmentation profile (i) massive fragmentation during ischemia-with no apoptosis activation, followed by re-fusion of mitochondrial networks after reperfusion and subsequent (ii) extensive fragmentation and apoptosis activation directly preceding cell death (n = 5, $p<0.05$). Mitochondrial dynamics *in vivo* was assessed with (i) 3D-electron microscopy (serial-block face scanning electron microscopy and 3D-reconstrucation) to quantify mitochondrial volume, shape, and length and (ii) immunofluorescence for ATP synthase. Immunofluorescence (n=5/group) and 3D-EM (n=3/group) of control brains both exhibit mitochondria with long tubular morphology and Opa1 fluorescence in CA1 neurons was consistent with mitochondrial localization. In contrast, ischemia followed by 6 or 24 hrs of reperfusion resulted in extensive mitochondrial fragmentation (i.e. reduced mitochondrial length $p<0.05$). These data provide novel evidence that dysfunctional mitochondrial dynamics may play a role in cell death following brain ischemia.

Disclosures: T.H. Sanderson: None. **M. Bukowski:** None. **R. Kumar:** None. **L. Calo:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.01

Topic: F.03. Motivation and Emotion

Support: 1-ZIA-MH002860-08

Title: Learning about object value through social cues in Disruptive Behavior Disorder

Authors: *H. MEFFERT[1], M. R. VANTIEGHEM[2], S. F. WHITE[1], J. R. BLAIR[1];
[1]Natl. Inst. of Mental Health, NIH, Bethesda, MD; [2]Psychology, Columbia Univ., New York, NY

Abstract: During social referencing, people gain knowledge about object value through the observation of others' emotional responses to these objects. Previous research has shown increased bilateral amygdala recruitment in adults when emotional expressions towards previously unfamiliar objects are more unexpected (Meffert et al. 2014). This suggests a role for

the amygdala in object valence learning, as a function of the unexpectedness of emotional expressions. In this study, we examined children diagnosed with Disruptive Behavior Disorders (Conduct Disorder and/or Oppositional Defiant Disorder) using functional Magnetic Resonance Imaging while they performed a similar social referencing task. During this task, participants viewed objects and faces that turned towards the objects and probabilistically displayed a fearful, happy or neutral reaction to them, whilst performing a gender discrimination task. The data suggest reduced amygdala responsivity to unexpected facial expressions and to learned object value in children with Disruptive Behavior Disorders compared to neurotypical individuals. Moreover, amygdala responses to object value in children with Disruptive Behavior Disorders are attenuated more with higher symptom severity. These results suggest a possible mechanism through which children with Disruptive Behavior Disorder are impaired in learning from social cues in their environment, which critically involves the amygdala.

Disclosures: H. Meffert: None. **M.R. VanTieghem:** None. **S.F. White:** None. **J.R. Blair:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.02

Topic: F.03. Motivation and Emotion

Support: Bayerische Forschungsstiftung 7207815

Deutsche Forschungsgemeinschaft 9209706

Title: Epigenetic regulation of oxytocinergic during social fear conditioning

Authors: *R. MENON, I. D. NEUMANN;
Dept. of Behavioral and Mol. Neurobio., Univ. of Regensburg, Regensburg, Germany

Abstract: Fear is an adaptive emotional response to threatening situations. Maladaptation of fear responses, in particular of social fear, are characteristic symptoms of psychopathologies such as social anxiety disorder (SAD). Treatment of SAD is rather unspecific and combines psychotherapy and pharmacotherapy (e.g., benzodiazepines or selective serotonin reuptake inhibitors). In order to reveal the molecular and neuronal underpinnings of SAD, we have established a model of social fear using a social fear conditioning (SFC) paradigm in male mice which resembles SAD in humans (Toth et. al., 2012). The neuropeptide OXT has been proposed

as a potential therapeutic agent for SAD due to its pro-social, anxiolytic and stress attenuating effects (Neumann and Landgraf 2012) mediated in the brain by OXT receptors (OXTR). Our results have shown that local infusion of OXT into the dorso-lateral septum (DLS) leads to rapid extinction of social fear in male and female mice. Social fear conditioned (SFC+) mice showed an increase in OXTR binding in the DLS which normalized after social fear extinction, while local OXT release in response to social stimuli was found to be blunted in SFC+ mice (Zoicas et. al., 2014). In line with the increase in OXTR binding we found an elevated Oxtr mRNA levels in the DLS, but not the dorsal hippocampus and amygdala, 2 hrs after fear acquisition. Similarly, the described attenuation of intracerebral OXT release was reflected by reduced Oxt mRNA levels in the PVN 2 hrs after social fear extinction. These results point towards a regulatory mechanism at the DNA level possibly via epigenetic modifications. Histone deacetylases (Hdac) are key enzymes which modify chromatin contributing to gene expression changes. Therefore, we studied the local expression of histone deacetylases (Hdac) as epigenetic markers in SFC+ versus SFC- mice. SFC exposure altered Hdac1 mRNA expression in the DLS of mice after 2 hrs. Hdac inhibitors are known to augment fear extinction and rescue cognitive deficits in animal models of impaired extinction (Fujita et. al., 2012). Local application of MS275, a potent Hdac1 inhibitor, in the DLS of mice 60 min before extinction training significantly increases extinction learning. Studies currently in progress are aimed at revealing the link between the SFC-induced alterations in the OXT system and the above mentioned alterations in HDAC activity within the DLS, which may play a role in regulating social fear in mice. Supported by Bayerische Forschungsstiftung and Deutsche Forschungsgemeinschaft.

Disclosures: R. Menon: None. **I.D. Neumann:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.03

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Athletic anxiety is associated with impaired pattern separation

Authors: *M. D. MCCRADY[1], P. I. ROSEBUSH[3], M. F. MAZUREK[2];
[2]Neurol., [1]McMaster Univ., Hamilton, ON, Canada; [3]Psychiatry, St. Joe's Hosp., Hamilton, ON, Canada

Abstract: Background: Hippocampal neurogenesis is the process of the functional integration of adult-born neurons within the dentate gyrus. Recent evidence has implicated impaired

neurogenesis in the aetiology of psychiatric disorders, and impaired pattern separation (PS) - the key function of adult-born neurons - may underlie the clinical manifestations of anxiety. Sport psychology posits that anxiety can be facilitative or detrimental, depending on the athlete's perspective. When an athlete believes they have sufficient resources to cope with the demands of the competitive environment, the stress of competing can be facilitative; without sufficient demands, competing is stressful and anxiety can be detrimental. While recent reports have found that poor PS test performance is linked with depression, none have yet examined anxiety. We hypothesize that athletes with anxiety disorders and those who are stressed will perform poorly on the PS test, reflecting impaired neurogenesis. Methods: We administered a pattern separation test to 112 athletes (90M 22F) from McMaster varsity teams. All athletes underwent a psychiatric screening interview and sport psychology questionnaires. Individuals with anxiety disorders were separated into the Psychiatric group. Remaining athletes were separated by sport psychology results into groups of facilitative (FCL) or detrimental (DTR) competitive stress. Results: Athletes with anxiety disorders performed significantly worse on the PS task than those without ($p<.0001$). Anxiety on the sport psychology tests alone was mildly associated with poor PS performance. The DTR group performed worse than the FCL group ($p<.05$). Conclusions: These results indicate that athletes with anxiety disorders show poor performance on the PS test, potentially reflecting impaired neurogenesis. Importantly, it appears that for most individuals rather than the absolute level of anxiety it is the interpretation of anxiety that can result in impairments to neurogenesis.

Disclosures: **M.D. McCrady:** None. **P.I. Rosebush:** None. **M.F. Mazurek:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.04

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NHMRC Grant

ARC DECRA Fellowship

University of Melbourne International Scholarship

Title: Hippocampal-dependent effects of environmental enrichment versus exercise in a serotonin 1A receptor knock-out mouse model of anxiety disorder

Authors: J. ROGERS[1], U. VO[1], T. PANG[1], L. BURET[1], H. MEIKLEJOHN[2], A. ZELEZNIKOW-JOHNSTON[1], L. CHURILOV[1], M. VAN DEN BUUSE[3], *A. J. HANNAN[1], T. RENOIR[1];
[1]Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia; [2]The Univ. of Melbourne, Melbourne, Australia; [3]La Trobe Univ., Melbourne, Australia

Abstract: Aim: Constitutive serotonin 1A receptor knock-out mice (5-$HT_{1A}^{-/-}$) have an anxiety-like phenotype as well as hippocampal-dependent learning and memory (L&M) deficits. We aimed to assess whether exercise (Ex) or environmental enrichment (EE) would rescue these behavioural deficits in 5-$HT_{1A}^{-/-}$ mice. Our hypothesis was that a robust gene-environment interaction to EE & Ex, increased neuronal turnover in the dentate gyrus, mediated at the molecular level by increased brain derived neurotrophic factor (BDNF) levels, would underlie the restoration of the behavioural phenotype. Through this study design, we also aimed to assess how critical the 5-HT_{1A} receptor is to these activity-dependent molecular & cellular processes stimulated by EE or Ex. Background: Anxiety disorders are the most common mental illness in the general population (>25% US lifetime prevalence) and are often accompanied by L&M impairments. 5-$HT_{1A}^{-/-}$ has been established as a mouse model of anxiety disorder. The anxiety phenotype has established developmental origins, and this mirrors the hypothesised effect of the C-109G functional polymorphism, which is associated with anxiety disorder in humans. In adult rodents, Ex or EE change emotionality-related behaviours as well as enhance aspects of L&M. Environmental manipulations could thus be seen as potential novel strategies for improving outcome in these disorders. Methods: 5-$HT_{1A}^{-/-}$ and wild-type (WT) littermate mice were either housed in environmentally enriched (EE) cages, exercise (Ex) cages with running wheels, or under standard housing conditions. After two weeks, their anxiety-like behaviour was assessed on the elevated plus maze (EPM). At the four-week point, their performance on the Morris water maze (MWM), a L&M task, was determined. Subsequently, hippocampal neurogenesis and BDNF protein levels were assessed. Results: We demonstrate experience-dependent changes to the different elements of the 5-$HT_{1A}^{-/-}$behavioural phenotype. Ex, but not EE, rescued the L&M impairment on the MWM retention probe and that correlated with increased hippocampal neurogenesis and mature BDNF protein levels. EE, but not Ex, rescued the anxiety-like behaviour on the EPM and these effects were not mediated by either increased neurogenesis or BDNF. The data suggests that the 5-HT_{1A} receptor is not critical for exercise-induced increases in neurogenesis or mature hippocampal BDNF protein levels. Our study demonstrates that these environmental interventions are differentially therapeutic in this mouse model, with implications for the understanding and treatment of anxiety disorder.

Disclosures: J. Rogers: None. **U. Vo:** None. **T. Pang:** None. **L. Buret:** None. **H. Meiklejohn:** None. **A. Zeleznikow-Johnston:** None. **L. Churilov:** None. **M. van den Buuse:** None. **A.J. Hannan:** None. **T. Renoir:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.05

Topic: F.03. Motivation and Emotion

Support: K08MH104743-01A1

NARSAD Young Investigator Award from The Brain & Behavior Research Foundation

University of Michigan

Title: Social fear learning emerges early in life

Authors: *J. DEBIEC[1], D.-J. CHANG[2], S. NUMBERS[1];
[1]The Mol. & Behavioral Neurosci. Inst., [2]Mol. & Behavioral Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Emotional trauma and fear may be transmitted across generations. We have recently demonstrated in a rodent model that maternal defense responses may be transferred to her infants through maternal fear expression and infant social fear learning (Debiec and Sullivan, PNAS 2014). We have demonstrated in our model the role of the olfactory modality in this transmission. Since the role of chemosignaling in communicating fear in humans is yet to be determined, we asked whether maternal stress vocalizations play a role in the mother-to-infant transmission of fear. Preweaning rat pups were exposed to the previously recorded and played back maternal stress vocalizations (22 kHz ultrasonic vocalizations known to trigger in rats distress and avoidance) paired with a neutral odor. Control group included pups exposed to the same odor alone. Subsequently, pups' behavioral responses upon re-exposure to this odor were tested. Statistical analysis revealed that pups that had received pairing of distress vocalizations with the neutral odor as compared to pups exposed to the neutral odor alone displayed fear ($p<0.02$) and avoidance ($p<0.05$) upon subsequent re-exposure to this odor. In a series of other experiments we characterized the neural and endocrine mechanisms of this fear transmission through maternal stress vocalizations. Our model demonstrates that maternal fear responses may be transmitted to pups through maternal stress vocalizations and infant associative learning.

Disclosures: J. Debiec: None. **D. Chang:** None. **S. Numbers:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.06

Topic: F.03. Motivation and Emotion

Title: Methylphenidate reduces anxiety effects on a working memory task in healthy subjects

Authors: *M. ERNST, A. DAVIS, C. GRILLON;
NIMH/NIH, NIMH-NIH, Bethesda, MD

Abstract: Anxiety affects two functional domains, cognitive (excessive worry) and physiological (hyperarousal), which are distinctly influenced by threat. The well-recognized modulatory effects of anxiety on cognitive function (such as working memory) and conversely, cognitive performance on anxiety (such as physiological startle), need to be better understood as they can provide insights into treatment. One way to examine this question is to manipulate separately cognitive function or anxiety level pharmacologically. We present data in 60 healthy adults on the effects of a single dose of 20mg methylphenidate (MPH), 40mg propanolol (PRO) or placebo (PLA) on startle response (ocular EMG) and working memory (n back task,1-, 2-, and 3-back) in a safe and anxiety-induced (threat of electrical shock) context. Compared to PLA, (1) MPH, a dopamine agonist used to treat attention deficit, was expected to improve memory performance and potentially decrease physiological anxiety, and (2) PRO, a beta-adrenergic receptor-blocking used to treat stage anxiety, was expected to reduce physiological anxiety, and potentially improve performance. MPH compared to PLA in the threat condition revealed better performance on the 3-back task, which was accompanied by stronger startle response. In contrast, PRO compared to PLA seemed to reduce startle, but did not affect performance. The amplification of the physiological response to anxiety (anxiety-potentiated startle) by MPH suggests that MPH impacts a component of the startle response that is different from the anxiety-related startle response. Subjective scores on anxiety and task difficulty will be analyzed to probe more specifically this question, as well as the potential role of physiological anxiety on performance.

Disclosures: M. Ernst: None. **A. Davis:** None. **C. Grillon:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.07

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Effect of Agmatine in chronic stress-induced anxiety and oxidative stress in mice

Authors: *M. GURSAHANI, N. GAWALI, A. CHOWDHURY, P. KOTHAVADE, V. BULANI, A. JUVEKAR;
Inst. of Chem. Technol., Mumbai, India

Abstract: Aim: Anxiety-related disorders are a common public health issue. Several lines of evidence suggest that altered NMDA receptors and nitric oxide synthase neurotransmission underlies anxiety. Thus, novel molecules targeting these pathways might be promising candidates for the treatment of anxiety related disorders. Agmatine is a NMDA receptor and nitric oxide synthase antagonist which may be useful for anxiety. In the present study, we investigated the effect of Agmatine (10, 20 and 40 mg/kg, i.p.) on behavioural and biochemical parameters in chronic stress induced anxiety in mice. Method: The normal and stressed male Swiss albino mice were administered Agmatine (10, 20 and 40 mg/kg, i.p.) for 21 days. Restraint stress was induced by immobilizing for 2 hours for 21 days. This induced anxiety. On 22nd day, anxiolytic effect was assessed by an elevated plus maze (EPM), open-field and locomotor tests. Restraint stress produced anxiety in EPM and open-field tests, raised corticosterone levels and oxidative stress (evaluated by lipid peroxidation, nitrite concentration, reduced glutathione and catalase activity) significantly as compared to naive group. Results: Chronic treatment with Agmatine for 21 days significantly reversed the chronic stress-induced behavioral (impaired locomotor activity, anxiety and percentage memory impairment) parameters. Oxidative defence system in the treated groups was strengthened as compared to naive group. Moreover, the plasma corticosterone level was significantly decreased with Agmatine (40 mg/kg). Conclusion: The study revealed that Agmatine ameliorates various chronic stress-induced behavioural and biochemical alterations in mice, thus showing protective effects against chronic stress.

Disclosures: **M. Gursahani:** None. **N. Gawali:** None. **A. Chowdhury:** None. **P. Kothavade:** None. **V. Bulani:** None. **A. Juvekar:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.08

Topic: F.01. Human Cognition and Behavior

Title: Striking results from deep brain stimulation for depression/obsessive-compulsive disorder

Authors: *R. MURROW;
Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Deep Brain Stimulation (DBS) is widely used as an effective treatment for a variety of movement disorders such as Parkinson's disease (PD) and essential tremor (ET) syndrome. DBS is now beginning to be used to treat psychiatric disorders such as severe obsessive-compulsive disorder (OCD) and depression, often with striking results. The DBS target structure for OCD and depression has been described in the literature under many names including the Nucleus Accumbens and the ventral anterior limb of the internal capsule and adjacent ventral striatum ("VC/VS"). Over time, due to improving results, the target has moved posteriorly. Our target is more accurately described anatomically as the Ventral Pallidum (VP). The video associated with this abstract demonstrates the striking intra-operative results of a patient during an awake craniotomy for DBS of the VP for severe OCD and depression. DBS of the ventral intermediate nucleus (VIM) of the thalamus and the subthalamic nucleus (STN) are well known to produce an immediate and profound resolution of contralateral extremity tremor. This dramatic result is felt to be due to disruption of the discrete pathological overactive and reverberating neural circuit which was previously mediating this disease symptom. In the case of PD, the circuit involved is known as the "dorsal loop" or the "motor loop". It is one of the classical "cortical-basal ganglionic-thalamic-and reentrant-cortical" loops which describes the basic architecture of the forebrain. There are many such "reentrant" loops in the forebrain. These loops are felt to sub-serve various aspects of motor behavior. There is also a "ventral loop", which is sometimes referred to as a "limbic loop". Disease within this loop has been associated with a variety of psychiatric disorders including depression and OCD. We targeted a component of this loop, the VP, in a patient with severe OCD and depression. Intra-operative high frequency electrical stimulation of the left VP resulted in immediate and marked affective improvement and contralateral (right) improved affective expression (smiling). Stimulation of the right VP resulted in immediate and significant affective improvement and asymmetric (left greater than right) affective expression (smiling). The profound, immediate, and lateralizing resolution of disease symptomatology with DBS in this case is highly reminiscent of the profound, immediate, and lateralizing resolution of tremor in PD and ET with DBS. This finding provides evidence that this "limbic loop" may be pathologically overactive in depression in a fashion that is analogous to the way that the "motor loop" is felt to be overactive in the case of tremor in PD.

Disclosures: R. Murrow: None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.09

Topic: F.03. Motivation and Emotion

Support: NIH Intramural Program

Title: The effect of threat on within-network functional connectivity across the entire human brain

Authors: *N. L. BALDERSTON, E. HALE, S. TORRISI, A. HSIUNG, K. O'CONNELL, M. ERNST, C. GRILLON;
Natl. Inst. of Mental Hlth., NIH, Bethesda, MD

Abstract: Anxiety, which is characterized by a sustained increase in arousal in response to unpredictable stressors, is difficult to study with traditional neuroimaging methods because it does not conform to the constraints of a typical event-related design. Several recent fMRI studies have used seed-based functional connectivity to study the neural correlates of anxiety, showing increases in connectivity among regions like the amygdala and mPFC during threat of shock. However, hypothesis-driven seed-based approaches do not provide information about global patterns in the data. Therefore, the purpose of this study was to use a data-driven approach to determine the effect of anxiety on functional connectivity across the entire brain. We induced anxiety in healthy individuals using the threat of shock paradigm. Subjects were exposed to alternating blocks of threat and safety and instructed that shocks would be randomly delivered during the threat blocks. Throughout the experiment, subjects provided continuous ratings of their anxiety using a button box, but no other task was performed. We recorded multi-echo fMRI and used an independent components analysis (MEICA; Kundu et al., 2012) to remove non BOLD-like artifacts from the data. We also masked out white matter and CSF, and removed variability accounted for by nuisance variables. Next we performed a group-level independent components analysis (ICA; Calhoun et al., 2005), and generated spatial maps corresponding to the 25 components identified. To characterize the connectivity within these components, we used 3dTcorrMap in AFNI to correlate the timeseries for each voxel in a given component with the timeseries of every other voxel in the component independently for safe and threat for each subject. We then averaged these values to obtain a single metric that reflected the connectivity within a given component for each subject/condition. Using a paired sample t-test we found that subjects reported significantly more anxiety during threat than safety. Using a mixed-effects GLM we found a significant increase in within-network connectivity across components during threat than safety. These results suggest that anxiety increases within network-connectivity, which may reflect an enhanced state of vigilance when potential threats are imminent. These results are consistent with recent work from our lab showing that threat improves performance in a sustained attention task, and current work showing that threat decreases alpha power (a possible sign of disinhibition) as recorded by magnetoencephalography.

Disclosures: **N.L. Balderston:** None. **E. Hale:** None. **S. Torrisi:** None. **A. Hsiung:** None. **K. O'Connell:** None. **M. Ernst:** None. **C. Grillon:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.10

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Kakenhi 26102704

Title: Post-traumatic stress disorder-like behaviors in FABP3 null mice

Authors: K. FUKUNAGA[1], Y. YABUKI[1], I. TAKAHATA[1], Y. OWADA[2], *N. SHIODA[2]; [1]Pharmacol., Tohoku Univ. Grad Sch. Pharm Sci., Sendai, Japan; [2]Tohoku Univ., Sendai, Japan

Abstract: [Introduction] We recently reported that fatty acid binding protein 3 (FABP3, H-FABP) binds to the intracellular loop of dopamine D2L receptor and that FABP3 null mouse reveals dysfunction of dopamine-regulated motor coordination (Shioda and Fukunaga. J Neurosci. 2010;30:3146-3155). We here document that FABP3 null mouse shows an enhancement of anxiety and locomotor behaviors. [Methods] Wild type mice (C57BL6) and FABP3 null mice underwent fear conditioning once a day with consecutive 5 days and measured the fear acquisition and extinction for 35 days. When mice were administrated with melatonin receptor agonist, the drug was orally administrated once a day before given unconditional stimuli. [Results & Discussion] FABP3 null mice had deficits in extinction of contextual fear memory. The acquisition of contextual fear memory in FABP3 null was not distinguished from those in wild type mice. In one month after exposure to contextual stimulation, wild type mice significantly reduced the elapsed time until entering the chamber given footshock, showing normal extinction. However, the elapsed time remained elevated in FABP3 null mice. Likewise, the cFos expression in the amygdala after exposure to conditional stimulation remained elevated in FABP3 mice but declined in the wild type mice. More importantly, the PTSD-like behaviors in FABP3 null mice were ameliorated by treatment with melatonin receptor agonist. [Conclusion] FABP3 null mice are novel model of PTSD and are useful for drug development to improve the PTSD-like behaviors. This work is supported by Kakenhi 26102704 (K.F.).

Disclosures: **K. Fukunaga:** None. **Y. Yabuki:** None. **I. Takahata:** None. **Y. Owada:** None. **N. Shioda:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.11

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Reversal of increased consolidation/expression of fear after chronic social defeat by TRPC4/5 inhibition

Authors: B. HENGERER[1], H. SIGRIST[4], *M. M. MORAN[5], B. L. CHENARD[6], R. J. GALLASCHUN[6], T. STRASSMAIER[5], C. EICKMEIER[2], A. SAUER[3], J. NICHOLSON[1], E. SEIFRITZ[4], S. JUST[1], C. PRYCE[4];
[1]Biol., [2]Chem., [3]DDS, Boehringer Ingelheim, Biberach an der Riss, Germany; [4]Preclinical Lab. for Translational Res. into Affective Disorders, Dept. of Psychiatry, Univ. of Zurich, Zurich, Switzerland; [6]Chem., [5]Hydra Biosci., Cambridge, MA

Abstract: TRPC4 and TRPC5 are subunits of calcium-permeant, non-selective cation channels predominantly expressed in the central nervous system. Expression studies reveal particularly high levels in the amygdala. Expression was also detected in the frontal cortex, hippocampus and hypothalamus, brain areas that show increased activity in patients with depression and anxiety disorders. In slices from TRPC4-/- and TRPC5-/- mice, cortico-amygdala EPSPs are significantly smaller than in control slices while basal synaptic transmission is unaltered, providing a mechanistic explanation for the anxiolytic phenotype observed in these mice. In addition, functional changes in the prefrontal cortex-amygdala circuit are thought to have important roles in stress-related symptoms in both human patients and animal models such as the chronic social defeat (CSD) model. We took a pharmacological approach to determine the role of TRPC4 and TRPC5 in the CSD stress model. To induce CSD stress, mice were exposed to 15 days of daily attacks by aggressive dominant mice. This protocol leads to exaggerated ("pathological") responses to a different stressor. CSD mice exhibit increased baseline freezing and acquire increased fear freezing when exposed to mild inescapable electroshocks. Furthermore, CSD increases acquisition and expression of fear to a conditioned stimulus (CS) that specifically predicts an aversive stimulus in a fear conditioning paradigm. A selective TRPC4/5 inhibitor or vehicle was given directly after the fear conditioning session and on the following day, prior to the tests of fear expression to context (environmental cues) and to CS. There were no effects of the compound in control mice. In the context test, there was increased freezing to context by CSD mice treated with vehicle relative to each of the other groups. In contrast, CSD mice that received the TRPC4/5 antagonist behaved similarly to mice naïve to the

CSD protocol. In the CS test, there was increased freezing to CS by CSD vehicle-treated mice relative to each of the other groups. Again, inhibitor-treated CSD mice behaved similarly to control mice. The latter effect resulted mainly from a more rapid extinction of the acquired fear. These data show that the TRPC4/5 inhibitor does not affect basal fear learning-memory but acts to reverse the CSD effect of increased expression of fear to general, contextual stimuli and to the CS that specifically predicts the aversive stimulus. Since the compound was administered directly after conditioning and directly before expression, its effects could be mediated by either decreased fear memory consolidation or recall and/or increased extinction learning.

Disclosures: **B. Hengerer:** A. Employment/Salary (full or part-time); Boehringer Igelheim. **H. Sigrist:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boehringer Ingelheim. **M.M. Moran:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Hydra Biosciences. **B.L. Chenard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Hydra Biosciences. **R.J. Gallaschun:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Hydra Biosciences. **T. Strassmaier:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Hydra Biosciences. **C. Eickmeier:** A. Employment/Salary (full or part-time); Boehringer Ingelheim. **A. Sauer:** A. Employment/Salary (full or part-time); Boehringer Ingelheim. **J. Nicholson:** A. Employment/Salary (full or part-time); Boehringer Ingelheim. **E. Seifritz:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boehringer Ingelheim. **S. Just:** A. Employment/Salary (full or part-time); Boehringer Ingelheim. **C. Pryce:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boehringer Ingelheim.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.12

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Grant of Mind Research Institute

Title: Effect of musical environment on emotional disorders associated with neuropathic pain

Authors: K. SANG, S. HU, X. GAO, Y. XING, *Z. X. DONG;
East China Normal Univ., Shanghai, China

Abstract: Patients with chronic pain not only suffer intolerable ongoing pain but also undergo accompanying cognitive impairment and emotional disorders. Music has been used as an adjuvant therapy to relieve pain and anxiety with variable effectiveness in clinic. However, little is known about the underlying mechanism. In the present study, we investigated the effect of musical environment on anxiety-like behaviors in a rat model of neuropathic pain with spare nerve injury (SNI). The rats showed apparent anxiety-like behaviors in both open field test and elevated-plus maze test two months after SNI surgery. Thus, the number of entries to central area decreased to 45% (±5%, n=20) of sham control (n=13) in the open field test, while overall motor activity (i.e., total distance) was unaffected. In the elevated-plus maze test, the percentage of entering open arms significantly ($p<0.001$) decreased in SNI rats (SNI: 12.58±2.7%, n=20; sham: 30.75±2.82%, n=13), so did the time spent in open arms (SNI: 4.35±1.45%, n=20; Sham: 11.65±2.18%, n=13). These anxiety-like behaviors were effectively reversed by sub chronic (15 days) treatment with citalopram (10mg/kg, i.p.), an anti-anxiety drug commonly used in the clinic. The anxiety-like behaviors were not observed with the SNI rats that received 2 month of music exposure (Mozart Sonata K.448 and Beethoven's fur Elise, 65dB, 12h/day, dark cycle). The performance of the music group in both open field test and elevated-plus maze test showed no significant difference from the sham control group, indicating that the music effectively prevented or reversed anxiety induced by chronic pain condition. This anxiolytic effect of music lasted for one week after the cessation of music treatment. No effect was observed with white noise. To explore the underlying mechanism, Western blot analysis was performed to examine the changes in the neurotransmitters associated with anxiety disorder. We found that there was a significant increase in the expression of serotonin transport (SERT) in the prefrontal cortex in SNI rats. However, the SNI rats treated with music did not show such an increase in the SERT expression, suggesting that music exerts its anxiolytic effect by modulating prefrontal serotonin level via suppressing chronic pain-induced increase in SERT expression. In summary, our study demonstrated the effectiveness of music in preventing/ reversing the anxiety-like state in an animal model of neuropathic pain. Our data provide important information for implementing music-based therapeutic intervention for anxiety disorders in patients with chronic pain.

Disclosures: **K. Sang:** None. **S. Hu:** None. **X. Gao:** None. **Y. Xing:** None. **Z.X. Dong:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.13

Topic: F.03. Motivation and Emotion

Title: The effect of experimental pain on hemodynamic responses measured by functional near infrared spectroscopy

Authors: *D. O. OMIRE-MAYOR, A. POURSHOGHI, A. WONG, K. POURREZAEI; Drexel Univ., Philadelphia, PA

Abstract: Pain is a phenomenon that most people experience at some point in their lives, whether minor and resulting from an injury, a symptom of a disease, or occurring chronically post initial injury or disease, making pain the problem itself. Previous neuroimaging studies have been able to identify ways of quantifying pain objectively, but fail in affordability and feasibility of use in a clinical setting. Functional near infrared spectroscopy has been used as a method to objectively measure the autonomic response to noxious stimuli and has proven to be linked to subjective responses; however, this has yet to be further explored through appropriate analysis of quantifiable subjective responses. Functional near infrared spectroscopy (fNIRS) is an optical brain imaging modality that uses near infrared light to track changes in cerebral hemodynamic responses. Recent research conducted in our lab suggests the use of fNIRS for monitoring cortical activation in response to a given external, noxious stimuli. The fNIRS system can penetrate tissue up to a few centimeters within the 700 to 900nm optical light window. At approximately 700nm, deoxy-hemoglobin is absorbed at a maximum and at approximately 900nm, oxy-hemoglobin is absorbed at a maximum. Through modified Beer-Lambert law calculations, we obtain the changes in oxy and deoxy-hemoglobin. In this study we investigated the fNIRS signals from the dorsolateral prefrontal cortex region, while inducing thermal pain through the use of the cold pressor test. Eight, healthy, right-handed individuals participated in this study, consisting of 14 trials of the experimental procedure. The procedure included placing the right hand in tepid water (maintained at 23°C) for 2 minutes, followed by immersion of the hand in 4°C water for 30 seconds. After 7 trials at 4°C, the subject then placed their hand in tepid water for 2 minutes to conclude the experiment. The procedure was then repeated at 15°C for 7 trials. This was done to appropriately compare the data generated from fNIRS to the perceptive response of each subject. We compared the fNIRS results obtained from experimentation to the Short Form McGill Pain Questionnaire and the State Trait Anxiety Inventory (administered during experimentation), both of which give quantifiable information about the subjective pain experience. From this data, our results show a link between the objective fNIRS results and subjective pain reporting, at different levels of stimuli. This suggests that the hemodynamic response to nociception is indeed correlated to the subjective report of pain, making fNIRS a potentially promising tool that in the future will help clinicians to objectively measure pain.

Disclosures: **D.O. Omire-Mayor:** None. **A. Pourshoghi:** None. **A. Wong:** None. **K. Pourrezaei:** None.

Nanosymposium

109. Stress and Anxiety

Location: S102

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 109.14

Topic: F.03. Motivation and Emotion

Title: Signaled active avoidance learning recruits a prefrontal-hippocampal pathway for the suppression of innate defensive reactions

Authors: *J. M. MOSCARELLO[1], J. LEDOUX[2,3];
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]NYU, New York, NY; [3]Emotional Brain Inst., Nathan Klein Inst., Orangeburg, NY

Abstract: Signaled active avoidance (SigAA) behavior models the proactive coping processes that can mitigate the impact of aversive or anxiety-provoking stimuli. In SigAA, subjects learn that a response performed during a CS causes the omission of an aversive US. Pavlovian reactions, such as freezing, predominate early on during training, but are suppressed as avoidance is acquired. Using a yoked control paradigm in which master subjects can control stimuli for themselves and their yoked partners, we demonstrate that masters display less CS-evoked freezing than yokes in both the avoidance context and an alternate context that does not allow for the avoidance response. These data indicate that acquisition of the avoidance contingency fundamentally alters the response to a threatening CS, attenuating its ability to drive innate defensive reactions. This process is mediated by a pathway including the infralimibic prefrontal cortex (ilPFC) and the dorsal hippocampus (DH). Chemogenetic inhibition of either structure robustly enhances freezing to an avoidance CS. In the case of both ilPFC and DH, inactivation produces levels of freezing comparable to poor performers, or subjects that fail to suppress freezing and acquire SigAA. We conclude that ilPFC and DH translate learning about the avoidance contingency into the diminution of freezing. These data suggest that an internal locus of control reduces the perceived intensity of a threatening CS, highlighting the potential efficacy of active coping based therapies for disorders of fear and anxiety.

Disclosures: **J.M. Moscarello:** None. **J. LeDoux:** None.

Nanosymposium

110. Eye Movements: Visual-Motor Transformations and Updating

Location: S402

Time: Sunday, October 18, 2015, 8:00 AM - 9:45 AM

Presentation Number: 110.01

Topic: D.06. Eye Movements

Support: NIH Grant 1R01 EY021286

Title: Different mechanisms for pursuing a spot target versus a feature on a large object

Authors: *S. N. WATAMANIUK[1,2], E. POTAPCHUK[2], S. J. HEINEN[2];
[1]Psychology, Wright State Univ., Dayton, OH; [2]The Smith-Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: Previously, we showed that pursuit of large objects is less saccadic and relatively inattentive compared to pursuit of a small spot (Heinen et al., Journal of Vision, 2011; Jin et al., Journal of Neuroscience, 2014). We suggested that a separate, motion-based mechanism is used to pursue large objects allowing the fovea to inspect object features. Alternatively, a feature on an object might simply become the pursuit target, pursued with the small spot mechanism. To test this hypothesis, observers pursued a single small spot (0.2 deg) or a small spot centered on a larger circular array (6° diameter) of 8 "feature" spots, in separate blocks. All stimuli translated across the screen at 7 d/s. Following a random fixation (500-1000 ms) and initial pursuit period (900-1400 ms), a randomly chosen feature on the circular array brightened and enlarged, and observers made a saccade to it and pursued it for the remainder of the 3 s trial. In single-spot blocks, the spot target disappeared simultaneously with the appearance of the saccade target corresponding to one of the 8 target locations as in the larger stimulus. We found that following the saccade, pursuit velocity for the single spot briefly increased when the new target appeared in the direction of pursuit, but decreased when the target appeared opposite the pursuit direction, indicating that a position signal generated by the second target was deviating pursuit velocity. No deviation occurred when the large circular array was visible, suggesting that conflicting position signals were not affecting pursuit. Interestingly, catch-up saccades were suppressed for an extended period preceding the targeting saccade, and more so for the large object, suggesting a predictive attention shift to possible upcoming target locations, that was greater when the targets were visible features on a large pursuit object. The results provide evidence that a different mechanism than that currently embodied in the classic pursuit pathway is used to pursue large objects, and that this mechanism is relatively independent of object feature inspection.

Disclosures: S.N. Watamaniuk: None. **E. Potapchuk:** None. **S.J. Heinen:** None.

Nanosymposium

110. Eye Movements: Visual-Motor Transformations and Updating

Location: S402

Time: Sunday, October 18, 2015, 8:00 AM - 9:45 AM

Presentation Number: 110.02

Topic: D.06. Eye Movements

Title: Mapping eye movement circuits across the entire hindbrain

Authors: *A. D. RAMIREZ, E. AKSAY;
Physiol. and Biophysics, Weill Cornell Med. Col., New York, NY

Abstract: Spontaneous eye movements are made in the absence of sensory input and provide a model behavior for studying the circuit mechanisms linking internal brain states to action. The control of spontaneous eye movements requires the coordinated activity of at least two groups of premotor neurons: burst neurons that fire a brief volley of action potentials resulting in a saccade and Velocity-to-Position Neural Integrator (VPNI) cells that convert burst neuron activity into persistent firing required to hold the eyes fixed at their new location. The mechanisms underlying these firing patterns are thought to rely heavily on network interactions, however the comprehensive locations of VPNI and burst neurons has never been determined in a single species. We address this in the larval zebrafish (7-8 dpf) by coupling focal laser ablations with calcium imaging throughout the entire hindbrain and cerebellum while simultaneously tracking spontaneous eye movements using two-photon microscopy from populations of neurons expressing GCaMP6f. Eye movements were made in the dark to remove confounding effects on cell activity from visual input and resultant feedback. We find the majority of cells correlated with eye movements could be classified as position or velocity related. Velocity neurons were distributed in the rostral-caudal axis across most of the hindbrain (rhombomeres 2-8). Position cells were more clustered: in addition to the previously observed cells in the caudal hindbrain (rhombomeres 7-8), cells were also clustered in more rostral locations (rhombomeres 5-6 and 2). Interestingly, we find a buildup of activity multiple seconds before a saccade in some neurons suggesting a novel cell type involved in eye movement control. We find few neurons in the cerebellum correlated with spontaneous eye movements. Using principal component analysis we find that saccade-triggered average signals can be described using a low-dimensional space. Focal laser ablations of cells rostral of rhombomere 7 have no effect on eye-movement persistence while ablations of cells in rhombomeres 7-8 show deficits in persistence, consistent with prior results. Furthermore, select position-dependent neurons in these rostral regions show a loss or gain saccade-triggered response following laser ablations in rhombomeres 7-8 suggesting a coupling between neurons in these different anatomical regions. These results provide the first comprehensive hindbrain map of the distribution of signals active during the generation of

spontaneous eye movements and begin to address the causal roles of different eye movement hindbrain nuclei.

Disclosures: **A.D. Ramirez:** None. **E. Aksay:** None.

Nanosymposium

110. Eye Movements: Visual-Motor Transformations and Updating

Location: S402

Time: Sunday, October 18, 2015, 8:00 AM - 9:45 AM

Presentation Number: 110.03

Topic: D.06. Eye Movements

Support: Canadian Institutes for Health Research

Canada Research Chair Program

Title: Comparison of visual, motor, and combined SC burst codes during reactive and delayed gaze shifts to visual stimuli

Authors: ***M. SADEH**, A. SAJAD, H. WANG, X. YAN, J. CRAWFORD;
Ctr. For Vision Res., Toronto, ON, Canada

Abstract: During reactive saccades to transiently presented visual stimuli,it is thought that oculomotor structures such as the superior colliculus(SC)show a burst of activity composed of both visual and motor signals,but it is not known how these components influence the spatial code within the burst.Our previous head-unrestrained experiments suggested that the combined visuomotor burst of neurons in Superior Colliculus(SC) primarily code target location in eye coordinates(Te) during reactive saccades (DeSouza et al.J.Neurosci.2011).However,in subsequent experiments(Sadeh et al. Submitted) we used a memory guided saccade task to identify different cell types (visual, visuomotor, and motor)and found that Te gives the best fit for visual activity whereas Ge(Final Gaze position relative to initial eye orientation)gave the best overall fit for motor activity.In addition several other models were significantly eliminated including Eye in head,head in space,head displacement,target relative to space and head and final gaze relative to head and space.In this current study we to quantitatively compare neural activity in the memory and reactive tasks for the same neurons.We recorded from the same neurons in head unrestrained monkeys during both the memory guided(where fixation is maintained for a period after the stimulus appears)and reactive tasks(where the stimulus appears simultaneously with extinguishing the fixation light).3-D eye and head rotations were recorded,and response field data were analyzed in multiple frames using a statistical method reported previously(Keith

et al. J.Neurosci.Meth.2009).62 neurons were recorded from the left and right SC of two monkeys and tested with both tasks.16 of these only showed a visual response to the stimulus,12 neurons only had a motor response during the saccade, and the rest(visuomotor neurons)showed both responses.So far we have analyzed the visual and motor activity of 12 motor and 24 visuomotor and 10 visual neurons.In general, our preliminary results support the notion that the separate visual response encodes Te,the separate motor response encodes Ge,whereas the combined reactive response shows a best fit for Te.Our aim is to do a detailed population-by-population and neuron-by-neuron analysis of where these various responses fall along the continuum between Te and Ge coding.Our preliminary results reconcile our previous two studies and show directly that unlike the memory guided paradigm that differences exist between spatial information encoded by visual and motor activities,in reactive saccades the visual code tends to dominate the motor code in both types of activities and across all neuron types.

Disclosures: **M. Sadeh:** None. **A. Sajad:** None. **H. Wang:** None. **X. Yan:** None. **J. Crawford:** None.

Nanosymposium

110. Eye Movements: Visual-Motor Transformations and Updating

Location: S402

Time: Sunday, October 18, 2015, 8:00 AM - 9:45 AM

Presentation Number: 110.04

Topic: D.06. Eye Movements

Support: CIHR Grant

Title: Microstimulation of the superior colliculus produces coordinated saccade and pupil responses

Authors: ***C.-A. WANG**, D. P. MUNOZ;
Queens Univ., Kingston, ON, Canada

Abstract: The appearance of a salient event in the environment initiates a wide repertoire of behavioral and physiological responses, including shifts of gaze and attention, and pupil dilation, which are thought to help to discern the event, and to mobilize the body for an upcoming action. The superior colliculus (SC), a midbrain structure, has been hypothesized to coordinate the orienting response. However, its role in coordinating orienting responses beyond gaze and attention shifts is poorly understood. Although the SC has been recently linked to pupil size because of pupil dilation evoked by weak microstimulation of the SC, the function of this dilation is still unexplored. Parameters of SC microstimulation are known to systematically

modulate properties of evoked saccades. If the SC is coordinating the whole orienting response, pupil responses and saccades evoked by SC microstimulation should be correlated. Here, we examined the coordination between saccade and pupil responses by microstimulation of the SC at suprathreshold current to evoke saccadic eye movements (> 30 μA; frequency: 200-300 Hz; stimulation train duration: 25-100 ms). While requiring subjects to maintain central fixation, we stimulated the intermediate SC layers. Stimulation parameters systematically modulated evoked pupil responses and saccades, showing faster and larger pupil responses with higher velocity, as well as faster saccades with higher velocity, observed with strong stimulation parameters (e.g., higher frequency). We further investigated the function of the pupil dilation by presenting a visual stimulus after microstimulation induced pupil dilation (stimulation occurred 250-1000 ms before target appearance, so pupil size was systematically varied), and the monkey required to look to visual target for reward. Pupil velocity was negatively correlated with saccadic reaction time (SRT), showing faster SRTs while pupil size was increasing, even when the visual target was presented in the opposite location to that represented by the stimulated area. Together, the results suggest that the pupil responses and saccadic eye movements, as components of orienting, are coordinated via the SC, and the function of pupil dilation could facilitate target detection processing.

Disclosures: C. Wang: None. **D.P. Munoz:** None.

Nanosymposium

110. Eye Movements: Visual-Motor Transformations and Updating

Location: S402

Time: Sunday, October 18, 2015, 8:00 AM - 9:45 AM

Presentation Number: 110.05

Topic: D.06. Eye Movements

Support: CIHR MOP 93796,123247

Title: Transient pupil dilation after subsaccadic microstimulation of primate FEF

Authors: *S. J. LEHMANN[1], B. D. CORNEIL[2];
[1]Robarts Res. Inst. / Univ. of Western, London, ON, Canada; [2]Physiol. and Pharmacol., Western Univ., London, ON, Canada

Abstract: The orienting response is an organism's reaction to changes in its environment in order to heighten perception and prepare for action; this can include changes in gaze, attention, neck and limb muscle recruitment, as well as pupil dilation. Pupil responses have been shown to represent cognitive processes like perception and attention, and also index more complex

processes like learning and memory. The frontal eye fields (FEF) are a part of the oculomotor system, and are known to be involved in the generation of voluntary saccadic eye movements, covert shifts in visuo-spatial attention, and decision-making. While microstimulation of the FEF can evoke saccadic gaze shifts, lower levels of stimulation current can elicit components of the orienting response, such as covert attentional shifts and neck muscle recruitment, without evoking saccades. Based on recent results showing that pupil dilation can be evoked by subsaccadic stimulation of the superior colliculus in primates and owls, we investigated the effects of subsaccadic FEF microstimulation on pupil dilation. Two non-human primates performed a fixation task in which we stimulated the right FEF with trains of biphasic pulses. In a total of 101 sites, we parametrically varied stimulation current (3- 60 μA), frequency (50-300 Hz), and duration (30-200 ms). Saccade thresholds in these sites averaged 21 and 23 μA for the two animals, respectively; saccade vectors ranged in eccentricity from 5 to 20°. In 48% of the sites, we found a significant increase in pupil diameter after subsaccadic stimulation for at least one of the 5 stimulation levels (t-test, $p < 0.01$), starting around 200 ms after stimulation onset. In general, the magnitude of pupil dilation scaled with increasing stimulation parameters. Furthermore, by trading off stimulation duration and frequency in a subset of 12 sites, we found a high correlation between the magnitude of evoked pupil dilation and the number of applied pulses ($cc = 0.87$). Our results demonstrate a role for the FEF in eliciting pupil dilation, which is presumably mediated via the superior colliculus. Our findings provide an important link for how high-level processes may influence pupil diameter, strengthening the use of pupil measures as potential biomarkers for oculomotor and cognitive processing in health and disease.

Disclosures: S.J. Lehmann: None. **B.D. Corneil:** None.

Nanosymposium

110. Eye Movements: Visual-Motor Transformations and Updating

Location: S402

Time: Sunday, October 18, 2015, 8:00 AM - 9:45 AM

Presentation Number: 110.06

Topic: D.06. Eye Movements

Title: Spatiotemporal dynamics of MT receptive fields during eye movements

Authors: *A. AKBARIAN AGHDAM[1], M. PARSA[2], B. NOUDOOST[2], N. NATEGH[1]; [1]Electrical and Computer Engin., [2]Cell Biol. and Neurosci., Montana State Univ., Bozeman, MT

Abstract: Our visual system scans the environment via directed, ballistic movements of the eyes known as saccades. Saccadic eye movements enable the visual system to gather information about our environment by bringing the stimulus of interest to the fovea for further visual

processing. Prior to an eye movement, neurons in the extrastriate visual areas change their receptive fields (RFs), thus altering the representation of saccade targets. However, the details of these dynamic changes are not known. We used a white noise analysis approach based on generalized linear models to characterize the dynamics of the cortical spatiotemporal RFs during a saccade task. The responses of multiple neurons within the middle temporal (MT) cortex of macaque monkeys were recorded using linear array electrodes. The animals performed a visually-guided saccade task while a set of probes flashed in pseudorandom positions around the estimated RF of MT neurons during fixation and saccades. Probe presentations were brief, enabling us to characterize the RF changes with a temporal resolution greater than the saccade execution time. To characterize the spatiotemporal RF changes, we fit the response of an MT neuron with a generalized linear-nonlinear-Poisson (LNP) cascade model, consisting of the neuron's spatiotemporal filter, an exponential nonlinearity, and a post-spike filter. The spatiotemporal filter was represented by a set of linear kernels, and its output was passed through an exponential nonlinear function to produce the neuron's instantaneous spike rate. A post-spike filter was used to account for the neuron's temporal response properties, e.g. refractoriness, burstiness, or adaptation. This model was able to predict the responses of MT neurons on a trial-by-trial basis, before, during, and after eye movements. The results of the model during fixation were validated by comparing them to the results from the non-parametric LNP cascade model, and provided a baseline for measuring the dynamics of RF changes during eye movements. Our findings demonstrate dynamic changes of MT neurons' spatiotemporal RFs during eye movements, enabling us to investigate the extrastriate mechanisms underlying changes in the representation of saccade targets.

Disclosures: **A. Akbarian Aghdam:** None. **M. Parsa:** None. **B. Noudoost:** None. **N. Nategh:** None.

Nanosymposium

110. Eye Movements: Visual-Motor Transformations and Updating

Location: S402

Time: Sunday, October 18, 2015, 8:00 AM - 9:45 AM

Presentation Number: 110.07

Topic: D.06. Eye Movements

Support: Wellcome Trust Programme Grant (092668/Z/10/Z)

Title: Longitudinal analysis of pro- and antisaccade development in retinopathy-confirmed cerebral malaria

Authors: *P. C. KNOX[1], I. J. C. MACCORMICK[2,3], E. MBALE[4], M. MALLEWA[4], S. P. HARDING[2];
[2]Eye & Vision Sci., [1]Univ. Liverpool, Liverpool, United Kingdom; [3]Malawi-Liverpool-Wellcome Trust Clin. Res. Programme, Blantyre, Malawi; [4]Dept. of Paediatrics, Univ. of Malawi, Blantyre, Malawi

Abstract: Survivors of paediatric cerebral malaria (CM) may suffer from long term cognitive impairment. However, the interpretation of neuropsychological tests is problematic, since tests developed in a Western context may not be appropriate for children in developing countries. Pro-saccade (PS) and anti-saccade (AS) tests allow for the measurement of visuomotor processes related to the function of discrete brain circuits. The AS directional error rate has a well-described developmental trajectory in which performance improves markedly between 8 and 12 years. We therefore measured PS and AS performance on three or four occasions over 20±4 or 32±4 months (mean±SD) respectively, in children who had survived a single episode of retinopathy positive CM (n=47; mean age 130 months), and control (CON) children with no history of coma or seizure (n=35; 124mo), recruited from a prospective CM study in Blantyre, Malawi. Retinopathy is highly associated with pathologically confirmed CM, in contrast to current diagnostic criteria. Eye movements were recorded in a quiet room using an infrared reflectance eye tracker, which projected targets 10° to the left and right of a central fixation target, after a randomised fixation period. Participants completed 100 PS and 100 AS trials. Tests were explained to children in the local language, and comprehension of instructions was checked before data collection. PS, AS and error PS latencies all declined with age as expected, with no consistent difference between groups. The AS directional error rate was strongly related to age in both groups (CM: r=-0.60, CON: r=-0.76, both $p<0.0001$) and not statistically different between them. Individual participant regressions of each test/age generated negative gradients (CM mean regression slope -0.47; 95% CI -0.28 to -0.68; CON -0.54; -0.26 to -0.82). However, error rates were much higher in both groups compared to those reported in the literature (at 120 months 63% compared to published rates of around 30%). While both groups exhibited comparable age-related performance on saccade tasks, their AS error rates were consistently higher than expected. We conclude that while CM might not pose specific additional risks of long-term damage, this population may face a range of other challenges (eg infectious diseases, nutritional challenges) that impact on brain development.

Disclosures: P.C. Knox: None. **I.J.C. MacCormick:** None. **E. Mbale:** None. **M. Mallewa:** None. **S.P. Harding:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.01

Topic: D.18. Brain-Machine Interface

Support: NSF CBET-1264782

NSF IGERT DGE-1069104

NIH R01 EB006433

Title: Improving single-trial classification of intuitive right hand motor imagery tasks using EEG source imaging

Authors: *B. J. EDELMAN[1], B. BAXTER[1], B. HE[1,2];
[1]Dept. of Biomed. Engin., [2]Inst. for Engin. in Med., Univ. of Minnesota, Minneapolis, MN

Abstract: Electroencephalography (EEG)-based brain-computer interfaces (BCIs) are used from sensorimotor rhythms recorded from scalp electrodes in response to performing motor imagery (MI). However, due to the low spatial resolution of EEG many usable MI tasks are cognitively disconnected from the corresponding action of the output device. Therefore in order to drive these systems towards more intuitive use, we attempted to decode MI of tasks common in everyday life including right hand flexion, extension, supination, and pronation. We hypothesize that EEG source imaging (ESI) will allow us to decode these signals. Five subjects were recruited to participate in this study according to a protocol approved by the University of Minnesota IRB. Subjects were asked to perform 2 Hz self paced MI of one of the aforementioned tasks in a set trial configuration while we recorded 64-channel scalp EEG (Neuroscan Compumedics, Singen, Germany). Subjects performed motor execution of the tasks prior to MI to get a sense of the pace, sensation, etc. The trial structure was as follows: three seconds of rest initiated each trial, followed by a task indicator cue and three seconds of preparation time, and finally a four second “go” cue when the subject would continuously perform the indicated task. Initially, data from all tasks were compiled into a single data set. Independent component analysis and ESI mapping were then used to identify a cortical region of interest (ROI) containing the overlapping right hand motor activity. In a parallel analysis, the time course of each individual task data set was projected onto a cortical model using the weighted-minimum-norm estimate in order to transform the neural data from the sensor domain to the source domain. For all dipoles within the defined ROI, their time-frequency representation (TFR) was calculated using a Morlet wavelet approach. Splitting the TFRs into different frequency bands and time windows created time-frequency features, which were then fed into a four-class linear classifier. The same feature extraction pipeline was applied in the sensor domain for comparison. The group-level four-class classification accuracy achieved by the sensor and source-based method was 69.5% and 82.2%, respectively. The source results were also greater

than the sensor results for classifying all individual tasks, ranging from an increase of 6.6% for extension and 18.6% for flexion. We found that the delta band (0-4 Hz) contained the most discriminable features for these tasks, which supports previous findings in literature. This work was supported in part by NSF DGE-1069104, CBET-1264782, and NIH EB006433.

Disclosures: **B.J. Edelman:** None. **B. Baxter:** None. **B. He:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.02

Topic: D.18. Brain-Machine Interface

Support: ERC-2012-AdG 320708-iCONNECT

Title: Decoding attempted hand movements from motor cortex in amputees using 7 tesla functional MRI

Authors: ***L. C. M. BRUURMIJN**, M. A. H. RAEMAEKERS, M. J. VANSTEENSEL, N. F. RAMSEY;
Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: The locked-in syndrome (LIS) is a condition of complete paralysis, which can be caused by strokes, tumours or neurodegenerative diseases. People with LIS lost nearly all their motor control, as a result of which communication is heavily hindered and may only be possible through eye movements. Brain-Computer Interfaces (BCIs) promise to restore communication by using brain activity to control external devices (Daly and Wolpaw, 2008). The somatotopic organisation of the motor cortex offers a detailed representation of the hand. This allows for restoring communication in an intuitive way by decoding hand gestures from sign language (Bleichner et al., 2013), which may be used for controlling a spelling BCI. Our previous results in decoding hand gestures using fMRI were obtained in healthy, able-bodied volunteers (Bleichner et al., 2013). By contrast, LIS patients can only attempt moving their hands. It is not yet known whether paralysis causes changes in the cortical sensorimotor representation that can affect gesture decodability of attempted movements. Therefore we investigated whether attempted hand gestures can be decoded from 7T fMRI in subjects who have lost motor control over their hand after transhumeral (above-elbow) arm amputation. Amputees are chosen because, similar to LIS patients, they lack explicit muscle activity and accompanying movement-related sensory feedback. We recruited 7 subjects with above-elbow arm amputation (amputation more

than one year ago). After a short training, they performed a task in which they had to articulate six different hand gestures from the American Manual Alphabet. In separate runs, subjects attempted making the gestures with their missing (right) hand. Every gesture was presented 10 times. A control group (N=6) performed the same task with motor execution of the right hand. Per subject, a support vector machine classifier was trained and tested on voxels in the contralateral sensorimotor cortex, using a leave-one-out cross-validation scheme. The classification score from the affected side of amputees (61±15%) was significantly above chance (chance level 16.7%; two-sample t-test, $p<0.01$) and not different from the control group (score: 62±23%; two-sample t-test, $p>0.90$). These results indicate that hand gestures can be decoded successfully from the sensorimotor cortex contralateral to the amputated arm a year or more after amputation. Although LIS can have multiple causes and neurodegenerative diseases might have an impact on the brain and therefore on BCI performance, this study in amputees suggests that detailed cortical organisation is kept intact if explicit movements are impossible.

Disclosures: L.C.M. Bruurmijn: None. **M.A.H. Raemaekers:** None. **M.J. Vansteensel:** None. **N.F. Ramsey:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.03

Topic: D.18. Brain-Machine Interface

Title: Silent Speech BCI: extension to recognition of consonant-vowel sequences in Japanese

Authors: *H. YAMAGUCHI[1], T. YAMAZAKI[2], T. ITO[2], S. HIROSE[2], S.-I. FUKUZUMI[1]; [1]NEC Corp., Kawasaki, Japan; [2]Biosci. and Bioinformatics, Kyushu Inst. of Technol., Iizuka, Japan

Abstract: A silent speech Brain-Computer Interface (SSBCI) is a method for outputting human intention by decoding brain activity during silent speech. In our past studies, we have developed a noninvasive SSBCI in terms of vowel recognition using formant frequency of speech feature and single-trial electroencephalograms (EEGs) response. The purpose of this study is to extend our method to continuous silent speech recognition including consonant using Mel-Frequency Cepstral Coefficients (MFCCs) as speech feature. A subject (Japanese male, right-handed) was required to overtly speak or to covertly speak /haru/ or /natsu/ (meaning “spring” and “summer” in English, respectively) whose vowel transitions are same. During his speech, we simultaneously measured speech signal, electromyogram (EMG) and 13-ch EEGs. The time

intervals in the EEGs for analysis were correspond to negative slope (NS') of Bereitschaftspotential (BP). First, speech signals were transformed into 39-dimentional MFCCs, and each Hidden Markov Models (HMM) was learned. Next, each Kalman filter parameters were obtained by MFCCs and EEGs data measured during the actual speech. "Silent speech MFCCs" was estimated by inputting the EEGs data during silent speech to Kalman filter with decided parameter. These MFCCs as speech signals are inputted to each HMM, and used for identifying "haru" or "natsu" by comparing likelihood outputted from the HMM. The recognition accuracy of "haru" and "natsu" was 45% and 89%, respectively. For this result, first 13-dimensional MFCCs were calculated from speech signals where the soundless intervals were removed from the speech signals. The rest 26-dimensional MFCCs were predicted from the estimated 13-dimensional ones by the regression analysis. The Kalman filter parameters was averaged to compensate for the difference in Kalman filters among the trials. By using the averaged Kalman filter, we were able to obtain 91-% and 89-% recognition accuracy of "haru" and "natsu", respectively. As a result, we showed the possibility that silent speech recognition including consonant one can be realized by estimating MFCCs generally used in speech recognition using the improved Kalman filter.

Disclosures: H. Yamaguchi: A. Employment/Salary (full or part-time); NEC Corporation. **T. Yamazaki:** None. **T. Ito:** None. **S. Hirose:** None. **S. Fukuzumi:** A. Employment/Salary (full or part-time); NEC Corporation.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.04

Topic: D.18. Brain-Machine Interface

Support: ERC-2010-AdG

Erasmus +

Title: Tactile hand and foot imagery for fMRI Brain Computer Interface applications: offline and online classification accuracy

Authors: *A. KAAS[1,2], R. GOEBEL[1,4,2], T. KADUK[3,5], C. VAN DE WAUW[3], B. SORGER[1,2]; [1]Dept. of Cognitive Neuroscience, Fac. of Psychology and Neurosci., [2]Maastricht Brain Imaging Ctr., [3]Fac. of Psychology and Neurosci., Maastricht Univ., Maastricht, Netherlands; [4]The Netherlands Inst. for Neuroscience, an Inst. of the Royal Netherlands Acad. of Arts and Sci.

(KNAW), Amsterdam, Netherlands; [5]Dept. of Psychology, Univ. of Social Sci. and Humanities, Warsaw, Poland

Abstract: Mental imagery (MI) of e.g. visual scenes[1], movement and speech[2] have produced reliable and repeatable activation for functional magnetic resonance (fMRI) brain computer interface (BCI) control. The current study investigates whether topographic tactile imagery generates a reliable BCI control signal from primary and secondary somatosensory cortex (SI & SII), usable for online communication. Functional (78 1.5mm isotropic slices, TR /TE 2s/21.6ms, 340 volumes) and anatomical MRI data (7T Siemens, 32 channel Nova head coil) were collected from 10 subjects (4 women, mean age 29, sd 5). Each subject completed 5-6 runs of a pseudorandom sequence of 9 left foot (LF) and 9 right hand (RH) tactile MI trials (18s), each followed by rest (16-20s). Subject 10 also completed 6 communication runs (5 trials) answering 3 questions that were decoded online. Auditory cues indicated start, end and MI type. Subjects were instructed not to move during scanning. Offline and online data analysis used standard settings (BrainVoyager QX2.8 and TurboBrainVoyager3.2, BrainInnovation, Maastricht, the Netherlands) including general linear model fitting with LF MI and RH MI predictors. T-values for support vector machine (SVM) training were obtained from SI[3-5] and SII[6, 7] (Jülich probability atlas), testing all combinations of 5 training runs and 1 test run offline. Average accuracy was 76% (sd 15%), with above chance classification for 8 out of 10 subjects. Best-performing subjects showed most-discriminative SVM weights in S1 hand and foot areas. In the online procedure, all answers were correctly classified. Somatotopic tactile MI is a promising BCI control strategy, which could be especially useful for the visually impaired and for neurofeedback-based rehabilitation in patients with tactile deficits and chronic pain.
1.Scharnowski, F., et al., J Neurosci, 2012. 32(49): p. 17830-41. 2.Sorger, B., et al., Curr Biol, 2012. 22(14): p. 1333-8. 3.Geyer, S., et al., Neuroimage, 1999. 10(1): p. 63-83. 4.Geyer, S., et al., Neuroimage, 2000. 11(6 Pt 1): p. 684-96. 5.Grefkes, C., et al., Neuroimage, 2001. 14(3): p. 617-31. 6.Eickhoff, S.B., et al., Cereb Cortex, 2006. 16(2): p. 268-79. 7.Eickhoff, S.B., et al., Cereb Cortex, 2006. 16(2): p. 254-67.

Average proportion of trials correctly classified by the SVM

subjects	left foot	right hand	average
S01	0,57	0,50	0,54
S02	0,83	0,91	0,87
S03	0,70	0,81	0,76
S04	0,70	0,70	0,70
S05	0,54	0,52	0,53

S06	0,70	0,81	0,76
S07	0,72	0,75	0,74
S08	0,87	0,98	0,93
S09	0,87	0,81	0,84
S10	0,98	0,94	0,96
average	0,75	0,78	0,76
sd	0,14	0,16	0,15
based on all combinations of 5 training runs and 1 test run			

Disclosures: **A. Kaas:** None. **R. Goebel:** A. Employment/Salary (full or part-time); The Netherlands Institute for Neuroscience, an Institute of the Royal Netherlands Academy of Arts and Sciences (KNAW), Amsterdam, The Netherlands. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainInnovation, Maastricht, The Netherlands. **T. Kaduk:** None. **C. Van de Wauw:** None. **B. Sorger:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.05

Topic: D.18. Brain-Machine Interface

Support: Internal Funding from the Cleveland Clinic Neurological Institute

NIH Grant 5TL1TR441-7

NIH Grant 5T32EB004314-15

Title: Enhanced modulation of mirror neuron networks to improve brain computer interface performance, via motor imagery training

Authors: *A. RASTOGI[1], R. ACHEY[2], R. BRENNAN[2], D. LOBEL[2], A. B. AJIBOYE[1,3]; [1]Case Western Reserve Univ., Cleveland, OH; [2]Biomed. Engin., Cleveland Clin. Foundation, Lerner Res. Inst., Cleveland, OH; [3]FES Ctr. of Excellence, Rehab. R&D Service, Louis Stokes Cleveland Dept. of Veterans Affairs Med. Ctr., Cleveland, OH

Abstract: Brain computer interfaces (BCIs) enable patients with neurological injuries to control assistive devices using cortical signals, produced during motor imagery (MI) tasks. Enhancing the ability to modulate neural signals during MI, particularly from neurons in the mirror neuron network (MNN), could therefore enhance BCI performance. To this end, four able-bodied participants (P1-P4) were trained in MI techniques to induce MNN activation. During training, participants observed either a virtual reality avatar or a video of a researcher performing three motor tasks: drinking from a glass, tapping the dominant foot, and walking. EEG signals, recording using a modified 10-20 montage, were common average referenced, and the average spectral power in the delta (0.5-4 Hz), alpha (8-12 Hz), beta (12-30 Hz), gamma (3050 Hz), and high gamma (50-70 Hz) frequency bands were determined. The multi-dimensional frequency band powers were used as input features for a linear discriminant analysis (LDA) classifier. Offline classification accuracies for execution and imagery of the three tasks were evaluated at baseline and after 12 training sessions. Classification of EEG activity associated with each motor imagery or motor execution task was evaluated through a multi-fold crossvalidation greedy search algorithm to determine optimal features for discrimination. To quantify the spatial and temporal distribution of selected features, we computed the number of times each feature was chosen across cross-validation folds. Motor imagery training improved discriminability between executed motor tasks by an average of 12.13% in subjects P1-P3, while subject P4 exhibited a 21.4% decrease in discriminability. In contrast, no overall trend in discriminability between imagined motor tasks occurred after MI training. Classification accuracy decreased by an average of 1.65% across all subjects, but notably, subject P3 showed an improvement in performance after training, while P1, P2, and P4 exhibited declines in performance. In participants with higher classification accuracies after MI training, the greedy search was more likely to choose fewer features, and the features chosen were more likely to correspond to beta and gamma activity in frontal channels. Participants with negative performance trends showed the opposite findings, in that chosen features were more likely to be spatially distributed across the scalp and to correspond to alpha and delta frequency bands. These findings suggest that participants who improved their motor imagery abilities were able to increase their ability to modulate beta and gamma activity in frontal regions of the brain.

Disclosures: **A. Rastogi:** None. **R. Achey:** None. **R. Brennan:** None. **D. Lobel:** F. Consulting Fees (e.g., advisory boards); FHC, Inc.. **A.B. Ajiboye:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.06

Topic: D.18. Brain-Machine Interface

Support: Universidad del Norte, Colombia

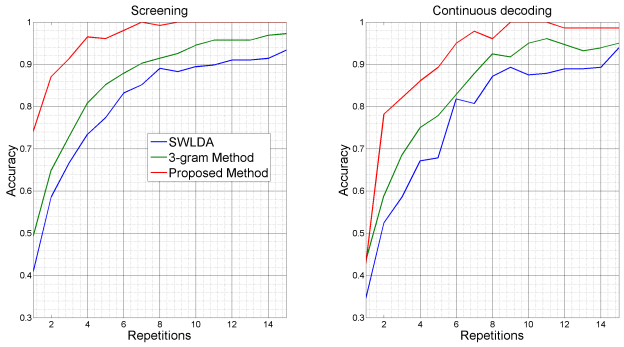
Scientific and Technological Research of Turkey 111E056

NIH Grant EB00085605

Title: A probabilistic graphical model for word-level language modeling in P300 spellers

Authors: ***J. F. DELGADO SAA**[1], A. DEPESTERS[2], M. CETIN[3], D. MCFARLAND[2]; [1]Univ. Del Norte, Barranquilla, Colombia; [2]Wadsworth Ctr., Albany, NY; [3]Sabanci Univ., Istanbul, Turkey

Abstract: Motivated by P300 spelling scenarios involving communication based on a limited vocabulary, we propose a probabilistic graphical model-based framework and an associated classification algorithm that uses learned statistical prior models of language at the level of words. Exploiting such high-level contextual information helps reduce the error rate of the speller. The proposed approach models all the variables in the P300 speller in a unified framework and has the capability to correct errors in previous letters in a word given the data for the current one. The structure of our model allows the use of efficient inference algorithms, which makes it possible to use this approach in real-time applications. Our experimental results demonstrate the advantages of the proposed method.



Disclosures: **J.F. Delgado Saa:** None. **A. dePesters:** None. **M. Cetin:** None. **D. McFarland:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.07

Topic: D.18. Brain-Machine Interface

Support: ERC

NSF CBET 0954243

NSF GRFP

Title: Emergence of task-relevant shared inputs coordinates population activity underlying neuroprosthetic skill learning

Authors: *V. R. ATHALYE[1,2], K. GANGULY[3], R. M. COSTA[1], J. M. CARMENA[2];
[1]Champalimaud Neurosci. Programme, Champalimaud Ctr. For the Unknown, Lisboa, Portugal; [2]UC Berkeley, Berkeley, CA; [3]UC San Francisco, San Francisco, CA

Abstract: Several studies on motor learning have found that initially the brain produces variable activity and with training it consolidates particular spatiotemporal patterns, suggesting that after initial exploration of parameter space, patterns which lead to desired outcomes are selected and consolidated. However, the specific source of the variability changes and how these variability changes relate to the consolidation of particular spatiotemporal patterns is still not well understood. To address these questions, we used an operant conditioning Brain-Machine Interface (BMI) paradigm with 2 rhesus macaques performing a two-dimensional self-paced center-out reaching task. By specifying the map between neural activity and sensory feedback (the decoder) and target locations (the goal), we define a priori task-relevant neural dimensions and the set of spatiotemporal patterns which accomplish the goal. This task design permits dissection of neural variability with respect to its causal role in producing goal-directed behavior. We found that along with accuracy and speed improvements, the cursor spatial occupancy was refined with training, entered less of the workspace and became more consistent across trials. Using population-level analysis, we found trial-to-trial neural variability decreased more dramatically in inputs private to each cell versus inputs shared by each cell. Furthermore, the geometry of the shared variability stabilized with training. At a finer timescale, we observed the emergence of specific temporal patterns of activity that became more stable as training progressed. We then asked if the emergence of fine-timescale population patterns was driven more by shared or private inputs. The population variance due to shared input grew prominently with training, and this explained the increase in dynamic range and trial-to-trial consistency. Finally, we confirmed that shared inputs preferentially drive the decoder by varying in the task-

relevant neural dimensions, showing that the emergent structure likely underlies skill improvement. In conclusion, the emergence of task-relevant shared inputs and pruning of private trial-to-trial variability explain the consolidated spatiotemporal patterns underlying improvement of neuroprosthetic skill.

Disclosures: V.R. Athalye: None. **K. Ganguly:** None. **R.M. Costa:** None. **J.M. Carmena:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.08

Topic: D.18. Brain-Machine Interface

Support: NIH Grant 5R01NS063372

Title: Neural ensemble dynamics during brain-machine interface controlled motor-like task

Authors: *M. ARMENTA SALAS, S. I. HELMS TILLERY;
Arizona State Univ., Tempe, AZ

Abstract: Brain-machine interface (BMI) technology has allowed us to gain insight about the internal mechanisms and computations the brain uses while performing movements or learning new tasks (Taylor et al, 2002; Carmena et al, 2003; Paz et al, 2003; Ganguly et al, 2009). Recent work has shown that non-human primates (NHP) and humans are able to adapt motor outputs to a variety of devices and virtual environments (Hochberg et al, 2012; Collinger et al, 2013; Sadtler et al, 2014). Our lab has recently tested the limits of brain adaptation by comparing uniform and non-uniform perturbations in a BMI controlled task. We trained two NHP to perform a 3D center-out task using signals from primary motor and premotor cortices. We introduced a uniform perturbation, doing a visuomotor rotation in the population vector, and a non-uniform perturbation through a decorrelation task, where we reassigned the preferred directions (PD) of a subset of neurons (<20%). These tasks allowed us to compare and measure changes in individual and population dynamics. We observed similarities in the strategies the subjects required to perform and adapt to each task, but we also measured some key differences in these adaptations. For example, both tasks produced changes in PD across the whole neuronal population, but the changes in the decorrelation task were not uniform across the ensemble. Similarly, we measured peak cross-correlation in both tasks, and did not observe any significant variations across the ensemble. Furthermore, we did not observe subsets of neurons that

displayed significant changes in their firing activity or their cross-correlation coefficients. Here we report further testing and quantitative analysis of both tasks. Using dimensionality reduction (Yu et al, 2009), we estimated underlying neural connections that might drive the activity of the recorded neurons. Similarly, using DataHigh toolbox (Cowley et al, 2013), we obtained the neural trajectories in these reduced spaces. We observed that the neural trajectories are not as well defined when subjects do not perform overt movements. Although we were able to isolate regions in the reduced neural space for the different trained targets. On the other hand, we observed overlapping regions when comparing the maps during baseline and the perturbed trials. This suggests that subjects might not have to generate completely new neural maps when solving the current task assignment. We also measured the largest principal angles (PA) between the estimated manifolds of baseline and perturbed trials. We found that a greater PA did not necessarily correlated with a more difficult task, neither were larger angles only present in the decorrelation task.

Disclosures: **M. Armenta Salas:** None. **S.I. Helms Tillery:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.09

Topic: D.18. Brain-Machine Interface

Support: DARPA Grant No. N66 001-12-1-4023

NIH R01 NS045853

Title: Emergence of effective connectivity networks in deafferented motor cortex after exposure to a brain machine interface

Authors: ***K. BALASUBRAMANIAN**, M. VAIDYA, K. TAKAHASHI, N. G. HATSOPOULOS;
Univ. of Chicago, Chicago, IL

Abstract: Causal networks can form among ensemble of neurons when engaged in learning novel behavioral tasks. It is, however, unclear whether such networks can form under the paradigm of cortically controlled brain-machine interfaces (BMIs). Emergence of connectivity patterns when exposed to BMIs for prolonged time can serve as indicators of motor learning. Using a statistically inferred technique, we show the gradual formation of functionally connected

neuronal networks in deafferented motor cortex (MI) of macaque monkeys and their relationship with behavioral control of a multi-DOF robot performing a reach and grasp task. Two macaques with unilateral, chronic transradial and transhumeral amputations, respectively, were implanted with 100-channel multi-electrode arrays in MI contralateral to the amputation and were operantly conditioned to control reaching and grasping movements of a robotic arm and hand. The region of implantation was deafferented for several years with complete absence of somatosensory inputs associated with grasping and partial loss of sensory inputs associated with reaching behaviors. Two distinct clusters of single-unit activities were decoded using static linear filters to generate velocity signals associate with two control dimensions, 1) reaching forward and back and 2) whole-hand grasp opening and closing. The underlying relationship among neurons within and between each cluster at specific velocity events were examined using a generalized linear model framework, and subsequently, the "causality" between the connected neurons was estimated using a point-process formulation of Granger analysis. The model selection was based on the Akaike Information Criterion (AIC) over 60 milliseconds of firing history. Sparse network connectivity was observed on the initial exposure to the BMI, which gradually emerged into much denser networks with well-defined excitatory/inhibitory connections, with continued exposure to the BMI. The *within-cluster* functional connectivity of the two networks increased in their number of in-and-out-degrees, and the *between-cluster* connectivity showed growing number of inhibitory connections. Behaviorally, the highly connected networks could enable the animals to generate velocities with larger magnitudes. The pronounced increase in the inhibitory connections between the reach and grasp clusters may reflect the strategy of the animals learning the BMI.

Disclosures: K. Balasubramanian: None. **M. Vaidya:** None. **K. Takahashi:** None. **N.G. Hatsopoulos:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.10

Topic: D.18. Brain-Machine Interface

Support: Eu grant SI-CODE 284553

Title: Experimental paradigm for exploring the dynamical properties of a bidirectional brain-machine interface based on force fields

Authors: M. SEMPRINI[1], F. BOI[1], F. A. MUSSA IVALDI[2,3], S. PANZERI[1], *A. VATO[1];
[1]Ctr. for Neurosci. and Cognitive Systems, Inst. Italiano di Tecnologia, Rovereto, Italy;
[2]Northwestern Univ., Chicago, IL; [3]Rehabil. Inst. of Chicago, Chicago, IL

Abstract: The main goal of a motor brain-machine interface (BMI) is to extract the motor intentions from the neural signals recorded directly from the brain, in order to control an external device. This approach is based on developing a decoder able to maximize the amount of information extracted from the brain activity and to translate the neural signals into meaningful motor commands. In this framework, we recently proposed a novel approach inspired by the spinal cord of the vertebrates, which can be considered as a brain-body interface, translating motor intention into muscle activations. The activation of multiple muscles by the spinal cord results into force-fields acting upon the limbs. In this respect the force fields generated by the spinal cord activity, are effectively control policies that translate motor intentions into motor behavior. In earlier work we were able to mimic this biological mechanism by developing a bidirectional communication channel that connects the motor and sensory cortices of an anaesthetized rat to a simulated dynamical system. We were able to use the neural signals to control the movement of a simulated point mass and to generate a family of trajectories that converges upon a target point corresponding to the fixed equilibrium point of a force field. We now explored how volitional control can affect the control policy established by the BMI by implementing the same paradigm on alert animals controlling an external device. We used 16-channels microelectrode arrays chronically implanted into two regions of the brain to record and electrically stimulate the cortex. A mobile feeder, controlled by two servomotors lying on a vertical plan and protected by a Plexiglas wall, is the external dynamical system. A decoder translates the neural activity into motor signals that drive the movable feeder. To obtain the reward the rat needed to modulate the brain activity in order to move the feeder into a target position, represented by a small window in the Plexiglas wall allowing access to the pellet inside the feeder. This closed-loop BMI is a tool for exploring the modulation of control policies by volitional input and the dynamical properties of the brain emerging from the bidirectional interaction with an artificial device.

Disclosures: M. Semprini: None. **F. Boi:** None. **F.A. Mussa Ivaldi:** None. **S. Panzeri:** None. **A. Vato:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.11

Topic: D.18. Brain-Machine Interface

Support: NIH R01NS062019

Title: Multimodal microelectrode failure analysis reveals complexity biotic and abiotic recording failure

Authors: ***T. D. KOZAI**, X. CUI;
Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Intracortical electrode arrays that can record extracellular action potentials from small, targeted groups of neurons are critical for basic neuroscience research and emerging clinical applications. In general, these electrode devices suffer from reliability and variability issues that impact their performance on the order of months to years. The failure mechanisms of these electrodes are understood to be a complex combination of the biological reactive tissue response and material failure of the device over time. The breaching of the blood-brain barrier (BBB) to insert devices triggers a cascade of biochemical pathways resulting in complex molecular and cellular responses to implanted devices. Molecular and cellular changes in the microenvironment surrounding an implant include the introduction of mechanical strain, BBB leakage, activation of glial cells, loss of perfusion, secondary metabolic injury, and neuronal degeneration. The resulting inflammation is a key hypothesized cause of neural recording failure. Our findings from electrophysiology, impedance spectroscopy, and post-mortem histology demonstrate a very poor relationship between histology and impedance to electrophysiology. For example, tissue with low-levels of glial encapsulation, healthy neuronal proximity, and low impedance can still have poor recording performance, even with neural activity is behaviorally driven. Previously, we demonstrated that mechanical mismatch between iridium and silicon led to material failure in chronically implanted planar silicon electrodes. These findings were confirmed with chronic *in vivo* data (133-189 days) in mice by correlating a combination of single-unit electrophysiology, evoked multi-unit recordings, electrochemical impedance spectroscopy, and scanning electron microscopy from traces and electrode sites with our modeling data. Several modes of mechanical failure of chronically implanted planar silicon electrodes were found that result in degradation and/or loss of recording. These findings highlight the importance of strains and material properties of various subcomponents within an electrode array. Here, we compare the results from histology and mechanical failure to recording performance. These results emphasize the complexity of the biological pathways that govern the reactive tissue response and longitudinal electrophysiological recordings from penetrating electrode arrays. BBB injury is not limited to chronic BBB leakage, but can include vascular occlusion, edema, and ischemia/hypoxia, which may not necessarily cause gliosis or neuronal death, but can heavily modulate nearby neural activity.

Disclosures: **T.D. Kozai:** None. **X. Cui:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.12

Topic: D.18. Brain-Machine Interface

Support: DoD NDSEG to RMN

NSF Grant CBET-0954243 to JMC

ERC Grant 617142 to RMC

Title: Operant control of primary visual cortex activity using a neuroprosthetic task in rodents

Authors: *R. NEELY[1], A. C. KORALEK[1,3], R. M. COSTA[3], J. M. CARMENA[1,2];
[1]Helen Wills Neurosci. Inst., [2]Electrical Engin. and Computer Sci., UC Berkeley, Berkeley, CA;
[3]Champalimaud Neurosci. Programme, Champalimaud Ctr. for the Unknown, Lisbon, Portugal

Abstract: It has been shown that animals can learn to generate arbitrary patterns of neural activity in the frontal and motor cortices in the context of closed-loop brain-machine interface (BMI) tasks. However, it is unknown whether this type of BMI learning can take place in other regions of cortex not typically associated with motor output. Although sub-regions of cortex are hypothesized to subserve particular functions, the general organization of neurons is similar across all regions, and some parts of the cortex have been observed to assume new functions following stroke or peripheral injury. In order to probe the flexibility of cortical circuits, we asked whether a low-level sensory region of cortex could be trained to control a neuroprosthetic device. Rats were trained to modulate single-unit activity in the primary visual cortex (V1) in order to move a 1-D auditory cursor that was linked to a sucrose water reward. After 2-3 sessions, animals were able to perform the task above chance level both in the presence or absence of visual input; however changing the light condition after learning had a notable effect on performance. Task performance was associated with changes in local network dynamics: correlations between neurons involved in cursor control ("direct neurons") increased or decreased depending on their relationship to cursor movement in the rewarded direction. Direct neurons were also more strongly coherent with local field potentials in V1 during rewarded trials compared to neighboring neurons. Local field potentials in V1, the dorsal striatum (DS), and the pre-limbic cortex showed transient increases in gamma power immediately prior to target hits. The low-frequency power of the spike-triggered average (STA) in V1 was attenuated during task performance. Task performance was dependent on reward: success rate remained at chance level during unrewarded sessions, and performance was sensitive to contingency degradation.

Furthermore, single units recorded in DS showed strong reward-related modulations following rewarded trials, and we also observed time-locked increases in coherence between direct units in V1 and local field potentials in DS. These results suggest that iterative selection of particular patterns of neural activity through primary reinforcement can alter cortical dynamics and ultimately modify the functional properties of cortical neurons.

Disclosures: **R. Neely:** None. **A.C. Koralek:** None. **R.M. Costa:** None. **J.M. Carmena:** None.

Nanosymposium

111. Decoding Brain Machine Interfaces

Location: S100B

Time: Sunday, October 18, 2015, 8:00 AM - 11:15 AM

Presentation Number: 111.13

Topic: D.17. Voluntary Movements

Support: DARPA N66 001-12-1-4023

IGERT NSF DGE-0903637

NINDS R01 NS045853

Title: Neural dynamics underlying emergent coordinated reach-to-grasp in a long-term bmi study

Authors: ***M. VAIDYA**[1], K. BALASUBRAMANIAN[2], J. SOUTHERLAND[3], A. ELERYAN[4], I. BADRELDIN[5], K. OWEISS[5], A. FAGG[3], N. HATSOPOULOS[2];
[1]Organismal Biol. & Anat., [2]Univ. of Chicago, Chicago, IL; [3]Univ. of Oklahoma, Norman, OK; [4]Michigan State Univ., East Lansing, MI; [5]Univ. of Florida, Gainesville, FL

Abstract: Extensive psychophysical work has shown that during reach-to-grasp, reaching of the proximal arm (reaching or transport component) is temporally and spatially coordinated with preshaping of the hand (grasp component) (Jeannerod, 1984; Haggard & Wing, 1995). The development of this coordinated behavior has been studied in infants and children (Hofsten, 1984; Kuhtz-Buschbeck et al., 1998). However, this line of inquiry has generally not focused on the role of primary motor cortex (MI) in the development of coordination. Here, we examined the neural dynamics in MI underlying the emergence of coordinated reach-to-grasp behavior in rhesus macaques that had been the recipients of therapeutic amputations and were operantly conditioned to use a brain machine interface to control a robotic arm and hand. This paradigm gave us a unique model for studying the development of coordination of a novel motor behavior at the behavioral and cortical level. In addition, the possibility of training subjects to perform a

naturalistic motor task by modulating cortical neurons using an artificial mapping, and of influencing network activity in a lasting manner could have clinical implications for patients with amputations or strokes.

Disclosures: **M. Vaidya:** None. **K. Balasubramanian:** None. **J. Southerland:** None. **A. Eleryan:** None. **I. Badreldin:** None. **K. Oweiss:** None. **A. Fagg:** None. **N. Hatsopoulos:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.01

Topic: E.07. Food Intake and Energy Balance

Support: NIH OD010662

CIHR MOP123208

Title: The neuropeptide processing enzyme EP24.15 is a regulator of xenin signaling

Authors: K. D. PHILIBERT[1], M. WUNGJIRANIRUN[1,2], P. LEW[3], T. M. MIZUNO[3], *M. J. GLUCKSMAN[4];
[1]Biochem. & Mol. Biol., RFUMS/Chicago Med. Sch., North Chicago, IL; [2]Beth Israel Deaconess Med. Ctr., Boston, MA; [3]Dept. of Physiol. and Pathophysiology, Univ. of Manitoba, Winnipeg, MB, Canada; [4]Biochem. & Mol. Biol., Rosalind Franklin Univ. of Med. & Science/Chicago Med. Sch., North Chicago, IL

Abstract: Xenin is a 25 amino acid neuropeptide produced by a subgroup of chromogranin A+ cells in the duodenum with sequence homology and actions similar to hypothalamic and ileal neurotensin (a satiety factor) as well as binding to the neurotensin receptor. This neurohormone is involved in glucose homeostasis and increases the response to glucose-dependent insulinotropic peptide (GIP). Upon release after meal ingestion Xenin inhibits secretion of acid and pancreatic exocrine peptides in the gastrointestinal tract. The mode of regulation of Xenin remains elusive. The metalloendopeptidase EC 3.4.24.15 (thimet oligopeptidase, EP24.15) has been demonstrated to play a key role in the cleavage and subsequent regulation of several neuropeptides that also exist in the gut such as neurotensin and somatostatin. These studies began from structural analyses and *in silico* molecular modeling and implicated Xenin as a substrate of EP24.15 and thus, this enzyme as a possible regulator of Xenin signaling. To substantiate a potential regulatory mechanism for the functioning of Xenin, we first identified the

cleavage site and measured enzymatic parameters, and then determined if EP24.15 and Xenin are co-expressed in gut regions relevant to glucose homeostasis function. EP24.15 and Xenin were co-incubated and subjected to matrix-assisted laser desorption ionization time-of-flight (MADLI-TOF) mass spectrometry to confirm that EP24.15 can cleave Xenin *in vitro* and enzyme kinetics performed with standards via high performance liquid chromatography yielded results consistent with known substrates. Notably, Xenin is cleaved in a homologous manner as neurotensin. Double-label immunohistochemistry demonstrated Xenin and EP24.15 immunoreactivity within the mouse small intestine and specifically co-expression within intestinal mucosa and submucosa. Furthermore, there is co-expression of EP24.15 and Xenin in cells of both human and mouse stomach in the gastric mucosa. Taken together this data suggests that EP24.15 may act to cleave Xenin *in vivo* and represents an additional facet of the control mechanism of glucose homeostasis. As a potential pharmacological therapeutic target, understanding regulation of Xenin by the neuropeptide processing enzyme, EP24.15, may provide insight into an alternative strategy for glucose regulation and diseases such as diabetes and obesity. Supported by NIH OD010662 (MJG) and CIHR MOP123208 (TMM).

Disclosures: K.D. Philibert: None. **M. Wungjiranirun:** None. **P. Lew:** None. **T.M. Mizuno:** None. **M.J. Glucksman:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.02

Topic: E.07. Food Intake and Energy Balance

Support: CNPq

FAPESP

Title: Adrenal glands are required for insulin-induced changes in the expression of hypothalamic neuropeptides

Authors: *E. T. UCHOA[1,2], P. B. MARANGON[2], R. C. RORATO[2], J. ANTUNES-RODRIGUES[2], L. L. K. ELIAS[2];
[1]Dept. of Physiological Sciences-CCB, State Univ. of Londrina (UEL), Londrina, Brazil; [2]Dept. of Physiol., Sch. of Med. of Ribeirao Preto, Univ. of Sao Paulo, Ribeirao Preto, Brazil

Abstract: Adrenal insufficiency induced by adrenalectomy (ADX) induces marked hypophagia and was shown to decrease the sensitivity to the hypophagic effect of central insulin treatment, suggesting that adrenal glands are required for insulin-induced hypophagia. However, the role of adrenal glands on insulin-induced changes in the expression of hypothalamic neuropeptides involved in the control of food intake is not established. Thus, in the present study, we evaluated the effects of ADX on icv (lateral ventricle) injection of insulin-induced changes on mRNA expression of: 1) anorexigenic neuropeptides proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART), and orexigenic neuropeptides agouti-related protein (AgRP) and neuropeptide Y (NPY) in the arcuate nucleus of the hypothalamus (ARC), 2) anorexigenic neuropeptides corticotrophin-releasing factor (CRF) and oxytocin (OT) in the paraventricular nucleus of the hypothalamus (PVN). For this purpose, after icv surgery, male Wistar rats (230-280g, n=5-10 per group) were subjected to ADX or sham surgery. ADX animals received 0.9% NaCl as drinking fluid, and half of them also received corticosterone in the drinking fluid (B: 25mg/l, ADX+B). Seven days after surgery, animals were treated with icv injection of insulin (12 μM/ 5 μl) or vehicle (0.9% NaCl/ 5μl). Two hours after the injection, animals were decapitated for brain tissue collection, and hypothalamic neuropeptides mRNA expression was determined by real time PCR. In vehicle treated animals, ADX reduced ($P<0.05$) POMC, CART, NPY and AgRP mRNA expression in the ARC, and it increased ($P<0.05$) CRF and OT mRNA expression in the PVN. Corticosterone replacement was able to reverse ($P<0.05$) these effects, except for OT mRNA expression in the PVN. In insulin treated animals, CART mRNA expression in the ARC was reduced ($P<0.05$) in ADX e ADX+B groups, and PVN CRF mRNA expression was augmented in the ADX group, with no changes on the expression of other neuropeptides. Central insulin injection was able to enhance ($P<0.05$) CART mRNA expression and to reduce ($P<0.05$) NPY mRNA expression in the ARC only in sham group, with no effects in ADX and ADX+B animals. Furthermore, insulin reduced ($P<0.05$) OT mRNA expression in the PVN of ADX animals, without changes on other neuropeptides expression. In conclusion, these data demonstrate that ADX reduces the responsiveness of insulin-induced changes in the expression of hypothalamic neuropeptides involved in the regulation of food intake, suggesting that adrenal glands are required for insulin-induced hypophagia mediated by hypothalamic pathways.

Disclosures: E.T. Uchoa: None. **P.B. Marangon:** None. **R.C. Rorato:** None. **J. Antunes-Rodrigues:** None. **L.L.K. Elias:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.03

Topic: E.07. Food Intake and Energy Balance

Support: Fapesp

Title: Predisposition to obesity is determined by nutrient-induced modulation of POMC but not steady-state gut microbiota

Authors: D. S. RAZOLLI[1], *L. A. VELLOSO[2];
[1]State Univ. of Campinas, Campinas, Brazil; [2]Unicamp, Campinas, Brazil

Abstract: Inflammation and dysfunction of the hypothalamus have emerged as important mechanisms connecting the increased consumption of dietary fats with obesity. Studies have also identified changes in gut microbiota as a mechanism potentially involved with increased adiposity. However, it is currently unknown if an altered gut microbiome can lead to hypothalamic dysfunction and, thus, act as a primary predisposing factor to obesity. To explore this question, we have employed an outbred mouse model that, upon feeding with a high fat diet, can be separated into groups with high predisposition to obesity (obesity prone, OP) or low predisposition to obesity (obesity resistant, OR) to test three hypothesis: i, there are primary differences in gut microbiome between OP and OR which determine differences in fatty acid harvesting; ii, there are no primary differences in gut microbiome but there are primary differences in fatty acid harvesting between OP and OR; and, iii, there are no primary differences in gut microbiome and fatty acid harvesting but there are primary differences in hypothalamic responsiveness to dietary fats. V2 region sequencing of the 16S rRNA gene revealed no differences in the distribution of phylum and genus of gut bacterial communities between OP and OR prior to high fat feeding. In addition, one day high fat feeding resulted in no differences on plasma free fatty acid composition between OP and OR. However, a continuous systemic infusion of palmitic acid using osmotic mini pumps for 24 h resulted in increased POMC and CART hypothalamic gene expression in OP as compared to OR. In addition, the infusion of palmitic acid led to increased hypothalamic expression of TNFα, F4/80, CD11b and fractalkine gene expression in OP as compared to OR. Thus, in an outbred mouse strain with different predisposition to obesity, there are neither differences in the landscape of gut microbiome before exposure to increased dietary fats, nor differences in fatty acid harvesting that could explain the induction of hypothalamic dysfunction in obesity. Nevertheless, OP mice present an early significant increase in hypothalamic markers of inflammation, which is accompanied by increased expression of POMC and CART. This data places a defect of hypothalamic responsiveness to dietary fats as an early and independent phenomenon that connects increased dietary fat with obesity.

Disclosures: D.S. Razolli: None. **L.A. Velloso:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.04

Topic: E.07. Food Intake and Energy Balance

Support: NIH Grant R01AA12882

NIH Grant F32DK100058

NIH Grant K99AA021782

Title: Prenatal exposure to a fat-rich diet alters embryonic neuronal responses to the chemokine, CCL2

Authors: *K. POON, H. T. HO, J. R. BARSON, S. F. LEIBOWITZ;
The Rockefeller Univ., New York, NY

Abstract: Maternal consumption of a high fat diet (HFD) during pregnancy stimulates the neurogenesis and migration of hypothalamic orexigenic peptide neurons in the offspring. This increase in neuropeptides may be attributed, in part, to the known stimulatory effects of a HFD on circulating inflammatory agents, such as chemokines. With our recent studies showing the inflammatory chemokine, CCL2, to stimulate the migration of hypothalamic neurons and their expression of orexigenic neuropeptides, this study tested whether prenatal exposure to a HFD alters these neuronal responses to CCL2. Using primary cell culture from dissociated hypothalamic neurons extracted from embryos on embryonic day 19, this study tested the effects of prenatal HFD exposure, first, on the expression of CCL2 and its receptors in embryonic hypothalamic neurons and, then, on CCL2's actions in stimulating neuronal migration and expression of the orexigenic neuropeptides, enkephalin (ENK) and galanin (GAL). Unexpectedly, we found that prenatal HFD exposure for 12 days caused a significant decrease in expression of CCL2 in hypothalamic neurons, suggesting downregulation of this chemokine, along with an increase in expression of its CCR2 and CCR4 receptors which in turn may contribute to the decrease in CCL2 activity. This HFD-induced reduction in CCL2 mRNA was associated with a decline in neuronal responsiveness to this chemokine. Whereas CCL2 treatment increased the number of migrated hypothalamic neurons from chow embryos, this effect was lost in the HFD embryos, suggesting a reduction in the sensitivity of these neurons to CCL2. This conclusion was substantiated by our additional finding that the CCL2-induced increase in the migrational velocity and distance traveled by neurons from chow embryos was absent in neurons from the HFD embryos. Lastly, the CCL2-induced increase in expression of

ENK and GAL in hypothalamic neurons from chow embryos was also markedly reduced by prenatal HFD exposure. These results, while confirming a stimulatory effect of CCL2 on the migration and neuropeptide expression of normal hypothalamic neurons from chow embryos, reveal a strong, HFD-induced attenuation of the actions of CCL2 on embryonic hypothalamic neurons. With published studies showing CCL2 to have neuroprotective effects, this evidence for decreased sensitivity to CCL2 suggests that prenatal HFD exposure may interfere with this neuroprotective function of this chemokine.

Disclosures: **K. Poon:** None. **H.T. Ho:** None. **J.R. Barson:** None. **S.F. Leibowitz:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.05

Topic: E.07. Food Intake and Energy Balance

Support: Fapesp

Title: Inhibition of leukocyte inhibitory factor (LIF) in the hypothalamus transforms mice that are obesity resistant in obesity prone

Authors: ***M. FIORAVANTE**, J. MORARI, R. F. MOURA, A. F. S. RAMALHO, L. A. VELLOSO;
Univ. of Campinas, Campinas, Brazil

Abstract: Hypothalamic inflammation has emerged as an important feature of experimental obesity. Studies have shown that dietary fat can trigger inflammation by activating TLR4 signaling in hypothalamic microglia and also by inducing endoplasmic reticulum stress in neurons. As in humans, some outbreed strains of mice display great variability in their predisposition to diet-induced obesity. However, it is unknown if hypothalamic inflammation is involved in the differences in the obese phenotype presented by outbreed mice fed on a high-fat diet. In the present study, the outbreed strain, Swiss, was submitted to a short-term protocol that allows early identification of obesity-prone (OP) and obesity resistant (OR) mice. Using a RNA array, we identified leukocyte inhibitory factor (LIF) as an early responsive transcript that is increased in the hypothalamus of OR and decreased in the hypothalamus of OP. By real-time PCR we showed that OP and OR have similar levels of LIF transcript under chow. Three days feeding on a high-fat diet resulted in a two-fold increase of LIF in OR and no modification of its expression in OP. This was accompanied by increased POMC expression only in OR. Confocal

microscopy of the hypothalamus identified LIF predominantly in POMC neurons, whereas low expression levels were detected in microglia and NPY neurons. Using an immuneneutralizing antibody, we inhibited LIF in the hypothalamus of OR and evaluated metabolic and inflammatory parameters. In the hypothalamus of mice fed on high-fat diet, LIF inhibition resulted in the increased expression of inflammatory cytokines. This was accompanied by increase caloric intake, increased body mass gain and increased adiposity, to levels similar to OP. In addition, LIF inhibition in the hypothalamus of OR resulted in impaired systemic glucose tolerance as determined by an intraperitoneal glucose tolerance test. All the metabolic and inflammatory changes induced by the inhibition of LIF in the hypothalamus of OR produced a phenotype similar to OP mice fed on a high fat diet. Thus, hypothalamic LIF is an early marker that allows the distinction of OP and OR mice fed on high-fat diet and the inhibition of LIF in OR mice results in metabolic and inflammatory changes, transforming OR mice in OP mice.

Disclosures: M. Fioravante: None. **J. Morari:** None. **R.F. Moura:** None. **A.F.S. Ramalho:** None. **L.A. Velloso:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.06

Topic: E.07. Food Intake and Energy Balance

Support: Medical Research Council, UK

Title: Differences in body-size, body-mass and fat composition of NK1R-/ mice and wildtype mice are consistent with an increased risk of comorbid obesity in ADHD patients

Authors: *C. STANFORD[1], K. PILLIDGE[2], D. J. HEAL[3];
[2]Neurosci. Physiol. & Pharmacol., [1]UCL, London, United Kingdom; [3]RenaSci, Nottingham, United Kingdom

Abstract: Evidence suggests that small body size is a risk factor for Attention Deficit Hyperactivity Disorder (ADHD) and that ADHD patients are vulnerable to comorbid obesity. Mice with functional ablation of the neurokinin-1 receptor gene (NK1R-/-) express abnormal behaviours that are analogous to those seen in ADHD (1). Here we investigated whether NK1R-/- and wildtype mice, of either sex, differ on measures of body size, body mass or %fat when fed either a normal or high fat ('Western') diet. Separate cohorts of mice (N=8-10 for each genotype & sex / cohort) were weaned onto normal (2018 global Rodent Diet, Harlan) or high fat (45%

calories from fat) diet (Research Diets, NJ, USA). The weight and body length of all mice was measured immediately after culling at either 6 weeks (normal diet) or 7 weeks (high fat) of age. The carcasses were stored at 20°C for subsequent chemical analysis of milled, freeze dried samples using a modified Soxhlet extraction protocol. The data were analysed by 2-way ANOVA (with repeated measures, when appropriate), and posthoc LSD tests. NK1R-/- mice were shorter than wildtypes, regardless of sex or diet. On a normal diet, NK1R-/- mice weighed less than wildtypes, especially the males. However, after 28 days of high fat diet, there was no difference in the weight of male wildtype and NK1-/- mice and female NK1R-/- mice weighed more than their wildtypes [P=0.002]. NK1R-/- mice had a higher density (g/cm2: 'mBMI') than wildtypes regardless of diet or sex [normal diet: P<0.001; high fat: P<0.001]. On the high-fat diet, %fat was increased in male, but not female, NK1R / mice [P=0.003]. These findings are consistent with evidence that small body size is a risk factor for ADHD and that these patients have a high incidence of comorbid obesity. In view of evidence that polymorphism(s) of the equivalent human gene (TACR1) increases vulnerability to ADHD (2), the possibility that these patients (especially males) comprise a subgroup, with increased risk of developing obesity, merits investigation. 1) Yan TC et al., (2011) PLoS One.6:e17586. doi:.1371/journal.pone.0017586 2) Sharp SI et al. (2014) Am J Med Genet B Neuropsychiatr Genet. 165B:373

Disclosures: **C. Stanford:** None. **K. Pillidge:** None. **D.J. Heal:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.07

Topic: E.07. Food Intake and Energy Balance

Title: Short-term effects of a western diet on the number of brain-derived neurotrophic factor immunoreactive neurons in the hypothalamic arcuate, ventromedial and paraventricular nuclei

Authors: *K. GILLAND, E. A. FOX;
Purdue Univ., West Lafayette, IN

Abstract: Brain-derived neurotrophic factor (BDNF) infusions into the paraventricular (PVN) and ventromedial (VMH) hypothalamus inhibit food intake, whereas BDNF knockout in the VMH region increases feeding, suggesting BDNF is an anorexigen (Wang AJP 293:R992 2007; Unger J Neurosci 27:14265 2007). A western diet (WD) high in saturated fat and refined sugars consumed ad lib or pair-fed to controls for 14 wk reduced BDNF mRNA in the VMH (Yu

Neurosci 160:295 2009). There has been no investigation, however, of how a WD impacts BDNF expression during initial consumption or weight gain. Should BDNF be altered at these early stages, and these changes contribute to obesity, they could be targeted for treatment and prevention of obesity. Consistent with this possibility, BDNF mRNA in the VMH is reduced after a 48 hr fast, and it increases within 30 min of a glucose injection in 48 hr fasted mice (Unger J Neurosci 27:14265 2007). We first examined whether the reduction of BDNF mRNA after a 48 hr fast was mirrored by BDNF protein. This was assessed by blind quantification of BDNF immunoreactive (IR) neurons in the VMH, PVN and arcuate (Arc) nuclei and 2 cortical control areas in fasted (n=6) and ad lib chow fed (n=6) mice with the aid of NIH Image J software. Fasting resulted in decreases in BDNF IR neuron numbers in the Arc (41%) and VMH (34%), but these were not significant. Next we examined short-term effects of a WD on BDNF IR neuron numbers in the VMH, PVN and Arc nuclei by feeding mice a WD (40% fat, 5TJN, TestDiets), chow, or the WD calorically paired to the chow gp (WD-PF) for 6 hr, 48 hr, 1 wk or 3 wk. Food intake and bodyweight were measured daily. For the 6 hr time point body weight significantly increased in the WD and the WD-PF gps compared to the chow gp, whereas at all other time points only the WD gp gained significant weight. A similar pattern across groups was observed for caloric intake except at the 3 wk time point, for which WD and chow gps were similar and the WD-PF food intake was lower than for these gps as some mice did not consume all their food. Preliminary results for the 1 wk time point surprisingly showed moderate increases rather than decreases in BDNF IR neuron numbers in the PVN (44%), VMH (15%) and Arc (29%) in WD (n=5) vs. chow (n=4) gps. These trends were not significant. Smaller increases occurred for the WD-PF gp (n=4) and in the cortex for WD (10%) and WD-PF (15%) gps compared to the chow gp. Failure of decreased BDNF IR cell counts to reach significance after a 48 hr fast could imply changes in protein are delayed compared to mRNA. Failure to observe decreased BDNF protein at 1 wk of WD feeding suggests either reduced mRNA does not result in reduced protein or reduced BDNF expression requires more prolonged WD feeding.

Disclosures: K. Gilland: None. **E.A. Fox:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.08

Topic: E.07. Food Intake and Energy Balance

Support: Yale-NUS Start-Up Grant R-607-264-057-121

Title: Exploring the relation between oxytocin receptor gene polymorphisms and eating behaviour

Authors: *B. C. Y. LOW[1], K. M. VIJAYAKUMAR[1], N. KARNANI[2], Y. S. LEE[3], F. YAP[4], M. F. F. CHONG[2], B. BROEKMAN[3], A. RIFKIN-GRABOI[2], M. MEANEY[2], P. GLUCKMAN[2], K. KWEK[4], Y. S. CHONG[3], J. C. J. LIU[1];
[1]Yale-Nus Col., Singapore, Singapore; [2]Singapore Inst. for Clin. Sci., Singapore, Singapore; [3]Natl. Univ. of Singapore, Singapore, Singapore; [4]KK Hosp., Singapore, Singapore

Abstract: Gene knockout studies in rodents have identified oxytocin as a causal factor in the development of obesity. Previous literature suggests that lower oxytocin levels may weaken responses to satiety signals after a meal and result in excessive carbohydrate consumption that could - eventually - predispose individuals to weight gain. Our study examined whether natural variants in the oxytocin receptor gene (OXTR) are involved in this process. We used child data (N=457) from the "Growing Up in Singapore Towards healthy Outcomes" longitudinal study (GUSTO). GUSTO tracks children from gestation to 7 years old. We compared OXTR genotype at birth to body mass index (BMI) at 3 years old, and eating behaviours at 1 year old. Eating behaviours were measured with the Child Eating Behaviour Questionnaire, a parent-reported index of children's behavioural responses to food and food consumption. A key construct in this questionnaire is 'satiety responsiveness' (SR), which measures the extent that children feel sated and avoid eating after meals. SR is sometimes combined with the 'slowness in eating' (SE) subscale as a single construct (SR+SE); higher scores on either scale indicate greater responsiveness to post-meal satiety signals. None of the extracted oxytocin single nucleotide polymorphisms (SNPs) had a direct main effect on BMI. However, there were significant differences in SR or SR+SE based on allelic variations in six SNPs after adjusting for multiple comparisons. The absence of a main effect between OXTR genotype and BMI is understandable. If this relationship exists, it should only become apparent through a process that translates genotypic variations into phenotypic differences. Previous studies suggest that oxytocin's effects on satiety may be one such process. Indeed, participants with the AA allele of rs1042778 had significantly higher satiety scores than those with the CC allele. This difference was consistent with previous research on oxytocin and sociability (e.g. empathy, prosocial behaviour), where the AA allele was related to sociability in a way that paralleled the administration of oxytocin in humans. Allelic variations in rs918316, rs2139184, and rs4686301 also showed significant differences in satiety response and may be involved in the same process; however, these have not received previous scientific attention, and their oxytocinergic effects remain unclear. Finally, SNPs rs237897 and rs11131149 show a counter-intuitive pattern, where the alleles with lower satiety scores have previously been associated with higher levels of oxytocin activity. This is not consistent with previous research on oxytocin and satiety.

Disclosures: B.C.Y. Low: None. **K.M. Vijayakumar:** None. **N. Karnani:** None. **Y.S. Lee:** None. **F. Yap:** None. **M.F.F. Chong:** None. **B. Broekman:** None. **A. Rifkin-Graboi:** None. **M. Meaney:** None. **P. Gluckman:** None. **K. Kwek:** None. **Y.S. Chong:** None. **J.C.J. Liu:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.09

Topic: E.07. Food Intake and Energy Balance

Support: CIHR MOP 84409

CIHR RNL-132870

RDC #5404.1171.102

CIHR/RDC Doctoral Fellowship

Title: Activation of MCH neurons with palatable high fat diet

Authors: *V. LINEHAN, M. HIRASAWA;
Div. of BioMedical Sciences, Fac. of Med., Mem. Univ. of Newfoundland, St John's, NL, Canada

Abstract: Melanin concentrating hormone (MCH) neurons of the lateral hypothalamus promote appetite and weight gain. We have found that they are chronically depolarized in diet induced obese mice and rats. However, questions remain as to whether the activation is a cause or effect of obesity, how they become depolarized, and how persistent the activation is. Therefore we tested MCH neuron activation with short term high fat diet feeding. Furthermore, we determined the mechanism underlying MCH neuron activation and whether it is reversible. We used whole cell patch clamp recording techniques on acute hypothalamic brain slices from male Sprague Dawley rats that were fed a high fat diet (Western Diet; WD) or a control low fat diet. An acute (1 week) WD feeding did not induce depolarization of MCH neurons. However, after 4 weeks of WD feeding, at the onset of excess weight gain, MCH neurons had significantly depolarized resting membrane potential (RMP) and higher firing frequency. Therefore activation of MCH neurons indeed occurs with short term high fat diet feeding corresponding to the onset of excess weight gain. Next, we determined the mechanism of MCH activation. MCH neurons were depolarized with no change in membrane resistance, indicating that an electrogenic pump or transporter is responsible. We tested ouabain, a Na+/K+ ATPase (NKA) inhibitor, as it is known to be inhibited in peripheral tissues during high-fat diet feeding. We found that the NKA is less active in the WD condition and its inhibition is the cause of depolarization in MCH neurons. Finally, we tested whether the NKA-induced activation of MCH neurons is reversible. After switching to the low-fat diet following 4 weeks of WD, we found that the RMP returned to

baseline levels, indicating that MCH activation was reversible. However, it has been reported that diet cycling (altering between low and high-fat diets) can lead to increased weight gain. Therefore we tested what effect re-exposure to WD following the low-fat diet recovery period would have on MCH neurons. We found that MCH neurons are again depolarized by this treatment, but this effect was present after 1 week of WD. Since 1 week of WD feeding is not sufficient to induce depolarization in naïve animals, it appears that a previous exposure to WD increases the sensitivity of MCH neurons to undergo high fat diet induced plasticity. To conclude, our study suggests that diet-induced depolarization of MCH neurons due to reduced NKA activity may contribute to the onset and maintenance of obesity. Additionally, MCH neurons become more sensitive to high fat diet with previous exposures, which may have implications for dieting strategies to lose weight.

Disclosures: V. Linehan: None. **M. Hirasawa:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.10

Topic: E.07. Food Intake and Energy Balance

Support: New York Stem Cell Foundation - Robertson Investigator Award

Alfred P. Sloan Foundation

Rita Allen Foundation

Joseph and Ester A. Klingenstein Foundation

Brain and Behavior Research Foundation

NIH Grant R00DK083531

Title: Temporal dynamics of the arcuate feeding circuit

Authors: *Y. CHEN, Y.-C. LIN, Z. A. KNIGHT;
Univ. of California, San Francisco, San Francisco, CA

Abstract: AgRP and POMC neurons in the hypothalamic arcuate nucleus (ARC) play critical roles in feeding regulation. Previous studies have shown that stimulation of AgRP neurons is sufficient to drive a fed mouse to eat while stimulating POMC neurons reduces long-term food

intake. While the ARC is known to integrate peripheral hormonal and humoral information related to an animal's energy state, the dynamics of AgRP and POMC neurons *in vivo* had not been described. We used fiber photometry, a method for deep brain calcium signal recording, to monitor the activity of these neurons in freely behaving mice. We found surprisingly that AgRP neuron activity was inhibited (dF/F = -37% ± 4%) and POMC neuron activity was activated (dF/F = 38% ± 5%) very rapidly following the sensory detection of food. This rapid response was triggered by the sight and smell of food alone and preceded the onset of food consumption. These effects were reversed after removal of food but the reversal happened at a slower pace compared to the initial change. We also found that these neural activity changes depend on the animals' satiety state, the palatability of the food, and the accessibility of the nutritional source in both AgRP and POMC neurons. Analysis of individual feeding bouts revealed that these neurons' activity is also correlated with intrameal dynamics. Together these data show that the ARC feeding circuit is modulated by the anticipation of food consumption that will occur following food discovery, in contrast to previous work which had focused on the slow homeostatic regulation of this circuitry by circulating hormones and nutrients. I will discuss implications of these findings and directions for future research.

Disclosures: **Y. Chen:** None. **Y. Lin:** None. **Z.A. Knight:** None.

Nanosymposium

112. Food Intake and Energy Regulation Nano

Location: S405

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 112.11

Topic: E.07. Food Intake and Energy Balance

Support: NIDDK P30 DK063720

NIDDK 1K08DK076721

Lawson Wilkins Pediatric Endocrine Society Clinical Scholar Award

AHA 13GRNT16120004

NIDDK R01DK09972

NIDA K01DA026504

Title: Eliminating Vglut2 in the VMH increases metabolic rate in females and reduces anxiety-like and aggressive behaviors in both sexes

Authors: *W. C. KRAUSE[1], C. C. CHEUNG[2], R. H. EDWARDS[3], C. F. YANG[4], N. M. SHAH[4], T. S. HNASKO[5], H. A. INGRAHAM[1];
[1]Dept. of Cell. and Mol. Pharmacol., [2]Pediatrics, [3]Neurol., [4]Anat., [5]Physiol. & Neurol., Univ. of California, San Francisco, San Francisco, CA

Abstract: The ventromedial hypothalamic nucleus (VMH) helps maintain energy homeostasis and regulates social and emotional behaviors. Nearly all VMH neurons, including those in the sexually dimorphic ventrolateral VMH (VMHvl) subregion, release the excitatory neurotransmitter glutamate. These neurons express the vesicular glutamate transporter 2 (Slc17a6 or Vglut2), which is required for packaging and release of glutamate. To assess how glutamatergic signaling contributes to the collective metabolic and behavioral responses attributed to both the VMH and VMHvl, Vglut2 was eliminated using Sf1-Cre (*Vglut2*$^{Sf1\text{-}Cre}$) in mice on the C57BL/6 background. Many phenotypes observed in these *Vglut2*$^{Sf1\text{-}Cre}$ mice are largely unexpected based on prior studies that perturbed VMH development or VMH function via knockouts of leptin or insulin inputs or glutamatergic output. Indeed, *Vglut2*$^{Sf1\text{-}Cre}$ mice fail to exhibit the anticipated increase in body weight after high fat diet (HFD) or the impaired glucose homeostasis after fasting. Instead, there is a sex-specific attenuation of body weight increase in response to HFD in *Vglut2*$^{Sf1\text{-}Cre}$ females, which mimics the negative energy state associated with estrogen receptor activity in the VMHvl. We hypothesize that this body weight phenotype reflects altered thermogenesis in *Vglut2*$^{Sf1\text{-}Cre}$ females and are currently evaluating the effect of this knockout on activation of thermogenic brown adipose tissue. In addition to the surprising metabolic phenotype, *Vglut2*$^{Sf1\text{-}Cre}$ mice have less anxiety-like behavior, unlike the anxiogenic phenotype previously observed in *Sf1*$^{Nestin\text{-}Cre}$ mice that lack a fully formed VMH. *Vglut2*$^{Sf1\text{-}Cre}$ males also display a sex-specific loss of conditioned-fear responses and aggression accompanied by more novelty-associated locomotion. Collectively, this study demonstrates that excitatory output from the VMH drives sex-specific differences in metabolism and social behaviors linked to the VMHvl, and is essential for adaptive responses to anxiety-provoking stimuli in both males and females.

Disclosures: W.C. Krause: None. **C.C. Cheung:** None. **R.H. Edwards:** None. **C.F. Yang:** None. **N.M. Shah:** None. **T.S. Hnasko:** None. **H.A. Ingraham:** None.

Nanosymposium

113. Influence of Memory on Perception

Location: N227

Time: Sunday, October 18, 2015, 8:00 AM - 10:15 AM

Presentation Number: 113.01

Topic: F.01. Human Cognition and Behavior

Support: BBSRC:H012508

EU:PITN-GA-2011-290011

Leverhulme Trust:RF-2011-378

Title: Human brain circuits for learning predictive hierarchical structures

Authors: *Z. KOURTZI[1], R. WANG[1], V. KARLAFTIS[1], Y. SHEN[2], P. TINO[2];
[1]Univ. of Cambridge, Cambridge, United Kingdom; [2]Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Making successful predictions about future events entails taking into account previous knowledge about the structure of the environment. Recent work has focused on simple structures defined by associative pairing, or probabilistic sequences. However, event structures in the environment (as in language, music, navigation) are typically hierarchical, comprising of simple repetitive to more complex probabilistic combinations. Yet, little is known about the neural mechanisms that mediate our ability to learn hierarchical structures. Here we combine behavioral, structural and functional brain imaging measurements to investigate the human brain circuits involved in predict upcoming events based on knowledge of hierarchical structures. We employed variable memory length Markov models to design temporal sequences of increasing complexity. We presented observers with a sequence of four symbols that differed either in their probability of occurrence (i.e. frequency statistics) or the length of the predictive temporal context (up to two items of context length). Observers were first trained with sequences determined by frequency statistics and then variable context length. In each trial, the sequence was interrupted by a test stimulus and observers were asked to indicate whether the test symbol matched their expectation based on the preceding sequence. Our behavioural results demonstrate different learning profiles across observers. Successful learners improved quickly (within 2 training sessions) and learned to predict the most frequent symbol for each context (i.e. probability maximization). In contrast, weak learners based their predictions on symbol probabilities (i.e. probability matching) and required more (4-5) training sessions to learn the correct hierarchical structure. Our brain imaging results demonstrate dissociable brain circuits for learning frequency statistics vs. probabilistic context. In particular, fronto-parietal circuits are involved in identifying novel patterns early in the learning of frequency statistics, while subcortical regions (i.e. putamen) are involved in the learning of probabilistic context. Finally, functional activations and white matter connectivity in fronto-striatal circuits correlate with learning rate, suggesting enhanced learning-dependent brain changes for successful learning based on probability maximization. Thus, our findings propose that predicting upcoming events from past experience is implemented by dynamically recruiting different brain circuits across stages of probabilistic learning for hierarchical structures.

Disclosures: **Z. Kourtzi:** None. **R. Wang:** None. **V. Karlaftis:** None. **Y. Shen:** None. **P. Tino:** None.

Nanosymposium

113. Influence of Memory on Perception

Location: N227

Time: Sunday, October 18, 2015, 8:00 AM - 10:15 AM

Presentation Number: 113.02

Topic: F.01. Human Cognition and Behavior

Support: NIMH K99MH099654

Howard Hughes Medical Institute

Picower Institute Innovation Fund

Title: Temporal memories modulate the dynamic response properties of neurons in mouse V1

Authors: *J. P. GAVORNIK[1], M. F. BEAR[2];
[1]Biol., Boston Univ., Boston, MA; [2]MIT, Cambridge, MA

Abstract: We have previously demonstrated that passive visual experience is sufficient to encode representations of temporally organized visual sequences in the primary visual cortex of mice. This encoding is highly specific for both the spatial and temporal components of visual stimuli. It is also predictive in the sense that V1 responds as if an expected element of a familiar sequence were seen even when it is actually omitted. These predictive responses occur at precisely the time omitted stimuli would normally have been presented. This form of learning seems to happen locally in V1, and involves a form of long-term plasticity that develops over days. While generally consistent with some predictive coding models, our data does not comport with the long-held idea that V1 is a simple feature detector which reliably reports retinal activity using receptive fields established during the developmental critical period . Rather, our results show that V1 maintains a high degree of plasticity into adulthood and can learn to recognize and anticipate complex temporal relationships. There are many open questions about the implications of this plasticity both as it relates to V1 and to the neocortex generally. Here we will discuss possible mechanisms that underlie this learning and the role of attention. We will also consider the perceptual consequences of activity patterns in V1 that are initiated by visual stimuli but proceed with dynamics determined by memories of previous visual experience.

Disclosures: J.P. Gavornik: None. **M.F. Bear:** None.

Nanosymposium

113. Influence of Memory on Perception

Location: N227

Time: Sunday, October 18, 2015, 8:00 AM - 10:15 AM

Presentation Number: 113.03

Topic: F.01. Human Cognition and Behavior

Support: NIH NRSA F32 EY021999

NIH R01 EY021755

Title: Object-based competition during long-term memory encoding

Authors: ***J. HUTCHINSON**, N. B. TURK-BROWNE;
Princeton Univ., Princeton, NJ

Abstract: Much like how attention prioritizes goal-relevant or perceptually salient bits of incoming information, our past experience might selectively filter our environment to promote the acquisition of new memories. A biased competition account of visual attention has been extremely fruitful in understanding how limited processing resources are allocated to sensory information, but less is known about how such competition plays out during long-term memory encoding. Here we examine the role of prior experience with an object in biasing the encoding of other objects. We tested the hypothesis that repetition of familiar objects will attenuate the neural response to those objects, in turn biasing processing toward other, novel objects presented simultaneously, and enhancing their encoding into long-term memory. This hypothesis was explored in a situation where, during each encoding trial, a novel object was presented in competition with a repeated object from a different visual category. We predicted that subsequent memory for the novel object would be associated with attenuated processing in brain areas coding for the repeated object, with enhanced processing in areas coding for the novel object, and with indices of competition between areas. These predictions were evaluated in an fMRI study in which participants were presented with the same face twice in a row, and then on the third event of each trial, the same face was surrounded by a novel scene. Consistent with a biased competition account, scenes were more likely to be later remembered when there was lower BOLD activity in face-selective fusiform gyrus, higher activity in scene-selective parahippocampal gyrus, and a greater difference in activity between scene- and face-selective areas. We further examined how these competitive dynamics impacted processing in other key brain structures involved in attention and memory beyond face- and scene-selective areas. Taken as a whole, these findings suggest that, like salience and goals, repetition attenuation can drive selection, especially as it relates to long-term memory encoding.

Disclosures: J. Hutchinson: None. **N.B. Turk-Browne:** None.

Nanosymposium

113. Influence of Memory on Perception

Location: N227

Time: Sunday, October 18, 2015, 8:00 AM - 10:15 AM

Presentation Number: 113.04

Topic: F.01. Human Cognition and Behavior

Support: R01 EY021755

R01 MH069456

Title: Prior contextual associations are weakened based on competition from new contexts

Authors: *G. KIM[1], K. A. NORMAN[1,2], N. B. TURK-BROWNE[1,2];
[1]Psychology, [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: We frequently encounter the same item in different contexts. How does this varied experience influence subsequent retrieval of the context(s) in which the item was experienced? We hypothesized that encountering a familiar item in a novel context will weaken prior contextual associations, but only insofar as these prior contexts are reactivated during this new encounter. To test this hypothesis, we ran an fMRI study that consisted of three phases. In the first phase, observers were exposed to a sequence of real-world objects that had been randomly assigned in advance to one of two orienting tasks: How easy would it be to draw the object? (artist task) or How useful is the object? (function task). These tasks served as the initial context to which the items were bound during encoding. In the second phase, some of these objects were presented again in a different task: How natural is the object? (organic task). Applying multivariate pattern analysis, we measured how much the initial artist or function task for each object was reactivated in the brain during the organic task. We predicted that such reactivation would trigger competition between this initial context and the current, novel context, weakening the initial association. More specifically, we predicted that stronger reactivation would induce more competition and greater weakening. To evaluate this possibility, we tested source memory for the initial context of each object in the third phase, with a forced choice judgment between the two initial tasks. Consistent with our hypothesis, greater classifier evidence for the artist/function task during the organic task was linked to worse subsequent source memory for the first task. These results could not be explained by an interference account in which memory for the initial task was overwritten by the organic task, as classifier evidence for the organic task during the second phase was not predictive of artist/function memory. Our findings emphasize the role of competition-dependent learning in updating episodic memory, both when binding multiple items to a single context (Kim et al., 2014, PNAS) and, as shown here, when binding multiple contexts to a single item. This kind of automatic regulation process might be adaptive, reducing potential clutter and interference from multiple related context memories.

Disclosures: **G. Kim:** None. **K.A. Norman:** None. **N.B. Turk-Browne:** None.

Nanosymposium

113. Influence of Memory on Perception

Location: N227

Time: Sunday, October 18, 2015, 8:00 AM - 10:15 AM

Presentation Number: 113.05

Topic: F.01. Human Cognition and Behavior

Support: 1R01MH097085

NSF GRFP

Title: Memory guided attention: Independent contributions of the hippocampus and striatum

Authors: ***E. V. GOLDFARB**[1], M. M. CHUN[2], E. A. PHELPS[1];
[1]New York Univ., New York, NY; [2]Yale Univ., New Haven, CT

Abstract: Attention can be strongly influenced by memory. While there is abundant evidence that the flexible, contextual representations encoded by the hippocampus can guide attention, there is less evidence suggesting other forms of memory--such as the rigid, stimulus-response associations learned by the striatum--can also facilitate attention. Here we present a new task in which participants show improvements in visual search by using mnemonic cues that depend on distinct memory systems. Participants are faster to respond to the target in a familiar context (a replication of the contextual cueing effect; Chun & Jiang, 1998) as well as when a stimulus-response association provides a probabilistic (80%) cue to the location of the target and the participant's motor response. Despite these improvements in reaction time, participants show no explicit memory for these associations. Using blood oxygen level dependent (BOLD) fMRI (N = 35), we demonstrate that these memory cues depend on distinct neural systems. Change in hippocampal BOLD correlates with later context-guided (but not stimulus-response-guided) attention, while change in striatal BOLD correlates with stimulus-response-guided (but not context-guided) attention. On a trial-by-trial basis, we show that BOLD activity in these regions separately predicts reaction time on the next memory-guided trial. Subsequent attention is predicted by hippocampal (but not striatal) BOLD on context trials, and by striatal (but not hippocampal) BOLD on stimulus-response trials. These data provide novel evidence for the role of the striatum in guiding attention, and illustrate a double dissociation between mnemonic cues supported by distinct memory systems.

Disclosures: **E.V. Goldfarb:** None. **M.M. Chun:** None. **E.A. Phelps:** None.

Nanosymposium

113. Influence of Memory on Perception

Location: N227

Time: Sunday, October 18, 2015, 8:00 AM - 10:15 AM

Presentation Number: 113.06

Topic: F.01. Human Cognition and Behavior

Support: Wellcome Trust

BSRC

Title: Dynamic mapping of spatial and temporal networks during memory-guided attention deployment using meg and fmri

Authors: *E. PATAI[1], M. WOOLRICH[1], K. WATKINS[2], A. NOBRE[1];
[1]Oxford Ctr. For Human Brain Activity, Oxford, United Kingdom; [2]Dept. of Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: Spatial and contextual associations in long-term memory are known to guide attention through top-down biasing of sensory processing. Brain-imaging studies of memory-based orienting of attention have revealed the involvement of the dorsal frontoparietal network implicated in spatial attention as well as the hippocampus. However, it remains unclear how the learning of spatial contextual associations comes to engage or implement attentional control over perceptual functions. In this study, we used magnetoencephalography (MEG) and complementary functional magnetic resonance imaging (fMRI) in order to reveal the spatial and temporal dynamics of the brain areas involved during the incremental learning of spatial contextual associations, and how this relates to neural and behavioural signatures of memory-based perceptual facilitation. We tested for increases of activation in the network of brain regions implicated in forming spatial contextual memories, involving hippocampus, prefrontal cortex, and precuneus; and we investigated the involvement of theta-band oscillations, which have been implicated in integrating information across this network. Sensor-space MEG analysis revealed a parametric modulation of early evoked-activity depending on learning stage, as well as increases in theta power. FMRI as well as source-space MEG analysis showed increased activity both hippocampus-based frontoparietal networks during learning. Activity levels in brain areas, and theta-band oscillations, implicated in learning correlated with behavioral benefits of memory-guided attention in a subsequent attention-orienting task. Our results provide important cross-validation between neural signatures derived using MEG and fMRI in addition to revealing the dynamics in networks participating in learning and using spatial-contextual information to guide

adaptive behavior. We aim to probe further the frequency specificity of the networks involved, and how these may change across learning and attention.

Disclosures: **E. Patai:** None. **M. Woolrich:** None. **K. Watkins:** None. **A. Nobre:** None.

Nanosymposium

113. Influence of Memory on Perception

Location: N227

Time: Sunday, October 18, 2015, 8:00 AM - 10:15 AM

Presentation Number: 113.07

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant EY022229

National Science Foundation Graduate Research Fellowship Grant No. DGE-1247312

Title: Cognitive control network contributions to long-term memory-guided attention in the human cerebral cortex, cerebellum, striatum, and thalamus

Authors: *D. C. SOMERS, C. E. STERN, K. J. DEVANEY, M. L. ROSEN;
Psychological & Brain Sci., Boston Univ., Boston, MA

Abstract: Human attentional and short-term memory capacity is extremely limited (~ 4 objects) while real-world human visual performance is remarkably strong, especially in familiar environments. This apparent discrepancy between superior visual performance and limited attentional capacity can be reconciled by considering the role of long-term memory, which can guide attention to the most relevant information in an environment. Recent work from our laboratory (Rosen et al., 2015) has highlighted the contributions of three posterior nodes of the cognitive control network (CCN as defined in Yeo, Krienen et al., 2011), that were more strongly recruited during long-term memory-guided attention compared to stimulus-guided attention, including the lateral intraparietal sulcus (latIPS), posterior callosal sulcus (CaS-p), and the posterior precuneus (PrC-p). Recent work has suggested that these three regions form a subnetwork and a meta-analysis suggested that they support long-term memory retrieval (Power et al, 2011; 2014). Here, we designed an experiment to directly contrast long-term memory-guided attention, stimulus-guided attention and long-term memory retrieval. Visual stimuli were matched in all conditions in order to investigate whether recruitment of these regions is specific for long-term memory-guided attention or general for long-term memory retrieval. Here, we replicate our previous finding that the PrC-p, latIPS, and CaS-p are recruited more strongly for long-term memory-guided attention than stimulus-guided attention and extend that finding to

show that these regions are not recruited for long-term memory retrieval alone. Rather, this finding suggests that these regions are specifically recruited to support processing that integrates memory- and stimulus-based representations during long-term memory-guided attention. Furthermore, we examined subcortical activation patterns, using publically available functional connectivity-based parcellations of the cerebellum, striatum, and thalamus that parallel the cortical atlas parcellation (Buckner et al., 2011; Choi et al., 2012; Yeo et al., 2011). We observed that long-term memory-guided attention drives activation within the cognitive control network regions of each of these subcortical structures more strongly than either long-term memory retrieval or stimulus-guided attention alone. Taken together, these findings suggest that long-term memory-guided attention is supported by a subnetwork within the cognitive control network that spans the cerebral cortex, striatum, cerebellum, and thalamus.

Disclosures: D.C. Somers: None. **C.E. Stern:** None. **K.J. Devaney:** None. **M.L. Rosen:** None.

Nanosymposium

113. Influence of Memory on Perception

Location: N227

Time: Sunday, October 18, 2015, 8:00 AM - 10:15 AM

Presentation Number: 113.08

Topic: F.01. Human Cognition and Behavior

Support: RO1 25-91551-F7034

Title: The influence of perceptual boundaries on the formation and organization of events in episodic memory

Authors: *A. C. HEUSSER[1], Y. EZZYAT[2], D. POEPPEL[1], L. DAVACHI[1];
[1]Psychology, New York Univ., New York, NY; [2]Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: While experience appears continuous and dynamic, reflecting on the past through memory is more discontinuous and discrete. Event segmentation theory hypothesizes that when an environment is stable and predictable, ongoing experience is bound together through the maintenance of an event model. However, a shift in experience (i.e. an event boundary) can lead to greater allocation of attentional resources towards the salient features of the environment. Prior empirical research has shown that event boundaries are associated with a loss in the accessibility of just experienced representations. However, the consequences of ongoing integration and event boundaries on long-term memory organization are less clear. In a series of behavioral and MEG experiments, we tested the idea that integration processes linking items

across time and memory for information on each trial are differentially influenced by event boundaries. Namely, we predicted that boundaries would lead to a reduction in across-trial associative binding while at the same time should lead to enhanced within-trial associative binding, due to attentional orienting to salient boundary information. Our results confirmed these predictions and also highlight a trade-off between across-trial associative binding and boundary processing. Specifically, we found that the speed of processing (as measured by response times) at event boundaries was inversely correlated to associative memory for trials that flanked the boundary. In a follow-up MEG experiment using the same experimental paradigm, we investigated how oscillatory brain activity is modulated by event segmentation. We found that accumulating power within an event in the theta (4-8 Hz) and beta (13-30 Hz) band was associated with successful within-event integration. Furthermore, sharp drops in power in these same frequency bands were evident at event boundaries and were related to mnemonic event segmentation. Together, these findings highlight how transient boundary-driven shifts in attention and ongoing mnemonic integration processes interact to support the transformation of continuous experience into long lasting memories for episodic events.

Disclosures: **A.C. Heusser:** None. **Y. Ezzyat:** None. **D. Poeppel:** None. **L. Davachi:** None.

Nanosymposium

113. Influence of Memory on Perception

Location: N227

Time: Sunday, October 18, 2015, 8:00 AM - 10:15 AM

Presentation Number: 113.09

Topic: F.01. Human Cognition and Behavior

Support: The Israeli Center of Research Excellence (I-CORE) in Cognition (I-CORE Program 51/11)

Title: Exploration vs. exploitation in the proactive brain

Authors: ***M. BAR**, S. BAROR, A. TAL;
Gonda Multidisciplinary Brain Res. Center, Bar-Ilan Univ., Ramat-Gan, Israel

Abstract: It is argued that the brain is a proactive organ, striving to know what is next. This proclivity for constant predictions creates an interesting paradox: we want to minimize uncertainty with predictions, but we also need to approach novelty and learn so that we can increase the pool of scenarios on which we are able to generate predictions in the future. These two conflicting demands imply different states of mind. There are states when we want to learn, and states when we prefer to exploit the certainty of a predictable environment; our minds

sometime seek to maximize gathering of novel information, and in other times it prefers to minimize surprise. This constant tension between exploration and exploitation modes will be illustrated through a discussion of top-down and bottom-up processing, mental simulations, and the influence of load. Implications to topics such as creativity and mood will be proposed.

Disclosures: **M. Bar:** None. **S. Baror:** None. **A. Tal:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.01

Topic: F.01. Human Cognition and Behavior

Support: NSF-GRFP DGE-11-44155

NSF BCS-0963750

NINDS R01-078784

NSF 0955454

Title: The role of dynamic network flexibility in probabilistic reinforcement learning

Authors: ***R. T. GERRATY**[1], J. Y. DAVIDOW[2], K. FOERDE[3], A. GALVÁN[4], D. S. BASSETT[5], D. SHOHAMY[1];
[1]Psychology, Columbia Univ., New York, NY; [2]Harvard Univ., Cambridge, MA; [3]New York Univ., New York, NY; [4]UCLA, Los Angeles, CA; [5]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Learning involves the adaptive reconfiguration of brain circuits based on experience. But understanding the changes in brain networks underlying learning and their relation to behavior has been challenging. One substantial roadblock to fully characterizing the role of networks in learning has been the lack of available tools to assess dynamic changes in brain networks and the ability to directly link such changes to specific aspects of behavior. Recent advances in dynamic network neuroscience have begun to allow for time-resolved descriptions of large-scale network coordination. Here we applied such an approach to data from functional magnetic resonance imaging in humans to explore the role of dynamic connectivity in learning from experience during a probabilistic reinforcement task. We found that learning was related to dynamic coupling of the striatum with different networks over time, a measure known as network flexibility. Flexibility on each learning block was significantly predictive of optimal

choice on the next. Moreover, this flexibility in network dynamics was related to individual differences in participants' learning rates as derived from standard reinforcement learning models. These results suggest that network dynamics play an important role in reinforcement learning. Further, these findings are consistent with the idea that flexible network communication provides a mechanism for information integration during reinforcement learning.

Disclosures: R.T. Gerraty: None. **J.Y. Davidow:** None. **K. Foerde:** None. **A. Galván:** None. **D.S. Bassett:** None. **D. Shohamy:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.02

Topic: F.01. Human Cognition and Behavior

Support: Kimmel Award for Innovative Research

Bikura Grant

Title: Incidental learning: covert neurofeedback can shape cortical network activations and spontaneous connectivity

Authors: *M. RAMOT[1,2], S. GROSSMAN[2], D. FRIEDMAN[3], R. MALACH[2];
[1]NIH/NIMH, Rockville, MD; [2]Weizmann Inst. of Sci., Rehovot, Israel; [3]Interdisciplinary Ctr., Herzlia, Israel

Abstract: There has been a growing interest in neuroscience in the use of Neurofeedback (NF) as a tool for plasticity training, as well as for the study and treatment of various clinical conditions. Recent advances in fMRI techniques and hardware have made real time fMRI (rtfMRI) a viable method for neurofeedback, allowing more accurate, spatially localized training than was previously possible with methods such as EEG. Recent studies have shown that participants can modulate their neuronal activity in the absence of an explicit strategy, thus greatly expanding the range of possibilities for neurofeedback. However, it is as yet unknown whether such training effects can be introduced without the active engagement or explicit knowledge of the participants. Here we show successful training effects that consequently produced long-term changes in functional connectivity. Participants received positive and negative rewards that were covertly coupled to activity in two high order category selective visual cortex regions (FFA and PPA). Participants had no knowledge of the nature of the

experiment or of the possibility of influencing the rewards. Yet our results show that a high percentage of participants learned to modulate activity in these regions to enhance the positive rewards without any reportable awareness that they were so doing. Furthermore, the resulting changes in connectivity were also evident days later. The results indicate that brain networks can be modified even in the complete absence of intention and awareness of the learning situation, raising new possibilities for research and for clinical interventions.

Disclosures: **M. Ramot:** None. **S. Grossman:** None. **D. Friedman:** None. **R. Malach:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.03

Topic: F.01. Human Cognition and Behavior

Title: Probabilistic classification learning with and without corrective feedback is improved by inhibition of DLPFC

Authors: *L. WILKINSON, P. KOSHY, A. STEEL, D. BAGEAC, E. WASSERMANN; Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD

Abstract: Functional neuroimaging has shown that non-declarative probabilistic classification learning on the Weather Prediction Task (WPT) with corrective feedback (i.e. rewards and punishments) involves the cortico-striatal circuits. During learning, activity increases an in the dorsolateral prefrontal cortex (DLPFC) and caudate nucleus and decreases in the medial temporal lobe (MTL). This decrease shows that learning on the task does not ordinarily require engagement of the MTL. In contrast, when the WPT is learned in a “paired associate” manner without corrective feedback, emphasizing declarative memory, MTL activity increases. Interestingly, inhibitory repetitive transcranial magnetic stimulation (rTMS) can be used to create a so called ‘virtual TMS lesion’ of specific cortical targets in healthy controls to determine their causal role during cognitive processes. The aim of the current study was to use the virtual lesion method to study the role of the DLPFC during WPT learning with (FB) and without (PA) feedback. In a parallel, sham-controlled design, we used inhibitory, continuous theta burst (cTBS) rTMS to inhibit the DLPFC in healthy volunteers during WPT learning with and without FB. Participants were assigned to one of two conditions that required completion of 150 trials of the WPT under FB or PA conditions, immediately after real cTBS over the DLPFC or sham cTBS. Real cTBS improved WPT learning under FB and PA conditions, relative to sham, with greater improvement in the PA condition. It is possible DLPFC inhibition, allows greater

activation of the episodic memory system than normal during both FB and PA learning, and this release of the MTL, had a more striking effect on PA than observed for FB learning.

Disclosures: **L. Wilkinson:** None. **P. koshy:** None. **A. Steel:** None. **D. Bageac:** None. **E. Wassermann:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.04

Topic: F.01. Human Cognition and Behavior

Support: AXA foundation

Fyssen foundation

Swiss National Science Foundation (No 320030-135653)

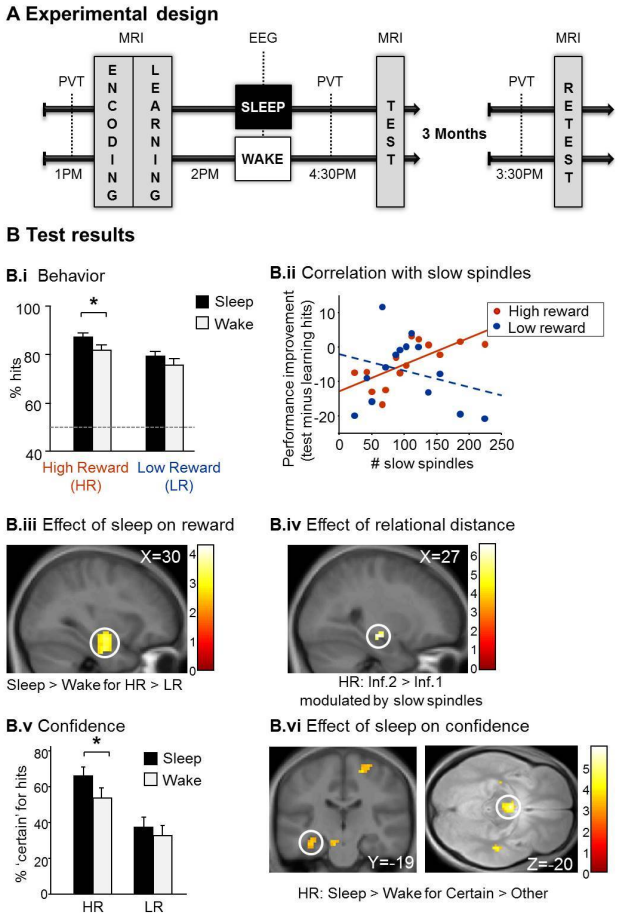
Swiss National Science Foundation (No 51NF40-104897)

Title: A nap to recap or how reward regulates hippocampal-prefrontal memory networks during daytime sleep in humans

Authors: ***K. IGLOI**[1,2], G. A. GAGGIONI[3], V. STERPENICH[1,2], S. SCHWARTZ[1,2,4]; [1]Neurosciences, Univ. of Geneva, Geneve, Switzerland; [2]Univ. of Geneva, Swiss Ctr. for Affective Sci., Geneva, Switzerland; [3]Univ. de Liège, Ctr. de recherches du cyclotron, Lège, Belgium; [4]Univ. of Geneva, Geneva Neurosci. Ctr., Geneva, Switzerland

Abstract: Sleep plays a crucial role in the consolidation of newly acquired memories. Yet, how our brain selects the noteworthy information that will be consolidated during sleep remains largely unknown. Here we show that post-learning sleep favors the selectivity of long-term consolidation by retaining the most important (i.e., rewarded) memories (Figure B.i) while also enhancing subjective confidence for well-remembered information (Figure B.v), when tested after a nap or wake period and three months after initial encoding (Figure A). Our brain imaging data reveals that the functional interplay between dopaminergic reward regions, the prefrontal cortex and the hippocampus contributes to the integration of rewarded associative memories (Figure B.iii, B.iv and B.vi). We further show that sleep spindles strengthen memory representations based on reward values, suggesting a privileged replay of information yielding positive outcomes (Figure B.ii). These findings demonstrate that post-learning sleep determines

the neural fate of motivationally-relevant memories and promotes a value-based stratification of long-term memory stores.



Disclosures: **K. Igloi:** None. **G.A. Gaggioni:** None. **V. Sterpenich:** None. **S. Schwartz:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.05

Topic: F.01. Human Cognition and Behavior

Support: This work was supported by the Intramural Research Program at NIH/NIDA.

Title: Individual differences in avoidance learning correlate with dopamine-dependent function and neuro-circuitry

Authors: *V. PARIYADATH[1,2], M. ZHOU[2], T. J. ROSS[2], B. SALMERON[2], M. J. FRANK[3], E. A. STEIN[2];
[1]Neuroimaging Res. Br., Natl. Inst. On Drug Abuse, NIH, Bethesda, MD; [2]Neuroimaging Res. Br., Intramural Res. Program, Natl. Inst. on Drug Abuse, Natl. Inst. of Hlth., Baltimore, MD; [3]Dept of Cognitive, Linguistic & Psychological Sciences, Dept of Psychiatry, Brown Univ., Providence, RI

Abstract: Reward and punishment learning plays a critical role in navigating a dynamic environment, and is thought to be impaired in several neuropsychiatric disorders including addiction. We currently have a limited understanding of individual differences in punishment processing and whether dopamine is critical to this function. Here, we combined an approach/avoidance learning task with cognitive assays of dopamine-dependent cognitive function and functional magnetic resonance imaging (fMRI) to investigate how dopaminergic function and circuitry modulate human avoidance behavior. Thirty-one healthy individuals participated in the study. Avoidance learning was tested using a probabilistic selection task (PS). Previous research indicates that performance on the Reading Span Task (RST) and Barratt Impulsiveness Scale (BIS) correlate with striatal dopamine synthesis and release, respectively. These cognitive measures were, therefore, collected from participants to indirectly assay diverse aspects of baseline dopamine function. To examine the underlying neural circuitry, fMRI was employed to measure BOLD activity during the PS task and resting state functional connectivity (rsFC) immediately preceding the task. Avoidance learning showed a significant interaction of RST and BIS, and suggested an inverted U-shaped effect of putative dopamine efficacy on avoidance learning. Concurrently, activity in bilateral dorsal striatum also revealed an RST - BIS interaction effect at feedback on loss trials, with activity in the right caudate correlating with avoidance performance. Finally, caudate-mediodorsal thalamus rsFC was influenced by the RST - BIS interaction, further bolstering the argument that dopaminergic mechanisms underlie the processing of loss and punishing stimuli. Taken together, our data suggests that a circuit consisting of the dorsal striatum together with its efferents may shape avoidance learning and may involve dopaminergic mechanisms. Our findings have implications for drug addiction and other neuropsychiatric disorders associated with punishment processing.

Disclosures: **V. Pariyadath:** None. **M. Zhou:** None. **T.J. Ross:** None. **B. Salmeron:** None. **M.J. Frank:** None. **E.A. Stein:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.06

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant MH091864

Title: Effects of early life stress on the development of ventral striatal resting-state connectivity in humans

Authors: *D. S. FARERI[1,2], L. GABARD-DURNAM[1], B. GOFF[3], J. FLANNERY[4], D. GEE[5], D. LUMIAN[6], C. CALDERA[3], N. TOTTENHAM[1];
[1]Psychology, Columbia Univ., New York, NY; [2]Derner Inst. of Advanced Psychological Studies, Adelphi Univ., Garden City, NY; [3]Psychology, UCLA, Los Angeles, CA; [4]Psychology, Univ. of Oregon, Eugene, OR; [5]Weill Cornell Med. Col., New York, NY; [6]Univ. of Denver, Denver, CO

Abstract: Across species, evidence highlights the ventral striatum (VS) as crucially important for evaluating and learning from affective and social incentives. The VS is anatomically connected to both cortical (e.g., prefrontal cortex; PFC) and subcortical (e.g., amygdala, hippocampus) structures also supporting affective valuation and learning, forming a neural incentive-based valuation circuit (Haber & Knutson, 2010). Early life is a time during which learning about affective and social signals occurs at a rapid rate, as we begin to understand how to engage with the world, but is also a time of significant neurodevelopmental change and vulnerability to external environmental stressors. Adverse early life experiences, such as the absence of a stable caregiving environment can significantly impact neural and behavioral development (Tottenham & Sheridan, 2012; Gunnar & Quevedo, 2007). Rodents experiencing repeated maternal separation early in life show altered reward-related behaviors later in life (Matthews and Robbins, 2003) (e.g., reduced preference for reward-predicting stimuli (Matthews et al., 1996)). Human fMRI studies report that lack of a stable caregiving environment—spending significant time in institutionalized care during infancy—is associated with decreased reward related activation in the VS to socially rewarding stimuli (Goff et al., 2013) and a decreased ability to learn the value of reward predicting cues (Metha et al., 2010). To date, there is little understanding of how early life stress in the form of maternal deprivation during the infancy period affects the development of functional relationships between the VS and connected structures in humans. We employed a seed-based correlation approach to investigate VS resting-state functional connectivity (rsFC) in a sample of typically developing (TD) children and adolescents and those with a history of institutionalized care (PI) early in life ranging from 6-18 years of age. Preliminary whole-brain analyses ($p<.01$, uncorrected) reveal stronger (i.e., more positive) VS rsFC with the amygdala/parahippocampus and lateral prefrontal cortex in TDs ($n = 46$) than PIs ($n = 39$). Conversely, PI individuals show positive rsFC between the VS and a region of anterior medial PFC (BA9) whereas TD individuals demonstrate no significant VS rsFC with this region. Future planned analyses will examine interactive effects of age (linear,

quadratic) and group on the development of VS rsFC. Taken together, these initial findings suggest that early life stress may alter normative development of VS functional connections with cortical and subcortical structures implicated in incentive-based behaviors.

Disclosures: D.S. Fareri: None. **L. Gabard-Durnam:** None. **B. Goff:** None. **J. Flannery:** None. **D. Gee:** None. **D. Lumian:** None. **C. Caldera:** None. **N. Tottenham:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.07

Topic: F.01. Human Cognition and Behavior

Support: MRF funded clinical research training fellowship

Title: Neural signatures of reinforcement learning in unmedicated depressed patients predict response to computerised Cognitive Behavioural Therapy

Authors: *F. QUEIRAZZA[1], E. FOURAGNAN[1], J. CAVANAGH[1], D. STEELE[2], M. PHILIASTIDES[1];
[1]Psychology, Univ. of Glasgow, Glasgow, United Kingdom; [2]Univ. of Dundee, Dundee, United Kingdom

Abstract: Major Depressive Disorder (MDD) is one of the leading causes of disability worldwide. At present there are no reliable biomarkers for treatment outcome prediction in MDD. Capitalising on previous evidence of impaired reinforcement learning in MDD, we hypothesized that responders and non-responders to computerised Cognitive Behavioural Therapy (cCBT) would exhibit differential neural activity in association with the update of choice value following negative and positive feedback information. We employed a longitudinal design. Prior to cCBT, unmedicated participants (n=40) meeting ICD-10 diagnostic criteria for MDD were scanned using functional magnetic resonance imaging (fMRI) whilst performing a probabilistic reversal-learning task. In order to track the trial-by-trial choice value update we fitted a computational model with a dynamic learning rate to each participant's observed behaviour and used the model's estimates of the dynamic learning rate to inform the analysis of the baseline fMRI data. Our results show a cluster in the paracentral cingulate cortex correlating with the model's dynamic learning rate. After assessing participants' response to cCBT at 4 months follow-up, we found differential patterns of baseline BOLD activity within the paracentral cingulate cortex to be more predictive of differential response to cCBT than the

model's estimates of the dynamic learning rate. This finding represents preliminary evidence that different neural signatures in the context of reinforcement learning might help predict treatment outcome in MDD.

Disclosures: F. Queirazza: None. **E. Fouragnan:** None. **J. Cavanagh:** None. **D. Steele:** None. **M. Philiastides:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.08

Topic: F.01. Human Cognition and Behavior

Support: Wellcome Trust Principal Research Fellowship

Virginia Tech

Title: Sub-second dopamine fluctuations in human striatum encode superposed error signals about actual and counterfactual reward

Authors: *K. KISHIDA[1], I. SAEZ[2], T. LOHRENZ[1], M. R. WITCHER[3], A. W. LAXTON[3], S. B. TATTER[3], J. P. WHITE[1], T. L. ELLIS[3], P. E. M. PHILLIPS[4], P. R. MONTAGUE[1,5,6]; [1]Human Neuroimaging Lab., VTC Res. Inst., Roanoke, VA; [2]Helen Wills Neurosci. Inst., Univ. of California, Berkeley, CA; [3]Neurosurg., Wake Forest Hlth. Sci., Winston-Salem, NC; [4]Univ. of Washington, Seattle, WA; [5]Physics, Virginia Tech., Blacksburg, VA; [6]Wellcome Trust Ctr. for Neuroimaging, Univ. Col. London, London, United Kingdom

Abstract: In the mammalian brain, the neuromodulator dopamine is critical for decision-making and adaptive behavior. To date, measurements of dopamine release with the requisite temporal resolution and cognitive challenges necessary to test hypotheses about the computational role of dopamine release in the human brain have been lacking. We monitored dopamine levels with sub-second temporal resolution in humans (N=17) with Parkinson's disease while they executed a sequential decision-making task. Participants placed bets and experienced monetary gains or losses. Dopamine fluctuations in the striatum fail to encode reward prediction errors as anticipated by a large body of work in model organisms. Instead, sub-second dopamine fluctuations encode an integration of reward prediction errors with counterfactual prediction errors; the latter defined by how much better or worse the experienced outcome could have been. Notably this combination of error terms is consistent with how one should feel given one's

decision, the resulting outcome, and the overall context of that outcome. This combination of information in a single physical signal could be one way that the human brain translates computations about actual and simulated experience to embodied states of feeling. How dopamine fluctuations combine the actual and counterfactual is unknown. One possibility is that this is the normal behavior of reward processing dopamine neurons, which previously had not been tested by experiments in animal models; alternatively, this superposition of error terms may result from an additional yet to be identified subclass of dopamine neurons.

Disclosures: **K. Kishida:** None. **I. Saez:** None. **T. Lohrenz:** None. **M.R. Witcher:** None. **A.W. Laxton:** None. **S.B. Tatter:** None. **J.P. White:** None. **T.L. Ellis:** None. **P.E.M. Phillips:** None. **P.R. Montague:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.09

Topic: F.01. Human Cognition and Behavior

Support: NWO Grant #404-10-062

Title: Human choice strategy varies with anatomical projections from ventromedial prefrontal cortex to medial striatum

Authors: ***P. PIRAY**, I. TONI, R. COOLS;
Donders Inst. for Brain, Cognition and Behavior, Radboud Univ. Nijmegen, Nijmegen, Netherlands

Abstract: Two distinct systems, goal-directed and habitual, support decision making. It has recently been hypothesized that this distinction may arise from two computational reinforcement learning mechanisms, model-based and model-free. Although individuals are largely different in the degree to which they employ model-based and model-free control, it is not known whether these differences depend on the relative strength of anatomical connectivity within frontostriatal circuits involved in learning and behavioral control. In this study, we fill this gap by combining diffusion tensor imaging with a multistep decision task known to distinguish model-based and model-free control. We exploited the presence of large inter-individual differences in the degree of model-based control in this task. We found evidence that the degree of model-based control is predicted by the structural integrity of white-matter tracts from the ventromedial prefrontal cortex to the medial striatum. Furthermore, a simulated lesion analysis suggests that this effect is

driven by top-down influences from ventromedial prefrontal cortex to medial striatum. Our findings indicate that individuals with stronger afferences from the ventromedial prefrontal cortex to the medial striatum are more likely to rely on a model-based strategy to control their instrumental actions. These findings suggest a mechanism for instrumental action control through which medial striatum determines, at least partly, the relative contribution of model-based and model-free systems during decision-making according to top-down model-based information from the ventromedial prefrontal cortex. These findings have important implications for understanding the neural circuitry that might be susceptible to pathological computational processes in impulsive/compulsive psychiatric disorders.

Disclosures: **P. Piray:** None. **I. Toni:** None. **R. Cools:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.10

Topic: F.01. Human Cognition and Behavior

Support: China Scholarship Council (CSC, grant 201208080013 to SL)

German Research Foundation (DFG, grant FOR 1617 to AH and MR)

Title: Music and video gaming during breaks: influence on habitual versus goal-directed decision making

Authors: ***S. LIU**[1], D. J. SCHAD[1], M. S. KUSCHPEL[1], M. A. RAPP[2], A. HEINZ[1];
[1]Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]Univ. Potsdam, Potsdam, Germany

Abstract: Decision making is shaped by many factors, such as stress and cognitive strategy. We aimed to investigate if and how decision making is differentially influenced by breaks filled with diverse everyday life activities. We had young adults listening to music and playing a video game during breaks, in between trials of sequential two-step Markov decision task, to assess habitual as well as goal-directed decision making. Based on computational mixed-effects modeling, we observed that video gaming, as compared to music, reduced reliance on the goal-directed decision-making system and led the habitual choices to become more dependent on intermediate value expectations as compared to final feedback. Our findings suggest differential effects of everyday activities on key decision-making processes.

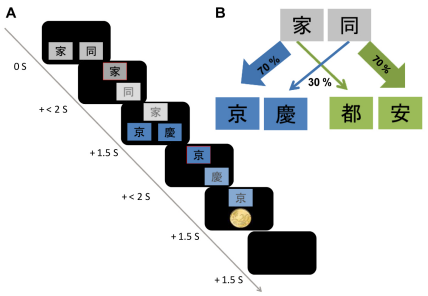


Figure 1. Two-step decision task. (**A**) Trial structure. Each trial consisted of choices at two steps. Step 1 involved the first choice between two abstract gray stimuli (Chinese characters, not known to German subjects). The chosen stimulus was framed with red color in the center-top of the screen for 1.5s. Subsequently, subjects were presented with another stimulus pair in step 2. The second choice was rewarded with money (20 cents) or nothing. (**B**) The transitions from step 1 to step 2 remained fixed, with 70% and 30 % of all trials as respectively common and rare transitions. The reward probabilities for each stimulus in step 2 changed independently between 25% and 75%, based on Gaussian random walks with reflecting boundaries (Daw et al., 2011). Win probabilities varied, therefore, as a function of the trial number.

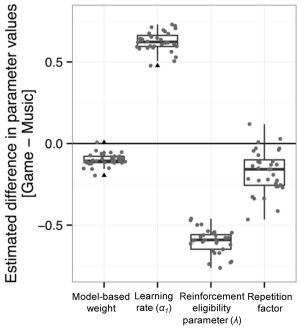


Figure 2. Computational model parameter estimates. Box-and-whisker plots of estimated differences in model parameter values between the break conditions gaming versus music (for parameters showing a significant difference between music and game break activities; $p < .05$).

Disclosures: **S. Liu:** None. **D.J. Schad:** None. **M.S. Kuschpel:** None. **M.A. Rapp:** None. **A. Heinz:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.11

Topic: F.01. Human Cognition and Behavior

Support: NIH 5T32NS047987

Title: Food odors reinforce human behavior in a value-based choice task

Authors: ***J. D. HOWARD**, T. KAHNT;
Northwestern Univ., Chicago, IL

Abstract: In order to make optimal choices, animals must generate internal representations of the value of available options. Numerous studies have focused on how such decision signals arise in the brain, and how they are implemented within a decision network to guide value-based behavior. However, these studies typically focus on the abstract value of outcomes as reflected on a "common scale", and tend to overlook the need for systems to represent value signals that are specific to the identity of the available outcomes. In order to examine whether and how identity-specific value computations are incorporated in human decision-making, we implemented an instrumental conditioning task using visual symbols as conditioned stimuli and different food odors as unconditioned stimuli. On each trial of the choice task, hungry participants (N=9) chose either a visual symbol that predicted a low-intensity food odor, or a visual symbol that predicted a high-intensity food odor. Immediately after their choice, participants sniffed the associated odor and then rated the odor's pleasantness. Analysis of choice frequencies in 12-trial bins revealed that subjects initially chose symbols at random (p(high intensity choice) = 0.51 ± 0.08, $t(8) = 0.14$, $p = 0.89$, t-test vs. chance). However, by the fourth bin of trials, subjects consistently chose the symbol leading to the higher intensity odor (p(high intensity choice) = 0.74 ± 0.09, $t(8) = 3.09$, $p = 0.015$). Pleasantness was significantly greater across all trial bins for high-intensity odors ($F(1,9) = 5.162$, $p = 0.053$, repeated measures ANOVA), indicating that higher intensity conferred increased value on the odor rewards. Additionally we found that the difference in pleasantness between high and low value odor rewards was directly related to the proportion of high intensity odor choices ($r = 0.79$, $p < 0.001$). Taken together, these results demonstrate that food odors serve as effective rewards that reinforce choice behavior during instrumental conditioning, such that human subjects will actively work to obtain them. By implementing this task in a forthcoming fMRI study, we will be able to directly test whether value-based choices rely on decision signals specific to the identity of the chosen reward outcome. Based on previous studies in our lab, we hypothesize that identity-specific value signals in the orbitofrontal cortex (OFC) would provide the neural basis for such choices.

Disclosures: **J.D. Howard:** None. **T. Kahnt:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.12

Topic: F.01. Human Cognition and Behavior

Title: Independent clustering and generalization of action-outcome and outcome-values in goal-directed learning

Authors: *N. T. FRANKLIN, M. J. FRANK;
CLPS, Brown Univ., Providence, RI

Abstract: A hallmark of goal-directed behavior is the ability to flexibly combine information about the effects of our actions with outcome values to devise a course of action. This can be difficult in a novel context as it often unclear to what degree learning from other contexts can apply to the new context. Often, it is adaptive to treat a new context as the same as an old context given substantial similarity between contexts. Previous behavioral and EEG data suggest that rather than learning about specific contexts, humans build abstract task structures and then learn which contexts should be linked to which structures. Computational models further suggest that this process involves context popularity-based clustering, such that task structures that are most popular across contexts are more likely to be revisited in new contexts. However, in ecological settings, often a novel context indicates that some aspects of task structure - such as what effects are actions have on subsequent states - should be generalized from one previous context whereas other aspects - such as the value of those states - might come from other contexts. A more flexible, goal-directed agent would treat action-effect and outcome-values separately. We first consider how a non-parametric Bayesian agent can learn and generalize latent structure in action effects and outcome values separately, forming independent clusters that may have different popularity across contexts. We show that this leads to qualitatively different predictions in behavior than an agent that considers generalizes both together. We develop a novel task to investigate how people can discover latent structure and generalize this knowledge in a flexible and goal directed way. We provide preliminary experimental evidence for this model of generalization and show that people generalize transition structure independently of reward value. These finding suggest people consider complex structures over their environment and are able to leverage these structures to act adaptively in novel situations.

Disclosures: N.T. Franklin: None. **M.J. Frank:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.13

Topic: F.01. Human Cognition and Behavior

Support: ERC-2010-AdG_20100407

DFG SFB 58

DFG SFB 936

Title: Reactivation of reward value-related patterns from single episodes and memory-based decision making

Authors: *G. WIMMER, C. BÜCHEL;
Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Rewarding and aversive experiences exert a strong influence on later decision making. While decades of neuroscience research have shown how repeated reinforcement gradually shapes preferences, decisions are often supported by single past experiences. Surprisingly, relatively little is known about how episodic experiences influence later behavior. We predicted that the reactivation of distributed value-related neural representations could bias decision making and support memory for the positive value of single experiences. We tested this prediction in experiments where human participants experienced episodes of high vs. low reward in conjunction with the presentation of incidental, trial-unique neutral object pictures. In a surprise memory test for the value incidentally associated with the objects, we found that participants could indeed remember the associated level of reward, as evidenced by preferences and accurate memory for value. Neurally, we found significant evidence for reactivation of value-related neural patterns of activity, such that reward patterns significantly classified later re-exposure to the originally neutral objects. Searchlight analyses demonstrated significant classification in the object-selective visual cortex as well as value-related regions of interest. Our results show that single affective experiences can build reliable associations between stimuli and value. Moreover, they provide a novel demonstration that affect-related neural patterns are reactivated during later experience. Taken together, our results demonstrate a mechanism by which episodic memory can guide value-based decision making.

Disclosures: G. Wimmer: None. **C. Büchel:** None.

Nanosymposium

114. Reward Processing and Reinforcement Learning in the Human Brain

Location: N228

Time: Sunday, October 18, 2015, 8:00 AM - 11:30 AM

Presentation Number: 114.14

Topic: F.01. Human Cognition and Behavior

Support: NSF 1358507

NSF GRFP DGE-114747

Title: Human reinforcement learning over latent sensory features

Authors: *I. C. BALLARD[1], S. M. MCCLURE[2];
[1]Psychology, Stanford Univ., Stanford, CA; [2]Arizona State Univ., Tempe, AZ

Abstract: Humans possess a remarkable ability to learn complex relationships from a cluttered and multifaceted world. Additive reinforcement learning models, in which learning occurs independently over different sensory features of stimuli, can compactly describe many aspects of this learning. However, animals display some behaviors that cannot be described within this framework. The serial feature discrimination task illustrates one way in which latent features of the sensory world are employed for learning reward contingencies. In serial feature discrimination, information must be maintained across time to learn reward associations. Specifically, subjects are required to learn that one stimulus feature (e.g. A) functions as an "occasion setter" so that a later stimulus (e.g. B) can be associated with reward (i.e. A→B+). Maintaining information about the occasion setter is critical for learning since the second stimulus does not predict reward when presented alone (i.e. B-). Behavioral testing indicated that serial feature learning involves different types of mental representations than does classical Pavlovian conditioning effects. Specifically, information learned about the occasion setter does not lead to subsequent blocking for conjoint reward learning (i.e. subsequent training on AC+ does not block new learning about C; $p>.05$). However, when the time delay is removed (i.e. AB+ is learned initially, followed by AE+) then blocking does occur ($p<.05$). Our task additionally presents an opportunity to investigate the representations employed by the brain during learning. The orbitofrontal cortex (OFC) is thought to combine information from sensory cortex, prefrontal cortex, and subcortical structures into abstract state representations that are critical for learning tasks with latent structure. Our novel behavioral paradigm will allow us to test the hypothesis that the OFC represents state space when information must be maintained over time. This research will ultimately contribute a more nuanced understanding of the neural basis of reinforcement learning as well as a more mechanistic understanding of OFC function.

Disclosures: I.C. Ballard: None. **S.M. McClure:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.01

Topic: F.01. Human Cognition and Behavior

Support: Felix Foundation

Medical Research Council, UK

Title: Spontaneous mimicry of dynamic facial expressions: effect of autistic traits and self-face priming

Authors: A. CHAKRABORTY, *B. CHAKRABARTI;
Univ. of Reading, Whiteknights, United Kingdom

Abstract: Individuals with autism spectrum disorders (ASD) display reduced spontaneous mimicry of facial expressions (McIntosh et al., 2006; Beall et al., 2008). Mechanisms underlying spontaneous facial mimicry (SFM) are not well understood and believed to involve access to self-representations, i.e. SFM occurs as a result of mapping/embodying another person's expression onto one's own face (Niedenthal, 2007). The current study tested a) the effect of self-face (compared to an unfamiliar other face) as a facilitating prime on SFM, and b) the effect of individual autistic traits in influencing SFM, using facial electromyography (EMG). 34 neurotypical adults (3 males) participated in a 2-part study. All participants completed the Autism Spectrum Quotient (AQ) online. In the first session participants face was photographed holding a neutral expression. In the second session participants viewed videos of happy and angry expressions. Before viewing each video, participants were subliminally primed with 'self' or 'unfamiliar other' face (33 millisecond) followed by a backward mask (66 millisecond). Spontaneous muscle activity was recorded using EMG as participants passively viewed the videos. Baseline normalized Spontaneous muscle activity from Zygomaticus Major (happy condition) and Corrugator supercilii (angry condition) was recorded over the 0-2000 millisecond window after the start of the video stimulus. Outliers were removed using Cook's d >4/N. Individuals with high autistic traits showed significantly reduced spontaneous mimicry for emotion expressions (N = (33); r =-.335, p=0.028). Specifically, this result was driven by the self-face prime condition (collapsed across emotions and muscles) [N= 31 pearson r=-.338 p=0.031], and not the other-face prime condition [N= 32; pearson r: -.181 p=0.156]. There was no main effect of priming identity on magnitude of spontaneous mimicry of either happy (zygomaticus) expressions [t=-.197 p=0.845] or angry (corrugator) expressions [t=-.834 p=0.410]. The present study shows high autistic traits reduce spontaneous mimicry of dynamic facial expression. Specifically, this relationship is statistically significant when the dynamic

facial expressions are primed with self-face but not when primed with other face. SFM thus constitutes a potential dimension relevant for examining social behavioral symptoms across psychiatric categories.

Disclosures: A. Chakraborty: None. **B. Chakrabarti:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.02

Topic: F.01. Human Cognition and Behavior

Support: MRC UK Grant G1100359/1

Title: Reduced ventral striatal response to mimicry in individuals with autism

Authors: *C.-T. HSU[1], J. NEUFELD[1,2], B. CHAKRABARTI[1];
[1]Dept. of Psychology, Univ. of Reading, Reading, United Kingdom; [2]KIND Lab., Karolinska Institutet, Stockholm, Sweden

Abstract: Imitation is a facilitator of social bonds in humans. Parents routinely imitate babies to build rapport. Behavioural studies show that neurotypical human adults like those who mimic them, and mimic others more that they like. Individuals with Autism Spectrum Disorders (ASD) show reduced spontaneous imitation and atypical social behaviour. Further, a recent fMRI study revealed that individuals high in autistic traits show a reduced modulation of mimicry-related brain regions by reward value, indicating an atypical link between reward and mimicry. Based on these observations, we hypothesized that being imitated may not be equally rewarding for individuals with ASD. 26 ASD and 30 neurotypical adults, matched for age, gender,and IQ, performed a 2-part task. The first part was a conditioning task outside the scanner, where participants were mimicked by one face and 'anti-mimicked' by another.The participants were instructed to make a facial expression (happy/sad) while watching faces on screen that would either make a congruent or an incongruent expression, 700ms after the participant initiated the instructed expression. This created the subjective impression of being mimicked/ anti-mimicked. The second part was done in a 3T fMRI scanner, where participants passively viewed the conditioned faces (mimicking vs anti-mimicking), one at a time, using an event-related design. We hypothesised that the neurotypical group would show greater reward-related ventral striatal (VS) response to the mimicking compared to the anti-mimicking faces. The VS cluster was defined using an independent meta-analysis of reward processing studies (Liu et al, 2010). The

mean t-value of the contrast [mimicking> anti-mimicking faces] of the left VS was found to be significantly lower in the ASD group ($t(54) = -1.69$, $p = 0.0486$); (2) the contrast t-values in the left VS negatively correlated with self reported autistic traits, in the whole sample ($r = -0.29$, $p = 0.0307$). No significant differences were observed in the right VS. The results support our hypothesis that in individuals with high autistic traits, and those with a clinical diagnosis of ASD being imitated is associated with lower reward-related striatal response as compared to controls.

Disclosures: C. Hsu: None. **J. Neufeld:** None. **B. Chakrabarti:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.03

Topic: F.01. Human Cognition and Behavior

Support: NIMH R01MH059282

NIDA DA022582

NHLBI HL114092

Neukom Institute for Computational Science at Dartmouth College

Title: Development and reliability of reward and self-regulatory systems at rest

Authors: *J. F. HUCKINS[1], R. S. COALSON[2], B. ADEYEMO[2], F. M. MIEZIN[2], T. F. HEATHERTON[1], S. E. PETERSEN[2], W. M. KELLEY[1];
[1]Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [2]Neurol., Washington Univ. in St. Louis, St. Louis, MO

Abstract: The neural mechanisms that underlie the relationship between reward and self-regulation are poorly understood. Behaviorally, adults demonstrate better self-regulatory ability than children and it has been hypothesized that this difference relates to differential rates of development between prefrontal control regions and subcortical structures such as the nucleus accumbens (NAcc) (Somerville and Casey, 2010). To investigate potential asymmetric development of reward and control systems we applied network-based resting-state functional connectivity (RSFC) MRI methods and support vector machine learning. We predicted adults and children would demonstrate similar RSFC within the reward system (early maturation) but would show differences in RSFC in control systems (e.g., frontoparietal and cingulo-opercular

systems; late maturation). Adults (N=48) and children matched on gender and motion parameters were included in the analysis. RSFC across 11 major systems incorporating 266 brain regions was measured. Whereas adults showed greater mean connectivity in the frontoparietal control system, children showed greater connectivity in the reward system. SVM classification between adults and children was significantly greater than chance using the whole brain network (>90%), and within individual systems. Adult/Children classification was significant in the reward system but not for the frontoparietal control system. A subsequent analysis (N=65) of individual differences within each system revealed that the reward system demonstrated reliable within-subject RSFC and low between-subject variability. By contrast, the frontoparietal system demonstrated reliable within-subject RSFC and robust between-subject variability. These findings explain the failure of the SVM to classify adults and children using frontoparietal RSFC. Indeed, SVM classification accuracy for each system between adults and kids correlated with between-subject variability (r = -0.85). These findings also highlight systems that capture robust individual differences _ a finding that offers a potential blueprint for linking individual differences in RSFC to individual differences in behavior and personality.

Disclosures: **J.F. Huckins:** None. **R.S. Coalson:** None. **B. Adeyemo:** None. **F.M. Miezin:** None. **T.F. Heatherton:** None. **S.E. Petersen:** None. **W.M. Kelley:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.04

Topic: F.01. Human Cognition and Behavior

Title: Psychopathy disrupts prefrontal regulation of striatal subjective value signals

Authors: ***J. G. HOSKING**[1], E. KASTMAN[1], H. DORFMAN[1], A. BASKIN-SOMMERS[2], K. KIEHL[3], J. NEWMAN[4], J. W. BUCKHOLTZ[1];
[1]Dept. of Psychology, Northwest Building, Harvard Univ., Cambridge, MA; [2]Yale Univ., New Haven, CT; [3]MIND Institute, Univ. of New Mexico, Albuquerque, NM; [4]Univ. of Wisconsin-Madison, Madison, WI

Abstract: Psychopathy is a personality disorder with strong links to criminal behavior and recidivism. While research on the disorder has primarily focused on empathy and threat detection, deficits in reward and motivation processing have also long been suggested. Previously we have shown in community volunteers that higher psychopathy scores predicted heightened nucleus accumbens activity to the anticipation of rewards; as virtually none of these

participants would meet forensic criteria for psychopathy, however, it is unclear whether these results generalize to a correctional setting, where rates of the disorder are disproportionately higher. Furthermore, whether this striatal hyperreactivity reflects circuit-level perturbations to reward and motivation, such as cortico-striatal connectivity, remained unclear. Here we use functional magnetic resonance imaging to examine the relationship between subjective-value-related brain activity, functional connectivity, and psychopathy in a population of adult male incarcerated criminals. We found that higher psychopathy scores were associated with heightened subjective-value-related neural signals in the nucleus accumbens, as well as diminished functional connectivity between nucleus accumbens and medial prefrontal cortex. Furthermore, psychopathy moderated the relationship between inmates' striatal connectivity and function: at low psychopathy scores, cortico-striatal connectivity was inversely correlated with striatal reactivity to subjective value, but at higher psychopathy scores this relationship broke down. Finally, weakened prefrontal-accumbens connectivity was associated with higher numbers of convicted crimes. These findings suggest that the neural circuitry underlying reward and motivated behavior is fundamentally perturbed in psychopathy, which in turn contributes to persistent antisocial behavior.

Disclosures: **J.G. Hosking:** None. **E. Kastman:** None. **H. Dorfman:** None. **A. Baskin-Sommers:** None. **K. Kiehl:** None. **J. Newman:** None. **J.W. Buckholtz:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.05

Topic: F.01. Human Cognition and Behavior

Support: NIDA022582

NICHD076097

NHLBI114092

NSF GRFP (DGE-1313911)

Title: Structural morphometry and connectivity in the human reward system predict obesity metrics

Authors: ***K. M. RAPUANO**[1], R. S. CHAVEZ[1], M. E. DECKER[1], D. GILBERT-DIAMOND[2], J. D. SARGENT[2], T. F. HEATHERTON[1], W. M. KELLEY[1];

[1]Psychological and Brain Sci. Dept., Dartmouth Col., Hanover, NH; [2]Norris Cotton Cancer Ctr., Dartmouth Hitchcock Med. Ctr., Lebanon, NH

Abstract: The human reward system functions to drive appetitive behaviors across domains. Prior work has implicated regions of the reward system_in particular, the nucleus accumbens (NAcc) and orbitofrontal cortex (OFC)_in processing appetizing food cues and motivating eating behavior. However, less is known about how the development of these structures may predispose individuals to become obese. Here, we consider the relationship between reward system structure and two known obesity predictors: percentage body fat and FTO genotype. High-resolution T1-weighted anatomical images and diffusion tensor imaging (DTI) scans were collected for a large cohort of subjects spanning childhood to young adulthood (ages 9-22). All participants were weighed on a clinical-grade Tanita body composition analyzer to determine percentage body fat. A subset of subjects (ages 9-12) was genotyped for the FTO SNP rs9939609. Using FreeSurfer, an automated segmentation tool, surface-based NAcc volume and OFC thickness estimates were extracted for each subject. These same regions were used as seeds to perform probabilistic tractography between the NAcc and OFC. For each subject, mean fractional anisotropy (FA) values were obtained within this tract to provide an estimate of white matter connectivity strength. Each of these structural measurements was used to predict an individual's percentage body fat or FTO genotype. Across all subjects, reward system structural metrics correlated with adiposity, including NAcc volume, OFC thickness, and white matter connectivity strength between these regions. Collectively, these measurements were able to predict adiposity in a novel set of subjects using leave-one-subject-out cross-validation and support vector regression. Separately, NAcc volume predicted the number of FTO obesity risk alleles independent of adiposity, such that children at a higher risk for obesity demonstrated greater NAcc volume. These results suggest that high-adiposity individuals exhibit structural differences in regions underlying reward system function, consistent with reports of altered task-based reward responsivity in individuals with obesity. Further, preliminary evidence suggests that children with a higher genetic risk for obesity may be predisposed to differentially represent reward signals, which may in turn lead to unhealthy eating behaviors.

Disclosures: K.M. Rapuano: None. **R.S. Chavez:** None. **M.E. Decker:** None. **D. Gilbert-Diamond:** None. **J.D. Sargent:** None. **T.F. Heatherton:** None. **W.M. Kelley:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.06

Topic: F.01. Human Cognition and Behavior

Support: Norwegian Research Council grant ES455867

Title: Sucrose preference in humans: effects of bidirectional opioid receptor manipulation and sweet liking phenotype

Authors: *M. EIKEMO[1,2,4], J. GJERSTAD[6], F. WILLOCH[3], S. LEKNES[5];
[2]Norwegian Ctr. for Addiction Res., [3]Inst. of Basic Med. Sci., [1]Univ. of Oslo, Oslo, Norway; [4]Div. of Mental Hlth. and Addiction, [5]Intervention Ctr., Oslo Univ. Hosp., Oslo, Norway; [6]The Natl. Inst. of Occup. Hlth. (STAMI), Oslo, Norway

Abstract: The μ-opioid receptor (MOR) system is central to 'liking' and 'wanting' of food in rodents. MOR blockade also decreases liking of high-sucrose and high-fat foods in humans. Sweet liking phenotype, an individual difference measure of sucrose preference, is higher in substance dependent populations and associated with addiction-related phenomena such as impulsivity, novelty seeking, binge eating, and excessive alcohol intake. Sweet liking phenotype has been proposed as a behavioral measure of OR system sensitivity in humans, yet how MOR drugs modulate sucrose preference is unclear. We hypothesised that MOR stimulation would increase, and MOR blockade decrease, relative preference for sucrose drinks, without affecting perceived sweetness intensity. In a double-blind, 3-way cross-over design, 49 healthy men received a MOR agonist (morphine 10 mg), OR antagonist (naltrexone 50 mg) and placebo before completing a standard sweet taste preference task In each session participants tasted 15 drinks of five sucrose levels in pseudorandomized order and rated perceived sweetness intensity and pleasantness. As hypothesized, a linear mixed model (LMM) showed no significant effects of either drug on sweetness intensity. An LMM of sweetness preference showed a significant interaction between drug and sucrose content ($F(2,114)=4.121$, $p <.001$). As expected, preference for high-sucrose drinks (slope across the five drink types) was significantly reduced by naltrexone compared to placebo. Morpine did not significantly increase slope, but planned comparisons revealed a significant morphine-induced increase in liking of the sweetest drink compared to placebo and naltrexone. We found no significant drug effects on sucrose preference between carriers of the A118G SNP of the OPRM1 gene coding for the MOR (AA=27, AG=22). Since our sample contained both participants who preferred the sweetest drinks ('sweet likers', n=23), and participants whose pleasantness ratings decreased with increased sweetness ('sweet dislikers', n=26), we were able to assess whether MOR manipulations would selectively affect pleasantness for sweet drinks that were perceived as pleasant. Analysis of phenotype*drug interactions indicated similar effects of MOR drugs on sweetness preference across 'sweet likers' and 'dislikers', consistent with a role for the MOR system in promotion of high-calorie food consumption rather than for hedonic eating. A neural system that promotes preference for sweet and fatty foods has clear evolutionary advantages. The mesolimbic MORs are a likely candidate system supporting high-calorie preference in humans.

Disclosures: **M. Eikemo:** None. **J. Gjerstad:** None. **F. Willoch:** None. **S. Leknes:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.07

Topic: F.01. Human Cognition and Behavior

Support: Research Council of Norway Grant ES455867

Title: μ-opioid effects on emotion recognition

Authors: ***G. E. LØSETH**[1], S. Ø. LIE[1], M. EIKEMO[2,4], B. LAENG[3], V. VINDENES[6], S. LEKNES[5];
[2]Norwegian Ctr. for Addiction Res. (SERAF), Fac. of Med., [3]Dept. of Psychology, [1]Univ. of Oslo, Oslo, Norway; [4]Div. of Mental Hlth. and Addiction, [5]Interventional Ctr., Oslo Univ. Hosp., Oslo, Norway; [6]Norwegian Inst. of Publ. Hlth., Oslo, Norway

Abstract: BACKGROUND: The endogenous μ-opioid receptor (MOR) system mediates positive responses to social rewards, and dampens pain and psychosocial stress. We have previously shown that the human MOR system promotes social motivation and gaze to the eye region of faces. Increased attention to the eyes enables more accurate assessment of social and emotional cues. We therefore hypothesised that morphine treatment would increase emotion recognition. A competing hypothesis is that MOR system activation with morphine would dampen responses to explicit negative expressions and promoting responses to positive ones. METHOD: We assessed evaluation of two facial expressions related to pro-social and aggressive behaviour in humans, happiness and anger, in a preliminary double-blind placebo-controlled cross-over study. So far, 11 healthy volunteers (4 female) received a MOR system agonist (morphine 10 mg) or placebo per-oral on separate sessions. As part of a larger task protocol, the participants viewed 200 images faces (20 males and 20 females) displaying explicitly angry, implicitly angry, neutral, implicitly happy and explicitly happy faces. Ratings of perceived anger and happiness were recorded for each image using visual analogue scales from 0 - 10, and were analysed in two generalized linear mixed regression models. Main factors were drug and facial expression. Control variables were session number, trial number and gender of participant and face stimulus. RESULTS: The morphine dose was chosen to activate mu-opioid receptors without causing sedation or euphoria. Indeed, t-tests revealed no significant differences between drug conditions on subjective reports of drug effect (M>P, p=.91), feeling high (M>P, p=.47), or feeling good (M>P, T.test p=.89). Preliminary analyses of perceived anger and happiness ratings

confirmed the expected stimulus category effects. Contrary to the main hypothesis, morphine did not enhance overall emotion recognition. Morphine significantly decreased overall ratings of perceived anger [$F(1,2169)=32$, $P<0.001$] but did not significantly affect happiness ratings. CONCLUSION: While the results from this preliminary study point to a dampening effect of morphine 10 mg on perception of anger, it is too early to make any conclusions as to the role of MOR system in processing of emotional facial expressions. Results from recent studies investigating effects of MOR system manipulations on face perception have been mixed. The current study will be expanded to a larger sample and to include measures of autism spectrum traits.

Disclosures: G.E. Løseth: None. **S.Ø. Lie:** None. **M. Eikemo:** None. **B. Laeng:** None. **V. Vindenes:** None. **S. Leknes:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.08

Topic: F.01. Human Cognition and Behavior

Title: Dopaminergic modulation of resting functional connectivity depends on individual differences in dopamine system function

Authors: *D. FURMAN, M. D'ESPOSITO;
Helen Wills Neurosci. Inst., Univ. of California - Berkeley, Berkeley, CA

Abstract: Despite a growing number of reports that dopamine impacts functional connectivity in brain imaging data, particularly within corticostriatal pathways, results of this work have been equivocal with respect to the nature and directionality of these effects. Variability in these results is likely related in part to the type of pharmacological agent used to perturb the dopaminergic system and the nature of the task performed during data acquisition. However, another important factor may be the composition of the study participants themselves. Previous research has indicated that the effect of dopamine intervention on working memory and attentional performance, task-evoked activation of the prefrontal cortex and striatum, as well as on the extent of correlated activity in corticostriatal pathways during task performance can vary substantially as a function of baseline dopamine synthesis or dopamine system genetics. Here, we test the hypothesis that dopamine intervention influences corticostriatal functional connectivity during rest in a way that is contingent on baseline dopamine system function and that conforms to an inverted-U-shaped function. Using a multisession, double-blind, crossover

design, participants underwent functional MRI scanning once each after administration of placebo and bromocriptine (1.25mg), a dopamine D2 receptor agonist. During each session, eyes-open resting BOLD data were collected with a Siemens 3T Trio scanner and a 12-channel head coil, and one of several echo planar imaging acquisition protocols. The sample was dichotomized according to score on a verbal listening span task (a measure of working memory capacity) previously found to correlate positively with striatal dopamine synthesis capacity. Relative to individuals with high listening span scores, low span participants exhibited greater corticostriatal resting functional connectivity spanning multiple regions of the striatum and cortex. Following administration of bromocriptine, corticostriatal connectivity was in general decreased in low span individuals, but increased in high span participants. This pattern of results is consistent with an inverted-U-shaped relationship between baseline dopamine levels and neurobiological phenotype. This finding suggests that care should be taken when interpreting brain imaging data following a dopaminergic intervention, as aggregating across samples that are heterogeneous or skewed with respect to dopamine system function might significantly bias the directionality of observed effects or mask them altogether.

Disclosures: **D. Furman:** None. **M. D'Esposito:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.09

Topic: F.01. Human Cognition and Behavior

Support: NIMH R01MH066079

NIDA R01DA031579

NIDA R01DA033369

Title: Associations between intrinsic neural activities and reactions to stressful events, narrative centrality, and negative affectivity

Authors: ***D. LI**[1], A. R. HARIRI[1], D. C. RUBIN[1,2];
[1]Duke Univ., Durham, NC; [2]Ctr. on Autobiographical Memory Res., Aarhus Univ., Aarhus, Denmark

Abstract: Reactions to stressful negative events as measured by tests of posttraumatic stress disorder (PTSD) symptom severity receive independent contributions from two factors: narrative

centrality and the personality of negative affectivity. Narrative centrality refers to the extent to which the narrative interpretation of a negative event is central to one's life; negative affectivity is a personality trait related to the tendency to suffer from negative feelings such as anxiety, anger, and depressed mood. Using resting-state functional magnetic resonance imaging, we investigated brain regions whose fractional amplitudes of low-frequency fluctuation (fALFF) associated with these three factors in a large sample (N = 599) of healthy college students. Reactions to stressful events were assessed using the Posttraumatic Stress Disorder Checklist (PCL), narrative centrality was assessed using the Centrality of Event Scale (CES), and negative affectivity was assessed using Neuroticism in the Revised NEO Personality Inventory (NEO PI-R). Reactions to stressful events were associated with fALFF in the medial frontal cortex and anterior cingulate cortex which are involved in appraisal and regulation of negative emotions. Narrative centrality was associated with fALFF in midline brain regions that are frequently reported to involve in self-referential processes. Negative affectivity was associated with fALFF in the anterior dorsal anterior cingulate cortex which is reported to be related to negative emotion processing and regulation. Interestingly, brain regions associated with narrative centrality and negative affectivity showed partial overlap with those associated with reactions to stressful events, which can clarify the neural basis of the contributions of narrative centrality and negative affectivity to reactions to stressful events. These results provide neural evidence for the relationship between these three factors, which is important for therapy developments for stress-related disorders such as PTSD.

Disclosures: **D. Li:** None. **A.R. Hariri:** None. **D.C. Rubin:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.10

Topic: F.01. Human Cognition and Behavior

Support: NIH F31 MH090672

NIH R01 MH080716

Title: The structural integrity of white matter fiber pathways between the amygdala and the lateral orbitofrontal cortex inversely predicts trait anxiety

Authors: *M. KIM, A. C. BROWN, A. M. MATTEK, S. N. JACOBS, J. M. TAYLOR, A. L. PALMER, P. J. WHALEN;
Psychological & Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Previous studies have shown that the degree of structural connectivity between the amygdala and the ventral prefrontal cortex - comprising multiple white matter fibers including the uncinate fasciculus - is inversely correlated with self-reported measures of trait anxiety. Here, we sought to replicate these findings in a larger study sample while adding a higher resolution imaging sequence. Our goal was to define any existing subdivisions within these amygdala-prefrontal pathways based on their terminal location within prefrontal cortex, and to investigate their relationship with trait anxiety. From two independent datasets - a 61-direction high angular resolution dataset of 77 diffusion-weighted images and a 32-direction dataset of 142 diffusion-weighted images - probabilistic tractography methods were applied to identify white matter fiber pathways that connected the amygdala with the ventromedial prefrontal cortex (vmPFC) and the lateral orbitofrontal cortex (lOFC). Each fiber pathway was defined using subject-specific amygdala masks, as well as vmPFC and lOFC masks. We used partial volume fractions (PVF), a fiber-specific measure analogous to fractional anisotropy that accounts for uncertainties associated with crossing fibers. Across the two datasets, trait anxiety showed a stronger inverse relationship with the average PVF of the amygdala-lOFC pathway than the amygdala-vmPFC pathway. Notably, this pattern was more prominent in the right hemisphere. Unexpectedly, this group effect was accounted for mostly by female participants. To summarize, we successfully replicated the inverse relationship previously observed between the structural integrity of an amygdala-prefrontal pathway and trait anxiety, in two independent datasets with a total of 219 diffusion-weighted images. The unexpected gender effect calls for more research on this subject. These data further support the framework that the capacity for crosstalk between the amygdala and the prefrontal cortex predicts beneficial outcomes in terms of anxiety.

Disclosures: **M. Kim:** None. **A.C. Brown:** None. **A.M. Mattek:** None. **S.N. Jacobs:** None. **J.M. Taylor:** None. **A.L. Palmer:** None. **P.J. Whalen:** None.

Nanosymposium

115. Individual Differences

Location: N226

Time: Sunday, October 18, 2015, 8:00 AM - 10:45 AM

Presentation Number: 115.11

Topic: F.01. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Numbers 23223003

Impulsing Paradigm Change through Disruptive Technologies Program (ImPACT) from the Cabinet of Japan

Title: Highly accurate predictions of intelligence and personality traits from brain structure

Authors: *R. KANAI[1], H. MIZUTANI[1], H. TAKAGISHI[2], T. YAMAGISHI[3];
[1]Dept. of Neuroinformatics, Araya Brain Imaging, Tokyo, Japan; [2]Brain Sci. Inst., Tamagawa Univ., Tokyo, Japan; [3]Grad. Sch. of Intl. Corporate Strategy, Hitotsubashi Univ., Tokyo, Japan

Abstract: The recent surge of interest in the relationship between brain structure and cognitive function has revealed numerous correlations between regional morphometric properties of the brain such as grey matter volume and cognitive traits such as cognitive abilities and personality traits (Kanai & Rees, 2011). While consistent results across multiple studies (e.g. Kanai, Dong, Bahrami & Rees, 2011; Sandberg et al., 2014; Kanai, 2015) suggest the presence of personal information in structural MRI data, it remains unknown to what extent such brain-behaviour correlations allow us to make predictions about an individual's traits. In the present study, we used a machine-learning approach to predict an individual's age, gender, intelligence, and big five personality traits from high-resolution T1 weighted MRI images (1mm isotropic). One of the challenges to construct a predictive model from MRI data is the dimensionality of features (i.e. the number of voxels), which is typically much higher than sample size (i.e. the number of participants). In our current study, we used a relatively large sample for a study of this sort (n=470), but there is still a 100-folds difference to the number of voxels corresponding to grey matter (i.e. ~450,000). To address this issue, we applied the regularization method called the elastic net, which has been shown to outperform other approach when the number of features is much larger than the number of samples (Zou & Hatie, 2005). Our results indicate that this approach can successfully construct highly accurate prediction models for age, gender, intelligence and all the five components in the Big Five Model of personality traits. This is in stark contrast with the conventional, univariate voxel-based morphometry (VBM) approach which shows only weak correlations between particular brain regions and traits. In summary, our study demonstrates the richness of the information we can extract from an individual's brain MRI scan, and suggests that possibility that we can create highly precise predictions models for intelligence and personality traits.

Disclosures: **R. Kanai:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Araya Brain Imaging. **H. Mizutani:** A. Employment/Salary (full or part-time); Araya Brain Imaging. **H. Takagishi:** None. **T. Yamagishi:** None.

Nanosymposium

193. Neuronal Lineage Reprogramming

Location: N426A

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 193.01

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS088095

NIH Grant NS070981

The Ellison Medical Foundation

The Welch Foundation

Texas Institute for Brain Injury and Repair

Title: *In vivo* reprogramming of reactive astrocytes to neural progenitors

Authors: *C.-L. ZHANG;
Mol. Biol., UT Southwestern Med. Ctr., Dallas, TX

Abstract: Injury to the central nervous system leads to irreversible neuron loss and the formation of a glial scar. This scar is initially beneficial for restricting secondary damage but ultimately inhibitory for neural regeneration. Strategies remodeling the scar-forming glial cells might enhance regeneration and promote functional recovery after neural damage. Through *in vivo* screens we recently showed that ectopic expression of SOX2 is sufficient to convert reactive astrocytes into neurons in the adult brain. Here we further demonstrate that a distinct cellular sequence is involved in SOX2-mediated *in vivo* reprogramming process. This includes ASCL1+ neural progenitors and DCX+ adult neuroblasts (iANBs) as intermediates. Importantly, ASCL1 is required but not sufficient for the robust generation of iANBs in the adult striatum. These progenitor-derived iANBs predominantly give rise to calretinin+ interneurons when supplied with neurotrophic factors or the small molecule valproic acid. Patch-clamp recordings from the induced neurons reveal subtype heterogeneity, though all are functionally mature, fire repetitive action potentials, and receive synaptic inputs. Together, these results show that SOX2-mediated *in vivo* reprogramming of astrocytes to neurons passes through proliferative intermediate progenitors, which may be exploited for regenerative medicine.

Disclosures: C. Zhang: None.

Nanosymposium

193. Neuronal Lineage Reprogramming

Location: N426A

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 193.02

Topic: A.01. Neurogenesis and Gliogenesis

Title: Direct *in vivo* glia-to-neuron conversion in the postnatal mouse cerebral cortex

Authors: *S. PERON[1,2], M. KAROW[1,3,2], B. BERNINGER[1,2];
[1]Inst. of Physiological Chem., Mainz, Germany; [2]Univ. Med. Center, Johannes Gutenberg Univ. Mainz, Focus Program Translational Neurosci., Mainz, Germany; [3]Biomed. Ctr., Ludwig Maximilian Univ. Munich, Munich, Germany

Abstract: Neuronal loss is common to numerous brain diseases or injuries and is often accompanied with irreversible dysfunctions. One strategy to overcome the limited regeneration capacity of the central nervous system relies on cell replacement based therapies. Among them, direct reprogramming without passing through a pluripotent state of resident brain cells into neurons has been proposed as a new innovative strategy and has gained significant momentum within the last few years. Previous studies from our lab have shown that forced expression of Ascl1 and Neurog2 can direct postnatal cortical astrocytes towards GABAergic and glutamatergic neurogenesis *in vitro* (Heinrich et al., 2010; Heinrich et al., 2011). In this study, we aim at testing whether glia can be lineage converted in the postnatal mouse cerebral cortex *in vivo*. Glial cells proliferate locally in the early postnatal cortex (Ge et al., 2012). To target these cells for lineage conversion we transduced proliferating glia with retroviruses encoding for various neurogenic transcription factors. We found that overexpression of the transcription factors Ascl1 and Neurog2 alone in the postnatal cortex *in vivo* hardly gives rise to doublecortin (DCX) expressing neuroblasts. This suggests that glial cells *in vivo* are less responsive and that additional obstacles may to be overcome to acquire a neuronal identity. Thus, we tested whether co-expression of Sox2 can facilitate reprogramming induced by Ascl1. Consistent with the previously observed synergism between Sox2 and Ascl1 on lineage reprogramming of adult cells (Karow et al., 2012; Heinrich et al., 2014), we found here that combined expression of these two transcription factors results in the lineage conversion of proliferative glia into DCX positive neuroblasts in the early postnatal cortex *in vivo*. Together, our work demonstrates for the first time the feasability of direct *in vivo* lineage reprogramming in the healthy cerebral cortex and emphazises the influence of the *in vivo* milieu on the susceptibility of glial cells to be directed towards a neuronal identity.

Disclosures: S. Peron: None. **M. Karow:** None. **B. Berninger:** None.

Nanosymposium

193. Neuronal Lineage Reprogramming

Location: N426A

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 193.03

Topic: A.01. Neurogenesis and Gliogenesis

Support: DFG grant:BE 4182/2-2

DFG grant: GO 640/9-2

BMBF grant:01GN1009A

BMBF grant: 01GN0976

ForNeuroCell

Title: Sox2-induced conversion of NG2 glia into neurons in the adult cerebral cortex following acute invasive injury

Authors: C. HEINRICH[1], M. BERGAMI[2], S. GASCÓN[2], F. VIGANÒ[2], *I. GUILLEMAIN[1], L. DIMOU[2], B. SUTOR[2], B. BERNINGER[3], M. GÖTZ[2];
[1]Grenoble- Inst. of Neurosciences, Grenoble, France; [2]Physiological Genomics, Inst. of Physiol., Munich, Germany; [3]Inst. of Physiological Chem., Mainz, Germany

Abstract: Conversion of non-neuronal cells into clinically relevant neurons emerges as a novel strategy to regenerate lost neurons for brain repair. We and others have explored the possibility of converting brain resident glia and non-neural cells into induced neurons (for review see Heinrich et al., 2015). This has led to the identification of astroglia and NG2 glia as well as pericytes as potential source cells for new neurons. Inducing the conversion of non-neuronal cells into neurons in the context of severe CNS injury remains a major challenge. Here we assessed whether glial cells proliferating during reactive gliosis can be reprogrammed in the adult mouse cerebral cortex following stab wound lesion. Forced expression of the potent reprogramming factors Neurog2 and Ascl1 failed in inducing neurogenesis. Based on our findings that co-expression of Sox2 and Ascl1 can reprogram adult human brain pericytes *in vitro* (Karow et al., 2012) we assessed the effect of combined expression of these factors within the lesioned brain. Retrovirus-mediated expression of Sox2 and Ascl1, but surprisingly also of Sox2 alone, could reprogram cells proliferating in response to stab wound injury. Intriguingly, the vast majority of the newly generated DCX-positive neurons originated from NG2 glia as revealed by genetic fate-mapping experiments. Sox2/Ascl1- and Sox2-induced neurons progressively acquire NeuN and a more complex neuronal morphology. Patch-clamp recordings showed that reprogrammed cells acquire the ability to generate action potentials and receive

synaptic inputs from neighboring neurons. Consistently, we found that endogenous interneurons formed synaptic boutons on induced neuron processes. We next assessed whether stab wound-induced changes are required for glia-to-neuron conversion. We performed injections of Sox2-encoding lentivirus specifically targeting glial cells, in absence of prior stab wound injury. Strikingly, despite its massive expression Sox2 failed to convert both oligodendroglial and astroglial cells into neurons, indicating that prior lesion facilitates or perhaps even preconditions Sox2-induced reprogramming. This raises the important question how prior injury alters the permissiveness of glial cells to undergo transcription-factor driven neurogenesis.

Disclosures: **C. Heinrich:** None. **M. Bergami:** None. **S. Gascón:** None. **F. Viganò:** None. **I. Guillemain:** None. **L. Dimou:** None. **B. Sutor:** None. **B. Berninger:** None. **M. Götz:** None.

Nanosymposium

193. Neuronal Lineage Reprogramming

Location: N426A

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 193.04

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH/NINDS R01NS088095

NIH/NINDS R01NS070981

The Welch Foundation I-1724-01

Title: The molecular mechanism of fibroblast-to-neuron reprogramming

Authors: *D. K. SMITH[1], C.-L. ZHANG[2];
[1]Dept. of Neurosci., [2]Dept. of Mol. Biol., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Transcription factor-mediated cell identity reprogramming has enabled the induction of functional neurons from terminally differentiated human fibroblasts. We have previously demonstrated that a single transcription factor (Neurogenin 2, NGN2) combined with two small molecules (forskolin, FSK and dorsomorphin, DM) can reprogram human fetal fibroblasts into functional cholinergic neurons with high efficiency 98±3% (doi:10.138/ncomms3138). To gain insight into the immediate-early mechanisms responsible for this fate respecification, we have focused on the synergistic actions of NGN2 and small molecules. An RNA-sequencing time course was performed to identify factor-dependent changes in transcription. The profiles of fibroblasts treated with NGN2 and small molecules independently and in combination were compared at three time points within the 48-hour period following treatment. In parallel, a ChIP-

sequencing time course was used to identify whether the binding dynamics of NGN2 change in the presence of FSK and DM. Interestingly, NGN2 binds more than 1,400 unique sites upon small molecules treatment and 46% of the genes upregulated during reprogramming are only induced in the presence of small molecules. The co-expression of NGN2 and the catalytic subunit of PKA, an enzyme activated though FSK-induced cAMP synthesis, is sufficient to generate neurons in the absence of FSK. Further, chromatin coimmunoprecipitation validated PKA-phosphorylated CREB1 as a co-binding partner of NGN2. NGN2-CREB1 co-binding at the *SOX4* locus upregulates *SOX4* expression within two days of treatment and short hairpin RNA-mediated knockdown indicates a critical role for SOX4 in the specification of neuronal fate. We are presently investigating the roles of SOX4 and other small molecules-induced factors that might have critical roles in the DNA binding activity of NGN2 through chromatin remodeling. Overall, this work aims to significantly advance the molecular understanding of the earliest stages of fibroblast-to-neuron reprogramming.

Disclosures: D.K. Smith: None. **C. Zhang:** None.

Nanosymposium

193. Neuronal Lineage Reprogramming

Location: N426A

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 193.05

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant AG20047

Rosalind Franklin-DePaul Alliance Pilot Award

Title: Neurogenin2-mediated direct *in vivo* reprogramming in adult rat cortex of cortical oligodendrocyte progenitor cells into cytoarchitecturally mature cortical neurons with subtype specification and synaptic contacts in the absence of injury

Authors: *D. A. PETERSON, S. BAZAREK, A. MHETA, R. PATEL, C. BRIGGS, S. CHAKROBORTY, E. REISENBIGLER, G. E. STUTZMANN, R. A. MARR;
Ctr. for Stem Cell & Regenerative Med., Rosalind Franklin Univ. Med. Sci., North Chicago, IL

Abstract: Reprogramming cell lineage using developmental transcription factors has recently emerged as a potential therapeutic strategy. Respecifying lineage of resident cells to a new fate in the context of their normal tissue environment may confer advantages for complete phenotypic maturation and function. In the brain, some success with phenotypic maturation of converted

non-neuronal cells has been reported, but, to date, only in the presence of an injury. The interplay of injury-response and inflammatory signals may alter phenotypic maturation in unpredictable ways. In this study, mature cortical neurons with subtype specification and synaptic contacts were generated from oligodendrocyte progenitor cells in two, distinct cortical regions by neurogenin2 (ngn2) expression in the absence of experimental lesion. Oligodendrocyte Progenitor Cells (OPCs) are the most abundant proliferating resident neural cell population in the adult CNS. Furthermore, there is evidence that OPCs maintain population homeostasis, suggesting the functional population of resident OPCs would not be depleted following lineage respecification to neurons. Adult rat cortical OPCs were isolated using magnetic activated cell sorting for O4 antigen selection and maintained as a primary culture for screening combinations of putative neurogenic transcription factors including neurogenin2 (ngn2), ascl1, dlx2, sox2, neuroD1, pax6, and VP16Olig2. Beta-III-tubulin-expressing cells were observed by 10 days post transduction (dpt) of OPCs with retroviral supernatants of ngn2, ascl1, ascl1/dlx2, or neuroD1, with ngn2 exhibiting the most robust response. Ngn2-transduced cells co-cultured with postnatal primary neurons expressed synaptophysin and displayed repetitive action potentials and spontaneous activity. As ngn2 also drove very high levels of neuroD1 expression, we delivered retroviral ngn2-GFP to adult rat motor cortex and entorhinal cortex. Delivery of vectors for GFP alone and an unsuccessful factor, pax6, validated that only proliferating OPCs had been transduced. By one week, cells transduced with ngn2 expressed DCX, weak NeuN, and displayed an elaborate, but still immature neuronal morphology. By three weeks, ngn2-converted cells displayed robust NeuN expression and subtype specification to glutamatergic neurons indicated by Tbr1 and CamKII staining. These newly-generated neurons displayed elaborate cytoarchitecture appropriate for their cortical location with abundant, but immature, dendritic spines with frequent synaptophysin-positive contacts.

Disclosures: **D.A. Peterson:** None. **S. Bazarek:** None. **A. Mheta:** None. **R. Patel:** None. **C. Briggs:** None. **S. Chakroborty:** None. **E. Reisenbigler:** None. **G.E. Stutzmann:** None. **R.A. Marr:** None.

Nanosymposium

193. Neuronal Lineage Reprogramming

Location: N426A

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 193.06

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS072631

NIH Grant NS075733

Title: *In vivo* reprogramming reactive glia into iPSCs to produce new neurons in the cortex following traumatic brain injury

Authors: *J. CHEN, X. GAO;
Indiana Univ., Indianapolis, IN

Abstract: Traumatic brain injury (TBI) results in a significant amount of cell death in the brain. Unfortunately, the adult mammalian brain possesses little regenerative potential following injury and little can be done to reverse the initial brain damage caused by trauma. There is a large number of reactive glia surrounding the injury area following TBI. Reprogramming adult cells to generate induced pluripotent stem cell (iPSCs) has opened new therapeutic opportunities to reprogram these reactive glia to neural fate for possible cell-replacement therapy *in vivo*. In this study we show that four retroviral mediated transcription factors, Oct4, Sox2, Klf4 and c-Myc, expressed in the reactive glial cells and cooperatively reprogrammed infected glia into iPSCs in the adult neocortex following TBI. These iPSCs further differentiated into a large number of neural stem cells, which further differentiated into neurons and glia *in situ*, and filled up the tissue cavity induced by TBI. The induced neurons showed a typical neuronal morphology with axon and dendrites, and exhibited action potential. The glia were preferentially astrocytes and oligodendrocytes, but not microglia. Our results report an innovative technology to transform reactive glia into a large number of functional neurons in their natural environment of neocortex without embryo involvement and without the need to grow cells outside the body and then graft them back to the brain. Thus this technology offers hope for personalized regenerative cell therapies for repairing damaged brain.

Disclosures: J. Chen: None. **X. Gao:** None.

Nanosymposium

193. Neuronal Lineage Reprogramming

Location: N426A

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 193.07

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R01 AG045656

NIH R01 MH083911

Title: Rebuilding mouse cortex after ischemic stroke by *in situ* reprogramming reactive astrocytes into functional neurons

Authors: *Y. CHEN[1], G. CHEN[2];
[1]Biol., [2]The Pennsylvania State Univ., State College, PA

Abstract: Keywords: reprogramming, NeuroD1, ischemic stroke. Our recent studies have demonstrated that overexpression of single transcription factor NeuroD1 enables direct reprogramming of reactive astrocytes into functional neurons, which can successfully integrate into the local neural circuits in adult mouse cortex (Guo et al., 2014, Cell Stem Cell). Our *in vivo* cell conversion technology makes it possible to develop a novel regenerative therapy to treat brain injury and neurodegenerative disorders, especially those with severe loss of neurons. Brain ischemic stroke is a major cause of death and disability, and there is no effective therapy currently available to restore neuronal loss or recover tissue damage after cerebral ischemia. After stroke, the injury core area is occupied with reactive astrocytes, which is a major obstacle for neuron functional recovery. Here we report an innovative approach to reprogram reactive astrocytes directly into functional neurons after stroke in order to restore the lost neuronal functions. We employed a mouse focal ischemic stroke model by injecting endothelin-1 into mouse cortex to cause blood vessel constriction and brain damage. After stroke, we regenerated functional neurons by infecting astrocytes with adeno-associated virus (AAV) expressing NeuroD1. Electrophysiological analysis demonstrated that the NeuroD1-converted neurons were functional in forming synaptic connections with other neurons. CTB retrograde tracing showed that the NeuroD1-converted neurons could project to long-range target regions. Intriguingly, we found great beneficial effects brought by NeuroD1-mediated glia-to-neuron conversion in the stroke area: (1) the cortical atrophy was significantly reversed, (2) loss of neuronal marker NeuN was greatly reduced, (3) the glial scar formation by reactive astrocytes and microglia was also significantly reduced. Taken together, our studies suggest that direct reprogramming of reactive astrocytes into functional neurons will provide a potential therapy for brain repair after stroke.
This project was supported by National Institutes of Health and Penn State University Endowment Fund.

Disclosures: **Y. Chen:** A. Employment/Salary (full or part-time); The Pennsylvania State University. **G. Chen:** None.

Nanosymposium

193. Neuronal Lineage Reprogramming

Location: N426A

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 193.08

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF DGE-1143954

NIH DP2

Edward J. Mallinckrodt Jr. Foundation

Ellison Medical Foundation

Presidential Early Career Award for Scientists and Engineers

Title: Modeling Huntington's disease with striatal neurons directly converted from patient fibroblasts

Authors: *M. B. VICTOR, M. RICHNER, A. S. YOO;
Developmental Biol., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Huntington's disease (HD) is an inherited neurodegenerative disorder characterized by the midlife onset of abnormal involuntary movements and cognitive decline. HD is caused by an inherited mutation in the Huntingtin (HTT) gene harboring an excessive expansion of CAG codons leading to elongated polyglutamine (polyQ) repeats. The mutant polyQ HTT can misfold and form aggregates in the brain, eventually leading to the degeneration of striatal spiny projection neurons, also known as medium spiny neurons (MSNs), a class of inhibitory projection neurons that comprise 95% of the striatum and control movement initiation. However, the cell type-specific features that differentially renders this neuronal subpopulation more susceptible to cell death in HD is still largely unknown. Recently, the ability to reprogram human skin fibroblasts into neurons has prompted development of protocols to generate specific neuronal subpopulations and model neurodegenerative disorders *in vitro*. We have recently developed a novel approach to directly convert human fibroblasts specifically into MSNs with high efficiency by expressing neurogenic microRNAs (miRNAs), miR-9/9* and miR-124 (miR-9/9*-124) with striatum-enriched transcription factors (CITP2, DLX1, DLX2 and MYT1L (CDM)) ectopically in human adult fibroblasts. Nonetheless, the applicability of this approach to reprogram fibroblasts from HD patients to generate MSNs and to model HD in tissue culture remains to be examined. In our current study we demonstrate the capability of miR-9/9*-124 + CDM to robustly reprogram fibroblasts from multiple HD patients of various ages and lengths of polyQ tract expansion. Furthermore, we show that HD-derived MSNs forms mutant HTT inclusion bodies, and display increased susceptibility to cell death in tissue culture. We believe this patient-specific neuronal subtype reprogramming may prove to be a useful approach for modeling Huntington's disease and identifying novel genes involved in HD pathogenesis.

Disclosures: **M.B. Victor:** None. **M. Richner:** None. **A.S. Yoo:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.01

Topic: B.08. Synaptic Plasticity

Support: 1F32MH101954-01

Title: Spatiotemporal activity of PKC isozymes during single spine structural plasticity

Authors: *L. A. COLGAN, M. HU, P. PARRA BUENO, R. YASUDA;
Max Planck Florida Inst., Jupiter, FL

Abstract: Synaptic plasticity is mediated by complex signaling cascades that transduce short-lived synaptic inputs into long-lasting changes of synaptic strength. The protein kinase C (PKC) family, consisting of more than 10 isozymes, has been shown to be involved in the induction, expression and maintenance of synaptic plasticity. However, technical limitations including poor isozyme discrimination, spatiotemporal resolution and sensitivity, impede our understanding of PKC function in plasticity. Here, we have developed highly-sensitive fluorescence-based sensors for PKC isozymes based on fluorescence resonance energy transfer (FRET) and 2-photon fluorescence lifetime imaging (2p-FLIM). These sensors report isozyme-specific PKC activity with high spatial and temporal resolution during structural plasticity of single spines. Through this approach, we have revealed the unique activity profiles of individual PKC isozymes during plasticity. These findings, together with molecular, genetic and behavioral approaches, clarify the role of PKC isozymes in the signaling cascades underlying plasticity, long term potentiation and learning and memory.

Disclosures: L.A. Colgan: None. **M. Hu:** None. **P. Parra Bueno:** None. **R. Yasuda:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.02

Topic: B.08. Synaptic Plasticity

Title: Heterogeneity of intracellular pH in dendritic spines; potential impact on synaptic signalling and plasticity

Authors: *T. J. JINADASA, T. WIESNER, P. DE KONINCK;
Biophotonics, Laval Univ., Quebec City, QC, Canada

Abstract: Neuronal plasticity is believed to involve activity-dependent changes of proteins at the synapse. Calcium entry and downstream signalling are critical for the induction of plasticity yet other ions such as protons, transiently increase and have the potential to modify the structure and function of the synapse. It has previously been proposed that microdomains of pH fluctuation, induced by membrane depolarization and calcium entry, could influence neuronal function. At the synapse, voltage gated channels as well as CaMKII, which is critically involved in spine potentiation, are known to be pH sensitive. Furthermore, pH has long been known to influence intracellular trafficking and signalling such as the Erk signalling pathway. The influences protons have on synapses have been principally examined extracellularly, while less attention has been given to proton fluctuations intracellularly. We are testing the hypothesis that changes in intracellular pH modulate plasticity, by combining optical imaging of pH and Ca2+ fluctuations simultaneously in cultured rat hippocampal neurons. With the use of a genetically-encoded ratiometric pH indicator (pHred), we have estimated the intracellular pH in various compartments of the neurons. Surprisingly, spines demonstrate a significantly more alkaline environment compared to dendrites. To further validate this observation, we repeated these measurements with a different fluorescent pH reporter (pHluroin2). We also used another method to quantify the pH, fluorescence lifetime imaging, since the fluorescence lifetime of pHred is also sensitive to pH. These experiments confirmed that several spines exhibit higher pH than their parent dendrite. This heterogeneity between spines might contribute to differential modulation of synaptic proteins. We are interested in understanding the impact of this heterogeneity in spine pH on synaptic plasticity. We have observed that chemical stimulation used to induce long-term potentiation in cultured hippocampal neurons (cLTP) results in an acidification of the soma, dendrites and spines. In our experiments recovery from this acidification is primarily dependent on sodium transport but is also influenced by bicarbonate-dependant transport. In order to determine how pH fluctuation in spines can influence synaptic function we are combining optical, genetic and pharmacological approaches. We found that disruption of the acidification associated with synaptic stimulation results in a reduction of CaMKII clustering. These data suggest a regulatory role for protons on synaptic signalling and remodelling in dendritic spines.

Disclosures: T.J. Jinadasa: None. **T. Wiesner:** None. **P. De Koninck:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.03

Topic: B.08. Synaptic Plasticity

Support: R01 MH081935

T32 NS007439

Title: Post-synaptic calcium dynamics associated with burst-timing dependent plasticity in the hippocampal CA3 area

Authors: *K. ALVINA[1], S. LUTZU[2], P. E. CASTILLO[2];
[1]Neurosci., Albert Einstein Col. of Med., Bronx, NY; [2]Neurosci., Albert Einstein Col. Medici, Bronx, NY

Abstract: In the hippocampus, the dentate granule cell axons (mossy fibers, mf) provide strong synaptic drive onto CA3 pyramidal neurons. The mf-CA3 synapse is formed by large complex mf terminals synapsing onto thorny excrescences (TEs), specialized postsynaptic structures located exclusively in proximal dendrites of CA3 pyramidal neurons. These neurons also receive ipsi- and contralateral inputs from other CA3 pyramidal cells forming associational/commissural (A/C) synapses. Unlike mf-CA3 inputs however, A/C inputs synapse onto regular dendritic spines (non-TEs) located on distal dendrites. Mf-CA3 synapses are well known for expressing presynaptic forms of long-term plasticity (LTP and LTD), uniquely robust short-term plasticity, and for their ability to fire the postsynaptic CA3 neuron upon repetitive activity. More recently, our group reported that mf-CA3 can also undergo postsynaptically-expressed forms of LTP and LTD of NMDA receptor (NMDAR)-mediated transmission, whose induction requires postsynaptic Ca2+ rise, and NMDAR and group I mGluR co-activation. However, the exact contribution of these receptors to intracellular Ca2+ dynamics associated with postsynaptic plasticity is not well understood. Here we combined electrophysiology with 2-photon Ca2+ imaging in order to determine the intracellular Ca2+ dynamics associated with mf and A/C basal transmission, and also with burst timing-dependent plasticity protocols known to trigger NMDAR-LTP/LTD at mf-CA3 synapses (Hunt et al. 2013). In acute rat hippocampal slices, pyramidal CA3 cells were whole-cell patch-clamped and loaded with fluorescent Ca2+ indicator Fluo-5F. Ca2+ transients (CaTs) were measured across TEs or regular spines after electrical stimulation of either mf or A/C inputs, respectively. We found that CaTs measured at TEs showed a greater degree of compartmentalization compared to regular spines located in distal dendrites. Furthermore, paired activity that triggers NMDAR-LTP was associated with significantly larger CaTs in TEs than patterns of activity that trigger NMDAR-LTD. This observation supports the notion that Ca2+ dynamics in TEs during paired activity determines the

direction of NMDAR plasticity (e.g. LTP/LTD). Ongoing experiments are focused on determining the different Ca2+ sources involved in the induction of NMDAR plasticity and the role of neuromodulatory pathways known to affect NMDAR Ca2+ permeability.

Disclosures: K. Alvina: None. **S. Lutzu:** None. **P.E. Castillo:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.04

Topic: B.08. Synaptic Plasticity

Title: Direct and indirect CaMKII-mediated activation of LIMK1 in hippocampal synaptic plasticity at glutamatergic synapses

Authors: *C. RIPOLI[1], T. SANEYOSHI[2], S. FUSCO[1], C. GRASSI[1], Y. HAYASHI[2,3]; [1]Inst. of Human Physiol., Univ. Cattolica Sch. of Med., Rome, Italy; [2]RIKEN Brain Sci. Inst., Wako, Saitama, Japan; [3]Saitama Univ. Brain Sci. Inst., Saitama, Japan, Japan

Abstract: The family of LIM serine/threonine kinases (LIMK) includes two highly related members: LIMK1 and LIMK2. LIM kinases regulate the architecture of actin cytoskeleton by phosphorylation and inactivation of the actin depolymerization factors cofilin, thereby participating in numerous biological processes of different cell types. LIMK1 is particularly important for axonal outgrowth and structural synaptic plasticity. NMDA receptor-mediated Ca2+ influx has been shown to induce CaMKII-mediated activation of Rho-associated protein kinase (ROCK) and p21-activated kinases (PAK), which trigger T508 phosphorylation of LIMK1 in its catalytic domain. Here we report that, during LTP, LIMK1 is directly and persistently activated by CaMKII independently of ROCK and PAK in dendritic spines. In hippocampal slice cultures, two-photon FRET-fluorescence lifetime imaging microscopy (FLIM) imaging experiments showed that LIMK1 persistently associates with CaMKII in single dendritic spines of CA1 pyramidal neurons after LTP induction by glutamate uncaging. This interaction is indicative of persistent phosphorylation of LIMK1 by CaMKII. Furthermore, CaMKII-mediated LIMK1 phosphorylation induced a significant increase in LIMK1-LIMK1 dimerization as revealed by FRET between LIMK1 monomers and immunoprecipitation experiments. *In vitro*, CaMKII specifically phosphorylates LIMK1 in 6 novel phosphorylation sites, i.e., S179, S216, S298, T556, S637 and S638, in addition to canonical T508. Among these 7 CaMKII-mediated phosphorylation sites of LIMK1, S216 was identified as a critical determinant of LIMK1 dimerization. Collectively, our findings provide novel evidence of a

direct functional interaction between CaMKII and LIMK1 in single dendritic spines. Therefore, CaMKII-mediated LIMK1 phosphorylation could be a key signaling component in the regulation of glutamatergic synaptic plasticity.

Disclosures: **C. Ripoli:** None. **T. Saneyoshi:** None. **S. Fusco:** None. **C. Grassi:** None. **Y. Hayashi:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.05

Topic: B.08. Synaptic Plasticity

Support: CIHR Grant MOP12046

NSERC CGS-Masters

FQRNT Masters Scholarship

CIHR CGS-Doctoral

FRSQ Doctoral Scholarship

Title: Calpain-mediated formation of protein kinase M during synaptic plasticity in *Aplysia*

Authors: ***M. H. HASTINGS**[1], C. ABI FARAH[2], T. W. DUNN[2], A. FREIBAUER[2], K. GONG[2], X. FAN[2], J. K. BOUGIE[2], D. BAKER-ANDRESEN[2], W. S. SOSSIN[3]; [1]Psychology, McGill University/Montreal Neurolog. Inst., Montreal, QC, Canada; [3]Neurol. and Neurosurg., [2]McGill Univ., Montreal, QC, Canada

Abstract: Ongoing activity of PKMs, persistently active truncated forms of PKC, has been proposed as a mechanism for memory maintenance. Yet the requirement for PKMs in memory is controversial, highlighting a need for clearer understanding. The sensory-motor neuron synapse of the mollusc Aplysia californica is an excellent reductionist model system for studying the molecular underpinnings of the synaptic changes that mediate memory. In Aplysia, calpain inhibitors block the formation of PKMs important for synaptic plasticity, but it is neither clear which isoforms of calpain are important for cleaving PKCs into PKMs, nor which PKCs are cleaved. We cloned the Aplysia Classical, SOL and PalB calpains, which we found to be expressed both in the presynaptic sensory neurons and postsynaptic motor neurons. We

overexpressed dominant negative forms of these calpains along with FRET-based PKC cleavage reporter constructs in either the pre- or postsynaptic neuron and observed the effect on plasticity and PKM formation in several synaptic plasticity paradigms. Our results implicate different PKMs in different forms of synaptic plasticity and suggest that different calpains may mediate formation of PKM under different circumstances. In particular, classical calpain cleaves PKC Apl I in the presynaptic sensory neuron and this is important for activity-dependent facilitation, while the classical calpain cleaves PKC Apl III in the post-synaptic motor neuron and this is important for massed intermediate facilitation. In contrast, the Sol calpain cleaves PKC Apl III when it is overexpressed in a model for the positive feedback mechanism important for PKM maintenance. These findings suggest roles for distinct calpains and distinct PKMs in maintaining synaptic strength.

Disclosures: **M.H. Hastings:** None. **C. Abi Farah:** None. **T.W. Dunn:** None. **A. Freibauer:** None. **K. Gong:** None. **X. Fan:** None. **J.K. Bougie:** None. **D. Baker-Andresen:** None. **W.S. Sossin:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.06

Topic: B.08. Synaptic Plasticity

Support: Moti-Vate Program, University Medical Centre Freiburg (T.H.)

DFG Grant BA 1582/2-1 (M.B.)

DFG Project FOR2143 (M.B., A.K.)

DFG Project BIOSS-2 A6 (A.K.)

DFG Project Brain-Links-Brain-Tools, Cluster of Excellence EXC 1086 (M.B.)

Volkswagen Foundation (M.B.)

Schram Foundation (M.B.)

Title: Molecular mechanism of long-term plasticity at synapses between dentate gyrus granule cells and fast-spiking interneurons

Authors: *T. HAINMÜLLER[1], A. KULIK[2], M. BARTOS[1];
[1]Univ. of Freiburg, Freiburg I. Br., Germany; [2]Inst. of Physiol. II, University of Freiburg, Germany

Abstract: Assemblies of hippocampal neurons provide the brain with an internal representation of space, a basis for the formation of memory episodes. Fast-spiking, parvalbumin (PV) expressing, perisomatic inhibitory interneurons (PIIs) support the formation of these content-bearing neuronal groups in the hippocampal CA3 area by suppressing competing cell assemblies. This function critically relies on long-term plasticity of mossy-fibre synapses, by which dentate gyrus (DG) granule cells (GCs) are connected with PV expressing interneurons (Ruediger et al., Nature, 2011). Synapases between GCs and PIIs in the DG can undergo a Hebbian form of long-term potentiation (LTP) or anti-Hebbian long-term depression (LTD; Alle et al., PNAS, 2001). The molecular mechanisms underlying synaptic plasticity at Mossy-fibre synapses onto PIIs, however, remain largely unknown. Using paired patch-clamp recordings between GCs and PIIs in acute brain slices of the rat DG, we show that blockade of group I metabotropic glutamate receptors (mGluRs), mGlur1a and mGluR5 abolishes LTP induction at GC-PII synapses. LTP is also abolished, when mGluR-evoked G-Protein signaling in PIIs is blocked. In contrast, exogenous activation of group I mGluRs disrupts the induction of LTD at the same synapse. Immunofluorescence and –electron microscopical investigation furthermore revealed, that mGluR1a as well as mGluR5 are located in the immediate vicinity of GC to PII synapses and are therefore likely to be activated by glutamate spill-over during high-frequent synaptic activity. Furthermore, our data indicate that group I mGluR signaling in PIIs depends on PII action potentials, which is likely to be caused by a voltage-dependent activation of mGluRs (Ohana et al., J. Biol. Chem., 2006). Previous studies revealed, that GC-PII LTP requires postsynaptic Ca^{2+} signals (Alle et al., PNAS, 2001). Using 2-Photon excitation Ca^{2+} imaging, we show that the main source of Ca^{2+} influx at GC-PII synapses arises from Ca^{2+} permeable AMPA receptors (CP-AMPARs) and no LTP can be evoked after CP-AMPAR blockade. Finally, our data indicate that Ca^{2+} from CP-AMPARs and G-Protein signals mediated by group I mGluRs converge in the postsynaptic PII in order to activate protein kinase C, which then drives LTP expression. An increased coupling of GCs to PIIs *via* LTP may be an important factor that helps to synchronize the DG network in fast gamma-oscillations (Bartos et al., Nature Reviews Neuroscience, 2007) and shape the extent of memory-encoding neuronal assemblies (Ruediger et al., Nature, 2011), thereby increasing the precision and stability of hippocampal memory representations.

Disclosures: T. Hainmüller: None. **A. Kulik:** None. **M. Bartos:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.07

Topic: B.08. Synaptic Plasticity

Support: Air Force Office of Scientific Research (DOD)

Title: Electrical stimulation accelerates the rate and capacity of synaptic learning

Authors: ***A. RAHMAN**[1], M. BIKSON[2];
[1]Biomed. Engin., The City Col. of The City Univ. of New York, New York, NY; [2]The City Col. of the City Univ. of New York, New York City, NY

Abstract: Transcranial electrical stimulation (tES) is a non-invasive brain stimulation technique that may improve motor learning, memory formation, and accelerate learning in humans. While, it is widely speculated that tES boosts synaptic plasticity little cellular evidence exists to suggest the rate of learning can be accelerated. Our results *in vitro* demonstrated that electrical stimulation increases both the rate and capacity of synaptic strengthening during ongoing synaptic plasticity. Direct current and alternating current stimulation (DCS and ACS) applied during theta-burst stimulation (TBS) produced long-term potentiation (LTP) and accelerated the rate of synaptic strengthening towards the maximum synaptic strength, here considered as a model of task-specific training in humans. Synaptic strengthening, however, is finite within a modification range. Electrical stimulation in hippocampal brain slices increased the ceiling for LTP enabling an increase in the capacity to learn on a cellular level. We reveal the underlying mechanism as input-specific voltage-dependent late-phase LTP. Furthermore, electrical stimulation is functionally-specific by selectively modulating ongoing synaptic plasticity in active pathways. In summary, ongoing synaptic plasticity with TBS in brain slices, which emulates training induced plasticity in humans, is modulated by electrical stimulation. Transcranial direct current stimulation (tDCS) may accelerate the rate of learning and increase the range/capacity of learning in humans when matched with a training task.

Disclosures: **A. Rahman:** None. **M. Bikson:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.08

Topic: B.08. Synaptic Plasticity

Support: SFB 779/B6

CBBS FKZ1211080005

Title: Theta burst firing recruits BDNF release and signaling in postsynaptic CA1 neurons in spike timing-dependent LTP

Authors: *E. EDELMANN[1], E. CEPEDA-PRADO[1], M. FRANCK[1], P. LICHTENECKER[1], T. BRIGADSKI[1,2], V. LESSMANN[1,2];
[1]Otto-von-Guericke Univ., Magdeburg, Germany; [2]Ctr. for Behavioral Brain Sci., Magdeburg, Germany

Abstract: Timing-dependent LTP (t-LTP) is a physiologically relevant type of synaptic plasticity that results from repeated sequential firing of action potentials (APs) in pre- and postsynaptic neurons. t-LTP can be observed *in vivo* and is proposed to be a cellular correlate of memory formation. While brain-derived neurotrophic factor (BDNF) is essential to high frequency stimulation induced LTP in many brain areas, the role of endogenous BDNF in t-LTP is largely unknown. Here, we demonstrate a striking change in the expression and signaling mechanism of t-LTP in CA1 of the hippocampus following two distinct modes of synaptic activation. Using patch clamp techniques, we investigated t-LTP in CA3-CA1 synapses in acute hippocampal slices of rats and mice. Single postsynaptic action potentials (APs) paired with presynaptic stimulation (1EPSP/1AP) activated a BDNF-independent canonical t-LTP, which is expressed most likely presynaptic. In contrast, a theta burst of postsynaptic APs preceded by presynaptic stimulation (1EPSP/4AP) elicited BDNF-dependent postsynaptic t-LTP that relied on postsynaptic BDNF secretion and AMPA receptor incorporation. The latter protocol is furthermore activated by postsynaptic BDNF/TrkB signaling. Both protocols can be induced subsequently and without obvious occlusion. Using live-cell imaging of BDNF-GFP expressing hippocampal neurons, we observed a comparable activity-dependent dendritic release of BDNF by repetitive firing of backpropagating APs . In ongoing experiments, we now focus on further differences between those two forms of t-LTP. Preliminary data show differences in intrinsic plasticity following successful t-LTP induction and different homo- or heterosynaptic forms of LTP, which suggest that the different induction protocols recruit not only different types of signaling and expression mechanisms, but also activate different homeostatic processes. Taken together our data show that similarly effective t-LTP can be induced with various patterns of STDP protocols at hippocampal CA3-CA1 synapses. However, these t-LTP forms are mediated by activation of distinct BDNF/TrkB-dependent or -independent signaling cascades. Hence, our data suggest the existence of multiple and distinct types of synaptic plasticity which can be expressed at the same synapse and that might contribute to memory formation in the hippocampus.

Disclosures: **E. Edelmann:** None. **E. Cepeda-Prado:** None. **M. Franck:** None. **P. Lichtenecker:** None. **T. Brigadski:** None. **V. Lessmann:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.09

Topic: B.08. Synaptic Plasticity

Support: NIH Grant MH609197

NIH Grant T32NS007101

NIH Grant T32GM065823

Title: Differences in theta-pulse stimulation induced LTP between dorsal and ventral hippocampus may rely on network properties

Authors: *W. E. BABIEC[1], S. A. JAMI[2], R. GUGLIETTA[3], T. J. O'DELL[4];
[1]Physiol., [2]Molecular, Cellular, and Integrative Physiol. Ph.D. Program, [3]Interdepartmental Ph.D. Program for Neurosci., [4]Dept. of Physiology, David Geffen Sch. of Med., UCLA, Los Angeles, CA

Abstract: Behavioral and anatomical studies support a functional segmentation between dorsal (dHC) and ventral hippocampus (vHC). dHC performs primarily cognitive functions. vHC is involved with stress, emotion, and affect. Interestingly, perhaps supporting this functional differentiation, Schaffer collateral (SC) synapses onto pyramidal cells (PCs) in the CA1 region of dHC and vHC exhibit differences in long-term plasticity (LTP), as determined using 100Hz stimulation protocols. To determine whether disparities in LTP exist for more naturalistic stimulation protocols, we subjected SC-CA1 synapses in acute HC mouse slices to theta pulse stimulation (TPS). Delivering 150 individual pulses to the SC at 5 Hz induces TPS-LTP. While the fEPSP slope of dHC SC-CA1 synapses potentiated by ~50%, similar synapses in vHC exhibited virtually no LTP. Investigation of field responses during TPS revealed marked differences. Frequency facilitation of the fEPSP, characteristic of dHC responses from the first third of the TPS protocol, and subsequent depression of the dHC fEPSP, during the last third of this protocol, were not evident in vHC synapses subjected to TPS. In addition, complex action potential (AP) bursting in vHC field responses was absent, which was confirmed with whole cell recordings. AP bursting, essential for TPS-LTP induction, is a hallmark response to TPS in dHC. Measures of PC excitability, including input resistance, resting membrane potential, and firing frequency did not show differences that might explain this lack of bursting. Nor did AP measures including rheobase, after-depolarization, and AP height. Also, investigations of synaptic properties, including AMPA/NMDA ratio, E-S coupling, and EPSC-to-EPSP coupling provided

no explanation for the observed differences in bursting. Tellingly, however, strong whole cell pairing-induced LTP protocols showed robust potentiation in SC-CA1 synapses from vHC, as well as dHC, arguing against insufficiency of vHC synapses to undergo LTP. In addition, whole cell recordings during TPS showed that, despite starting TPS at the same resting membrane potential, dHC PCs depolarized ~5 mV relative to vHC PCs during TPS, suggesting that an activity-dependent increase in $[K^+]_o$ might occur and be necessary for TPS-LTP induction. When $[K^+]_o$ was lowered at dHC synapses, TPS-induced AP bursting and LTP were prevented. At vHC SC-CA1 synapses, raising $[K^+]_o$ during TPS, by blocking astrocytic K^+-buffering with $BaCl_2$, resulted in TPS-LTP. Together, these data suggest that differences in network, rather than neuronal, properties is responsible for differences in TPS-LTP induction between dHC and vHC.

Disclosures: **W.E. Babiec:** None. **S.A. Jami:** None. **R. Guglietta:** None. **T.J. O'Dell:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.10

Topic: B.08. Synaptic Plasticity

Support: NIH Grant 1F31 NS086174

NIH Grant 5R01 NS37112

NIH Grant 1R21NS074975

NIEHS/NIH Intramural Program Z01-ES-100221

Title: Regulator of G protein signaling 14 (RGS14) interactions with CaM/CaMKII: new insights into synaptic plasticity restriction in hippocampal area CA2

Authors: *P. R. EVANS[1], N. T. SEYFRIED[2], P. R. GRIFFIN[3], M. ZHAO[4], S. M. DUDEK[4], J. R. HEPLER[1];
[1]Pharmacol., [2]Biochem., Emory Univ., Atlanta, GA; [3]Mol. Therapeut., The Scripps Res. Inst., Jupiter, FL; [4]Neurobio. Lab., Natl. Inst. of Envrn. Hlth. Sci., Research Triangle Park, NC

Abstract: Pyramidal neurons in hippocampal area CA2 differ dramatically from neighboring CA3/CA1 pyramidal neurons in that synaptic long-term potentiation (LTP) is not as readily induced. We previously identified Regulator of G Protein Signaling 14 (RGS14) as a critical brake on CA2 synaptic plasticity and learning and memory. RGS14 knockout (RGS14-KO) mice

display a robust and nascent capacity for LTP in CA2 pyramidal neurons, which is absent in wild-type (WT) mice, and exhibit enhanced hippocampus-dependent learning and memory. However, the cellular mechanism(s) by which RGS14 suppresses LTP in CA2 remain unknown. The lack of plasticity in CA2 has been attributed to robust calcium (Ca^{2+}) buffering and extrusion mechanisms relative to CA3/CA1, but RGS14 has not been functionally linked to Ca^{2+}-activated signaling pathways critical for LTP induction. Therefore, we investigated whether RGS14 restricts LTP in hippocampal CA2 by regulating Ca^{2+}-stimulated pathways required for LTP. To identify candidate signaling pathways through which RGS14 natively inhibits LTP in CA2, we first co-immunoprecipitated RGS14 from mouse brain. We find that RGS14 interacts with calmodulin (CaM), Ca^{2+}/CaM-dependent kinase II (CaMKII), and other members of Ca^{2+}-activated LTP signaling pathways. We validated these novel binding partners using biochemical assays and demonstrate that RGS14 directly binds CaM in a Ca^{2+}-dependent manner. Differential hydrogen/deuterium exchange (HDX) mass spectrometry reveals that Ca^{2+}/CaM binding to RGS14 causes significant conformational changes. Further, we show RGS14 binds to and is phosphorylated by CaMKII *in vitro*. We also find that viral expression of RGS14 in CA1 pyramidal neurons inhibits LTP induction, suggesting that RGS14 acts through pathways common to CA2 and CA1. To overcome technical barriers in identifying CA2 pyramidal neurons in hippocampal slices, we crossed RGS14-KO mice with an Amigo2-eGFP reporter mouse line. We demonstrate by confocal imaging that these Amigo2-eGFP mice specifically express eGFP in all CA2 pyramidal neurons of brain sections immunolabeled for CA2/CA1 molecular markers. To determine if RGS14 limits LTP in hippocampal CA2 through these candidate pathways, we performed whole-cell recordings from CA2 neurons with pharmacological inhibitors to determine whether LTP in CA2 of RGS14-KO mice was blocked by agents that block 'typical' LTP. Our findings suggest a critical role for NMDA receptors, postsynaptic Ca^{2+} entry, and downstream pathways. These studies provide novel mechanistic insight into the cellular regulation of synaptic plasticity in area CA2 and the key role RGS14 plays in this process.

Disclosures: **P.R. Evans:** None. **N.T. Seyfried:** None. **P.R. Griffin:** None. **M. Zhao:** None. **S.M. Dudek:** None. **J.R. Hepler:** None.

Nanosymposium

194. Synaptic Plasticity: Mechanisms and Modulation

Location: N226

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 194.11

Topic: B.08. Synaptic Plasticity

Support: NIH Z01 ES100221

Title: Perineuronal nets in hippocampal area CA2: a role in restricting synaptic plasticity?

Authors: K. E. CARSTENS[1,2], R. J. WEINBERG[3], *S. M. DUDEK[4];
[1]Neurobio. Lab., Natl. Inst. of Env. Hlth. Sci., NIH, Research Triangle Park, NC; [2]Curriculum in Neurobio., [3]UNC Neurosci. Ctr., Univ. of North Carolina, Chapel Hill, Chapel Hill, NC; [4]Lab. of Neurobio., Natl. Inst. of Envrn. Hlth. Sci., Research Triangle Park, NC

Abstract: Perineuronal nets (PNNs) are a specialized form of extracellular matrix proteins that ensheath specific neuron cell types in the brain and spinal cord. The matrix predominantly concentrates around the cell soma and proximal dendrites of inhibitory interneurons and has been functionally implicated in inhibiting structural and synaptic plasticity during early development. PNNs have been linked to several disorders such as schizophrenia and epilepsy in that the lattice-like structure of PNNs is either disrupted or fully degraded. We have characterized a dense population of PNN-positive cells in stratum pyramidale of mouse hippocampal area CA2 that appear to be pyramidal neurons. CA2 pyramidal neurons differ from other pyramidal neurons in hippocampus because they are resistant both to the induction of synaptic plasticity and to damage from seizures. In this study, we find evidence that PNNs in CA2 are developmentally regulated and are modulated by early-life experience. Staining for PNN markers in hippocampus is highly enriched in the pyramidal and dendritic regions of CA2 neurons, relative to the adjacent CA regions. Electron micrographs reveal that PNNs are localized to the membrane of CA2 pyramidal cell somata and perisynaptically around dendritic spines. Staining for PNNs in CA2 increases during early postnatal development, and early-life environmental enrichment from birth increases expression of PNNs in adult CA2 compared to control animals reared in standard housing: the largest difference was observed at postnatal day (PND) 45, with enriched environments having a 1.96-fold increase in staining intensity for wisteria floribunda agglutinin over controls (N=4). Differences were detected as early as PND14. Finally, we investigated PNNs in a mouse model of the neurodevelopmental disorder Rett Syndrome. We found that PNNs developed precociously in CA2 of MeCP2 KO mice, apparent at PND21. Together these data suggest that expression of PNNs in a population of excitatory hippocampal neurons is similar to that associated with interneurons. These studies may ultimately provide insight into a possible role for PNNs in regulating synaptic plasticity at excitatory synapses in normal and abnormal postnatal development.

Disclosures: K.E. Carstens: None. **R.J. Weinberg:** None. **S.M. Dudek:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The Coins for Alzheimer's Research Trust (C.A.R.T) Fund

The BrightFocus Foundation

The National Center for Advancing Translational Sciences through CTSI Grant UL1TR000124

The Maurice Marciano Family foundation

The Saban Family foundation

Title: Grafted bone marrow-derived monocytes and glatiramer acetate maintain cognitive function associated with synaptic preservation in a murine model of AD

Authors: *M. KORONYO-HAMAOUI[1], S. LI[1], E. Y. HAYDEN[2], D. DALEY[1], L. ZUROFF[1], T. TORBATI[1], D.-T. FUCHS[1], J. SHEYN[1], A. RENTSENDORJ[1], Y. KORONYO[1], D. B. TEPLOW[2], K. L. BLACK[1];
[1]Neurosurg., Cedars-Sinai Med. Ctr., Los Angeles, CA; [2]Neurol., David Geffen Sch. of Med. at UCLA, Los Angeles, CA

Abstract: Loss of synaptic connections in Alzheimer's disease (AD) is believed to lead to cognitive impairments, a seminal feature of AD. Evidence suggests that fibrillar and oligomeric forms of Aβ1-42 inhibit synaptic formation during the development of AD. Our studies indicate that glatiramer acetate (GA) immunization or grafting bone marrow (BM)-derived CD115+ monocytes into APPSWE/PS1ΔE9 double transgenic ADtg mice, prevents cognitive decline, reduces cerebral Aβ burden, and regulates neuroinflammation, at least partly through increased recruitment of monocyte-derived macrophages. However, it is unknown how GA immunotherapy or monocyte enrichment maintains cognitive functions and possibly impact synaptic preservation. To this end, we tested *in vitro* the effects of well-defined fibrillar and stabilized oligomeric forms of Aβ1-42 on synapses in primary cortical neuronal cultures. After 12 hours of incubation, cortical neurons were highly susceptible to both oligomeric and fibrillar Aβ1-42, with a substantial loss of presynaptic VGluT1, postsynaptic PSD95, and co-localized synaptic puncta. Remarkably, co-culturing primary cortical neurons with BM-derived macrophages completely prevented this Aβ1-42-induced synaptic loss. We next explored *in vivo* the possible effects of GA immunization or blood infusion of BM-CD115+ monocytes on synaptic preservation in ADtg mice. Our studies indicated a significant 40-70% loss of presynaptic VGluT1 and postsynaptic PSD95 immunoreactive puncta areas and numbers in entorhinal cortex (ENT) and hippocampus of 13-month-old symptomatic ADtg as compared to age-matched non-transgenic wild-type mice. Notably, GA immunization led to substantial synaptic rescue, especially in ENT and molecular layer (ML) of the dentate gyrus. A significant

preservation of synapse structure and number following GA immunotherapy was also seen in stratum lacunosum-moleculare (SLM), stratum oriens (SO), and in stratum radium (SR) of CA1. Blood enrichment with BM-monocytes, with or without GA, resulted in significant synaptic preservation, especially in the post-synaptic areas in ENT layers 2/3, ML, SLM, SO and SR. Moreover, significant correlations were noticed between synaptic area, cognitive function, and astrogliosis. Synaptic preservation was positively associated with improved cognitive scores (Barnes maze test) and negatively correlated with Aβ-plaque burden and astrogliosis. In conclusion, our combined *in vitro* and *in vivo* studies indicate that GA immunization or monocyte enrichment prevents synaptic loss and maintains cognitive function in ADtg mice.

Disclosures: M. Koronyo-Hamaoui: None. **S. Li:** None. **E.Y. Hayden:** None. **D. Daley:** None. **L. Zuroff:** None. **T. Torbati:** None. **D. Fuchs:** None. **J. Sheyn:** None. **A. Rentsendorj:** None. **Y. Koronyo:** None. **D.B. Teplow:** None. **K.L. Black:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NS37853 (C.I.)

Leon Levy Foundation (M.I.)

BrightFocus Foundation (M.I.)

Title: Voltage-gated Ca^{2+} influx plays a role in Aβ1-42-induced depolarization of hypothalamic arcuate NPY neurons

Authors: *G. WANG, M. ISHII, M. MCGUIRE, M. PENSACK, J. ANRATHER, C. IADECOLA;
Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Leptin is an adipocyte-derived hormone that negatively regulates body weight, mainly through hypothalamic pathways. We previously reported that GFP-labeled NPY neurons in the arcuate (Arc) nucleus exhibit abnormal electrophysiological responses to leptin in hypothalamic slices from Tg2576 mice overexpressing the Swedish mutation of amyloid precursor protein (APP) or wild-type (WT) hypothalamic slices treated with oligomeric Aβ1-42 (J. Neurosci., 2014, 34:9096). Since dysregulation of intracellular Ca2+ homeostasis has been implicated in

Aβ1-42-mediated neuronal dysfunction (Cell 2012, 148: 1204), we tested the hypothesis that Aβ1-42 alters intracellular Ca2+ homeostasis in Arc NPY neurons leading to neuronal dysfunction and insensitivity to leptin. We first examined if Ca2+ influx is involved in leptin-mediated electrophysiological changes in Arc neurons. Hypothalamic slices from WT mice were loaded with the cytosolic-free Ca2+ indicator fura-2 AM (5 μM) that was alternately excited through 340/380 nm filters. Application of leptin (100 nM) in a subset of Arc neurons decreased neuronal cytosolic-free Ca2+ (-56.7 ±21%; $p<0.05$, n=41 cells in 5 slices), while high K+ (30 mM) and 4-bromo A23187 (5 μM) increased it (+259±17%, $p<0.01$; +199±26%, $p<0.05$; respectively, slice n=3-7, cell n=21-45). Next, we examined if the neuronal dysfunction caused by APP overexpression or Aβ1-42 in Arc NPY neurons was due to changes in Ca2+ influx. Using whole-cell current-clamp in GFP-labeled Arc NPY neurons from WT slices, we found that leptin hyperpolarized NPY-GFP neurons in WT (-9±1.8 mV; $p<0.05$). Moreover, Aβ1-42 dose-dependently depolarized WT NPY-GFP neurons (EC50=29.7 nM, $p<0.01$ from 10 nM, n=7-25), and, importantly, the Aβ1-42-mediated depolarization was reversed by the voltage-gated L-type Ca2+ channel blocker nimodipine (5 μM; $p<0.05$, n=6). Similarly, nimodipine restored the resting membrane potential of Tg2576 NPY-GFP neurons to WT levels (vehicle: -65.3+/-6.42, nimodipine: -75.5+/-6.20 mV, $p<0.01$, n=6). These data suggest that oligomeric Aβ1-42 and APP overexpression may disrupt hypothalamic responses to leptin by changing the Ca2+ influx in Arc NPY neurons. Collectively, these findings implicate a cellular mechanism by which Aβ1-42, through voltage-gated L-type Ca2+ channels, counteracts the hyperpolarizing effects of leptin in Arc NPY neurons and disrupts homeostatic mechanisms controlling body weight. These changes may underlie the body weight and metabolic deficits seen early in Tg2576 mice and, possibly, in patients with early-stage Alzheimer's disease.

Disclosures: **G. Wang:** None. **M. Ishii:** None. **M. McGuire:** None. **M. Pensack:** None. **J. Anrather:** None. **C. Iadecola:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: PRES Euro mediterranean project 2013

Local funds 2013/2014 from Department of Drug Science and Technology (Torino University)

Title: Early alteration of hippocampal neuronal firing induced by Abeta42 oligomers in Alzheimer's disease

Authors: A. MARCANTONI[1], A. ALLIO[1], C. CALORIO[1], D. GAVELLO[1], *P. MONTAROLO[2], H. MARIE[3], E. CARBONE[1];
[1]Drug Sci. and Technol., Torino Univ., Torino, Italy; [2]Univ. Turin, Turin, Italy; [3]Inst. de Pharmacologie Moléculaire et Cellulaire (IPMC), CNRS (UMR7275), Valbonne, France

Abstract: Among the various hallmarks of Alzheimer's Disease (AD), the activation process of the "amyloid-cascade" is one of the most studied. It assumes that the accumulation of oligomers of Amyloid Beta peptides (Abeta), produced by the proteolytic processing of the amyloid precursor protein (APP) is the initiating event that triggers the progressive dismantling of the synapses, neuronal circuits and networks. However, so far there are not yet clear data regarding any possible Abeta-induced impairment of neuronal excitability. Our previous results indicate that in Tg2576 mice neurons from Lateral Entorinhal Cortex (LEC) are characterized by early impairments of their excitable profile. Tg2576 mice are characterized by over-production of different Abeta peptides, like Abeta40, Abeta42, Abeta*56 and exhibit hyperphosphorylated tau. These considerations suggest that any difference between WT and Tg2576 mice on neuronal function cannot be related to a precise cause. To address this issue, here we propose to test the effects of Abeta42 on Ca2+ dependent excitability profile of hippocampal neurons from WT embryonic mice. This peptide is known to be able to induce severe and permanent changes of synaptic functions. Our preliminary experiments on cultured hippocampal networks reveal that pre-incubation of neurons with Abeta42 oligomers increases intracellular Ca2+ concentration (measured by Ca2+ fluorescence microscopy). This effect is accompanied by a paradoxical firing inhibition. The study of the cause of the Abeta42 dependent Ca2+ dyshomeostasis let us to conclude that both ryanodine (RYRs) and NMDA receptors (NMDARs) function is altered. When we focused on hippocampal network excitability, we indicated RYRs as the main target of Abeta42, being their inhibition followed by a (partial) recovery of both firing frequency and synchronism. We also found that incubation of the BK channels inhibitor paxilline with Abeta42 oligomers revert the oligomers-induced inhibition of firing activity, thus indicating that BK channels may be a possible early target of AD. Finally, the block of NMDA receptors is followed by an increased firing synchronization, but a decreased firing frequency. In conclusion, by focusing on the Abeta42 dependent early effects on Ca2+ dependent neuronal excitability, we identified three main direct or indirect targets represented by RYRs, NMDARs and BK channels. Accordingly to previous reports, we further indicate RYRs as critically involved in AD development. Their inhibition may in turn be useful for identifying effective therapies that could enhance the quality of life of AD patients.

Disclosures: A. Marcantoni: None. **A. Allio:** None. **C. Calorio:** None. **D. Gavello:** None. **P. Montarolo:** None. **H. Marie:** None. **E. Carbone:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Conacyt Grant 514592

Conacyt Grant 235789

Conacyt Grant 181323

DGAPA-UNAM Grant IN200715

DGAPA-UNAM Grant IN201415

Title: Exercise prevents amyloid-β-induced hippocampal network disruption by inhibiting gsk3β activation

Authors: *A. GONZÁLEZ ISLA, F. PEÑA-ORTEGA, F. VAZQUEZ-CUEVAS;
Univ. Nacional Autónoma De México, Mexico, Mexico

Abstract: Exercise can produce neuroprotective changes in different neural networks, including the hippocampus, and can prevent amyloid beta (Aβ) accumulation in transgenic models of Alzheimer disease. However, it is not known if exercise could change hippocampal activity and render the hippocampus resistant to Aβ itself. Thus, we tested whether voluntary-exercise modulates hippocampal network activity and if this modulation prevents the deleterious effects of Aβ. By means of local field potential recordings of hippocampal slices, and western blot analysis of GSK3β phosphorylation state, we found that mice voluntary exercised exhibited a change in their hippocampal spontaneous network activity, recorded *in vitro*, toward faster frequency components: power reduction of slow activity (1-5 Hz) along with power enhancing of fast activity (20-25 Hz). Exercise also rendered the hippocampus protected against Aβ ex vivo. Whereas the hippocampal network activity of slices obtained from sedentary animals was reduced upon Aβ application *in vitro*, this activity was no affected by Aβ in slices obtained from exercised animals. We also found that the inhibitory effect of Aβ on hippocampal activity correlated with the activation of GSK3β in slices obtained from sedentary animals and that this activation is precluded in those from exercised animals. We conclude that exercise produces a protective state in the hippocampus that prevents the inhibition by Aβ by avoiding GSK3β activation.

Disclosures: **A. González Isla:** None. **F. Peña-Ortega:** None. **F. Vazquez-Cuevas:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Synaptic function alterations induced by Herpes Simplex Virus type-1 infection *in vitro* depend on Glycogen Synthase Kinase 3 activation and intraneuronal accumulation of amyloid-β protein

Authors: *R. PIACENTINI[1], D. D. LI PUMA[1], C. RIPOLI[1], M. E. MARCOCCI[2], G. DE CHIARA[4], A. T. PALAMARA[3,5], C. GRASSI[1];
[1]Inst. of Human Physiol., Univ. Cattolica, Med. Sch., Rome, Italy; [2]Dept. of Publ. Hlth. and Infectious Dis., [3]Dept. of Publ. Hlth. and Infectious Dis. - Fondazione Cenci Bolognetti, Sapienza Univ. of Rome, Rome, Italy; [4]Inst. of Translational Pharmachology, Natl. Res. Council, Rome, Italy; [5]IRCCS San Raffaele Pisana, Rome, Italy

Abstract: Synaptic dysfunction is responsible for the cognitive deficits associated with Alzheimer's disease (AD). Increasing evidence suggests that recurrent Herpes Simplex virus type-1 (HSV-1) infection in the brain is a risk factor for AD but the underlying mechanisms have not been fully elucidated yet. Aim of the present study is to check whether HSV-1 infection alters synaptic function and to identify the underlying molecular mechanisms. In cultured mouse cortical neurons, HSV-1 (5 MOI) triggered amyloid precursor protein phosphorylation at T668 (pAPP; +185±8% vs. mock-infected cells at 24 hours post infection [hpi]; $P<0.01$). This effect primarily depended on activation of Glicogen Sinthase Kinase (GSK)-3 with smaller contribution of cyclin-dependent kinase 5 and c-Jun N-terminal kinase, as demonstrated by experiments with the specific inhibitors SB216763 (10 μM), roscovitine (10 μM) and Inhibitor I (5 μM) that reduced pAPP immunoreactivity by 54%, 39% and 20%, respectively ($P<0.01$ vs. HSV-1 alone). pAPP is a key event for Aβ production and HSV-1-infected neurons exhibited intracellular accumulation of Aβ assessed by Western Blot and immunofluorescence. HSV-1-infected neurons (24 hpi) had reduced expression of the presynaptic proteins synapsin-1 and synaptophysin (-58% and -39% vs. mock, respectively; $P<0.05$) that was paralleled by a marked reduction of the frequency of spontaneous miniature excitatory post-synaptic currents (from 7.6 to 3.7 Hz; $P<0.01$). These effects were significantly reversed by SB216763 and depended on Aβ accumulation. Indeed, an antibody recognizing Aβ and being uploaded intracellularly (4G8)

rescued synaptic protein expression and synaptic transmission from the effects of HSV-1. In HSV-1-infected neurons derived from APP KO mice GSK-3 activation was not associated with Aβ accumulation and significant changes in synaptic protein expression, thus suggesting that GSK-3 alone is not sufficient to induce synaptic alterations in infected cells. Among the downstream components of the molecular pathways potentially responsible for the HSV-1-induced synaptic dysfunction, we studied cAMP responsive element-binding protein (CREB) because it is target of GSK-3 and is modulated by Aβ. We found that 24 hpi the activatory phosphorylation of CREB (at S133) was reduced whereas the inhibitory one (at S129) was increased (-25±2% and +35±4% vs. mock, respectively; $P<0.01$). Either SB216763 or 4G8 completely reversed these effects. Our data indicate that HSV-1 infections may contribute to the pathophysiology of AD by a mechanisms likely involving GSK-3 activation, Aβ accumulation and inhibition of CREB-dependent transcriptional program.

Disclosures: **R. Piacentini:** None. **D.D. Li Puma:** None. **C. Ripoli:** None. **M.E. Marcocci:** None. **G. De Chiara:** None. **A.T. Palamara:** None. **C. Grassi:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant P20 GM109098

NIH Grant P01 AG027956

NIH Grant U54 GM104942

Title: Expression of micro-RNA-34a in late-onset Alzheimer’s disease (LOAD) brain mechanistically links synaptic plasticity and energy metabolism dysfunction via simultaneous repression of target genes

Authors: ***S. N. SARKAR**, S. JUN, S. RELLICK, D. D. QUINTANA, J. W. SIMPKINS; PHYSIOLOGY AND PHARMACOLOGY, WEST VIRGINIA UNIVERSITY, Morgantown, WV

Abstract: Characteristics of association of multiple genetic loci as risk factors for LOAD and the multifactorial nature of its etiopathology impede the generation of LOAD mice model and the discovery Alzheimer’s disease modifying therapies. To circumvent these obstacles it is necessary

to identify novel target(s) that simultaneously dysregulate functions of many genes involved in initiation and or progression of LOAD. To this end, we selected five miRNAs by target prediction algorithms that have potential to simultaneously dysregulate genes known to be involved in synaptic plasticity, neuronal survival, and energy metabolism. When profiling specific miRNA expression in LOAD brain regions, we found that expression of miR-34a and miR-146a compared to other three, namely miR-19, -132, -15 significantly increased in temporal cortex, less in frontal cortex, but not at all in the same subject's cerebellum regions. Increased expression of miR-34a positively correlated with subject's neuropathology. We also found that the level of synaptic proteins SYT1, VAMP2, HCN, GluR1, and NR2A; glycolytic enzymes, H6PD, PFK1, PFK2; and the protein components of electron transport chain, NDUFC2, SDHC, UQCRB, UQCRQ AND COX10 were significantly reduced in AD temporal cortex region compared to normal AMC and respective AD subject's cerebellum. Ectopic expression of miR-34a in primary neuronal culture *in vitro* severely decreased both glycolysis and oxidative phosphorylation, as well as reduced protein levels necessary for glycolysis and oxidative phosphorylation. In conclusion, simultaneous ability of miR-34a to repress target genes involved in neural circuit function and energy metabolism provides as a possible mechanism-based novel target overcoming the problems to discover LOAD modifying therapies.

Disclosures: S.N. Sarkar: None. **S. Jun:** None. **S. Rellick:** None. **D.D. Quintana:** None. **J.W. Simpkins:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01NS041783

Title: Presenilin function in the hippocampal schaffer collateral and mossy fiber synapses

Authors: *S. LEE[1], J. GRAW[2], M. FROTSCHER[2], J. SHEN[1];
[1]Ann Romney Ctr. for Neurologic Dis., Brigham & Women's Hospital, Harvard Med. Sch., Boston, MA; [2]Dept. for Structural Neurobio., Ctr. for Mol. Neurobio. Hamburg (ZMNH), Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Synaptic dysfunction has widely been considered to play a key role in Alzheimer's disease (AD) pathogenesis, and the hippocampal network is particularly vulnerable in AD.

However, there have been few studies addressing whether AD genes are involved in the regulation of the hippocampal network. Despite presenilin (PS) is normally expressed highly in the entire hippocampus and plays essential roles in synaptic plasticity in the Schaffer collateral (SC) pathway, the role of PS in the regulation of other hippocampal synapses is unknown. In this study, we used excitatory neuron-specific *presenilin* conditional double knockout (cDKO) mice to determine and compare the role of PS in hippocampal SC and Mossy fiber (MF) pathways. We found unaltered synaptic transmission but impaired LTP in the MF pathway of *PS* cDKO mice. We further showed that paired-pulse facilitation (PPF) and frequency facilitations induced by 10 stimuli were significantly impaired. These results suggest that similar to the SC pathway, PS is required for normal presynaptic short-term and long-term synaptic plasticity at the MF pathway. Mitochondrial Ca^{2+} is also part of the intracellular calcium pool, contributing to the $[Ca^{2+}]_i$ increment at presynaptic terminals during high-frequency stimulation (HFS), and is specifically required for post-tetanic potentiation (PTP). Our further analysis of MF and SC synapses in *PS* cDKO mice showed that PTP induced by HFS was significantly reduced at MF synapses, but not in SC synapses in *PS* cDKO mice. Interestingly, our quantitative analyses of electron microscopy (EM) study revealed the number of mitochondria in MF synapses is much higher relative to SC synapses. The hippocampus, particularly in the CA3 synapse, mediates pattern completion during memory recall, an ability to retrieve stored memory traces in response to incomplete sensory cues. According to the result of learning and memory task, *PS* cDKO mice displayed reduced target quadrant occupancy under partial-cue conditions, suggesting impaired hippocampal pattern completion. Our results underscored the importance of PS in the regulation of short-term and long-term synaptic plasticity in the hippocampal SC and MF synapses, and the difference between these two synapses in the mechanisms of regulation.

Disclosures: **S. Lee:** None. **J. Graw:** None. **M. Frotscher:** None. **J. Shen:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Medical Research Council

Title: Narrowing down a common neurophysiological hallmark of pre-clinical models of dementia

Authors: *T. L. KERRIGAN[1], J. T. BROWN[2], A. D. RANDALL[2,3];
[1]Univ. of Exeter, Exeter, United Kingdom; [2]Univ. of Exeter Med. Sch., Inst. of Biomed. and Clin. Services, Exeter, United Kingdom; [3]Univ. of Bristol, Sch. of Physiol. and Pharmacol., Bristol, United Kingdom

Abstract: Over the past 15 years, there has been a plethora of neurophysiological studies on a wide variety of amyloidogenic mice. More recently, the importance of altered intrinsic excitability (IE) of single neurons have received increased attention. We have previously reported changes in IE in relation to action potential (AP) properties from two different amyloidogenic mouse models. A common feature in their neurophysiological properties was the narrowing of the AP spike width. This in itself can produce substantial effects on activation of other downstream cellular processes e.g. presynaptic calcium entry. In this study we investigate whether the TASTPM mouse model, a heterozygous transgenic mouse with the Swedish (K670N; M671L) double familial mutation (Thy-1-APP695Sw, Line 10 (TAS10)) and the presenilin-1 (M146V) mutation (Thy-1-PS-1M146V) display any similarities. Horizontal hippocampal slices were prepared from TASTPM mice and their respective age-matched controls (9-10 month old). Whole-cell current clamp recordings were made from CA1 pyramidal neurones (CA1-PN). To highlight any changes that may occur in this particular amyloidogenic model, we used a series of different electrophysiological protocols to examine IE of both the passive and AP properties of single neurons. We found that although there was no significant difference in the passive properties, there was a significant narrowing in AP width, between the controls and the TASTPM mice. These data conform to the narrowing of AP spikes observed in our previous studies. Thus based on three mice lines (PSAPP, PDAPP and TASTPM) we have studied and one study performed elsewhere (CRND8), it would seem that a 10–15% narrowing of spikes in CA1-PC of Aβ overproducing transgenic mice is a repeatable finding across multiple transgenic lines. This may start to highlight the possibility of a pre-clinical neurophysiological hallmark that occurs in multiple Aβ overproducing lines.

Disclosures: T.L. Kerrigan: None. **J.T. Brown:** None. **A.D. Randall:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CIHR RN120654 - 244847

Title: 82-kDa choline acetyltransferase and SATB1 co-locate at synapse and cell-stress related genes after amyloid beta exposure

Authors: *W. WINICK-NG[1], F. A. CAETANO[2], B. HEIT[3], J. WINICK-NG[4], R. RYLETT[1]; [1]Physiol. and Pharmacol., [3]Microbiology and Immunol., [4]Surgery, and Epidemiology and Biostatistics, [2]Western Univ., London, ON, Canada

Abstract: The M-transcript of human choline acetyltransferase (ChAT) produces an 82-kDa protein (82-kDa ChAT) that localizes to nuclei of cholinergic neurons, with this localization reduced in elderly individuals and Alzheimer's disease (AD) subjects. The function of 82-kDa ChAT, and how the localization of the protein is altered in AD is currently unknown. Thus, in the present study we assessed whether the nuclear distribution of 82-kDa ChAT could be altered by cellular perturbations. Acute exposure of SH-SY5Y cells to oligomeric β-amyloid1-42 (Aβ1-42) resulted in the association of 82-kDa ChAT with chromatin and formation of 82-kDa ChAT aggregates in nuclei. These aggregates were co-localized with special AT-rich binding protein 1 (SATB1), a protein that forms scaffolding/matrix attachment regions (S/MARs). Based on the interaction between 82-kDa ChAT, SATB1 and chromatin, we performed chromatin immunoprecipitation followed by next generation sequencing (ChIP-seq) for both proteins. We found associations in 885 common genes between both proteins, with the highest significant associations found in cell stress response genes and synapse formation/maintenance genes. In addition, we found several genes with altered expression in AD or associated with AD risk. After Aβ1-42 exposure, both SATB1 and 82-kDa ChAT were associated with the same region on the APP gene, which coincided with an in silico predicted S/MAR. Finally, we found that 82-kDa ChAT expression prevented an increase in an isoform specific APP mRNA transcript, which is increased in AD and is correlated with levels of Aβ1-42. These experiments suggest that 82-kDa ChAT may play a critical role in how cells respond to Aβ exposure, with implications for understanding the etiology and progression of neurodegenerative diseases such as AD. These studies were funded by a CIHR grant to RJR and a Dean's PhD Scholarship to WW-N.

Disclosures: W. Winick-Ng: None. **F.A. Caetano:** None. **B. Heit:** None. **J. Winick-Ng:** None. **R. Rylett:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NHMRC

ARC

Alzheimer's Association

Title: p38 MAP kinase-mediated NMDA receptor-dependent suppression of hypersynchronicity in a mouse model of Alzheimer's disease

Authors: *A. A. ITTNER, A. GLADBACH, J. BERTZ, L. M. ITTNER;
UNSW Australia, Sydney, Australia

Abstract: Hypersynchronicity of neuronal brain circuits is a feature of Alzheimer's disease (AD). Mouse models of AD expressing mutated forms of the amyloid-ß precursor protein (APP), a central protein involved in AD pathology, show cortical hypersynchronicity. We studied hippocampal circuitry in APP23 transgenic mice using telemetric electroencephalography (EEG), at the age of onset of memory deficits. APP23 mice display spontaneous hypersynchronicity in the hippocampus including epileptiform spike trains. Furthermore, spectral contributions of hippocampal theta and gamma oscillations are compromised in APP23 mice, compared to non-transgenic controls. Using cross-frequency coupling analysis, we show that hippocampal gamma amplitude modulation by theta phase is markedly impaired in APP23 mice. Hippocampal hypersynchronicity and waveforms are differentially modulated by injection of riluzole and the non-competitive N-methyl-D-aspartate (NMDA) receptor inhibitor MK801, suggesting specific involvement of voltage-gated sodium channels and NMDA receptors in hypersynchronicity thresholds in APP23 mice. Furthermore, APP23 mice show marked activation of p38 mitogen-activated protein (MAP) kinase in hippocampus, and injection of MK801 but not riluzole reduces activation of p38 in the hippocampus. A p38 inhibitor induces hypersynchronicity in APP23 mice to a similar extent as MK801, thus supporting that suppression of hypersynchronicity involves NMDA receptors-mediated p38 activity. In summary, we characterize components of hippocampal hypersynchronicity, waveform patterns and cross-frequency coupling in the APP23 mouse model by pharmacological modulation, furthering the understanding of epileptiform brain activity in AD.

Disclosures: **A.A. Ittner:** None. **A. Gladbach:** None. **J. Bertz:** None. **L.M. Ittner:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: France Alzheimer

Title: Dysregulation of neuronal protein synthesis and mTOR by the amyloid peptide

Authors: *F. DARCHEN, Z. JAFFAL, D. KHAMSING, A. SOLTANI, S. LEBRUN, I. FANGET, D. CARREL, C. DESNOS;
Paris Descartes Univ., Paris, France

Abstract: Alzheimer's disease (AD) is the most common senile dementia. Cognitive deficits are widely believed to result from progressive synaptic dysfunction and neurodegeneration, most likely caused by soluble oligomers of the amyloid peptide (AbO). Synaptic plasticity (for instance long term potentiation (LTP)) that underlies memory, involves changes in synapse efficacy associated with a variation in number, size and morphology of dendritic spines. AbO induce dendritic spine abnormalities and inhibit synaptic plasticity. These effects are likely to account for the cognitive defects associated with AD but the mechanisms remain obscure. LTP depends on de novo protein synthesis. Using a non-radioactive technique known as surface sensing of translation, (SUnSET) and based on the detection of puromycin incorporated into nascent peptide chains, we observed an increase in de novo protein synthesis in dendrites of cultured hippocampal neurons upon induction of chemical LTP with Forskolin, BDNF, or dopamine. This activity-dependent mRNA translation was severely blocked by AbO (500 nM, 3h). In contrast, in unstimulated neurons, lower doses of AbO (100 nM, 3h) increase de novo protein synthesis. Similar results have been obtained using cultures of neurons from Tg2576 mice expressing a pathogenic mutant of the amyloid precursor protein APP. These effects of AbO on mRNA translation are due to changes in the activity of mTOR. Indeed, we observed that AbO at 100 nM increased mTOR activity by activating the BDNF/PI3-kinase/Akt pathway. Higher doses of AbO impair mRNA translation in neurons by activating NMDA receptors, Calcium/Calmodulin kinase kinase and AMP-kinase. The latter phosphorylates Raptor, a component of mTORC1, leading to mTOR inhibition at least in part by preventing the recruitment of mTOR on late endosomes and lysosomes. This dysregulation of mTOR activity and protein synthesis could play an important role in the early synaptic defects observed in Alzheimer's disease. Thus, the correction of mRNA translation dysfunction could represent a new interesting angle to develop an effective cure for this disease.

Disclosures: F. Darchen: None. **Z. Jaffal:** None. **D. Khamsing:** None. **A. Soltani:** None. **S. Lebrun:** None. **I. Fanget:** None. **D. Carrel:** None. **C. Desnos:** None.

Nanosymposium

195. Alzheimer's Disease: Synaptic and Neuronal Dysfunction

Location: S401

Time: Sunday, October 18, 2015, 1:00 PM - 4:00 PM

Presentation Number: 195.12

Topic: B.08. Synaptic Plasticity

Support: The Mitchell Center for Neurodegenerative Diseases

NIA R01 AG042890

Title: Reduced expression of Phospholipase D (PLD) isoforms in the synaptosomal fractions of the frontal cortex from Alzheimer's disease (AD) patients

Authors: *B. KRISHNAN, W.-R. ZHANG, G. TAGLIALATELA;
Dept. of Neurol., Univ. of Texas Med. Br. At Galveston, Galveston, TX

Abstract: Alzheimer's disease (AD), the most common and severe age-associated neurodegenerative dementia, currently affects one in every nine Americans >65 years of age and one in every three >85 years. There is currently no cure and the need to identify innovative targets for prevention and treatment are an urgent need. The accumulation of β-amyloid peptides (Aβ) at the synaptic level is an important mechanism that leads to the progression of cognitive decline, subsequent neuronal degradation and other hallmarks that characterize the loss of long-term memory mechanisms in the progression of AD. Recent studies from our group have demonstrated a role for phospholipase D (PLD) as a key signaling element in the maintenance of long-term memory. Interestingly, studies conducted by independent groups over the past decade have elucidated a role for different isoforms of mammalian PLD (PLD1 and PLD2) in negatively regulating Aβ production/accumulation using in-vitro approaches. More importantly, it was demonstrated very recently that a variant of a third isoform, PLD3 expressed in lower levels is directly associated with progression of one form of late-onset AD. Such evidence provide a strong rationale to further study the role of PLD signaling as a possible biomarker/therapeutic target in AD. In the present study, we demonstrate that PLD levels are significantly lower [PLD1: 0.020 ± 0.001 (Control) vs 0.016 ± 0.0005 (AD); PLD2: 0.151 ± 0.005 (Control) vs 0.120 ± 0.007 (AD), n=4-5, $p<0.05$] in the frontal cortex (synaptosomal fractions) of AD patients compared to age-match controls. Interestingly, this change is not reflected for PLD1 in the total homogenate fraction, while PLD2 is reduced [0.144 ± 0.008 (Control) vs 0.120 ± 0.009 (AD)]. Intriguingly, the phosphorylation states of the two isoforms do not show any significant change in the synaptosomal fractions. Taken together, these results suggest that PLD signaling, that is important for long-term memory, is altered in the synapses of AD patients.

Disclosures: B. Krishnan: None. **W. Zhang:** None. **G. Taglialatela:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.01

Topic: D.04. Vision

Support: NEI Grant EY020484

NSF BCS-1134780

Feodor-Lynen Humboldt Scholarship

Athinoula A. Martinos Imaging Center at McGovern Institute for Brain Research, MIT

Title: Neural dynamics in the cortical representation of scenes

Authors: *R. M. CICHY[1], A. KHOSLA[1], D. PANTAZIS[2], A. OLIVA[1];
[1]CSAIL, [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA

Abstract: Perceiving the geometry of space for navigation is a core ability shared by all animals, with brain structures for spatial layout perception and navigation preserved across rodents, monkeys and humans. Spatial layout perception, that is demarcating the boundaries and the size of visual space plays a mediating role in spatial cognition between lower-level image analysis and navigation-related processing. Although the cortical loci of spatial layout perception have been well described, the dynamics of spatial cognition in humans remain unexplained because neuronal markers indexing spatial processing remain unknown. Here, we report the first electrophysiological cortical signal of spatial layout perception in the human brain. We recorded MEG in 15 healthy participants while those viewed 48 scene images differing in size and other factors (Fig. 1a). Using multivariate pattern classification and representational similarity analysis, we identified a marker of scene size perception around ~250ms (Fig. 1b). The scene size marker was independent of low-level image and semantic properties (i.e. luminance, contrast, clutter, semantic category) (Fig. 1c), thus indexing neural representations robust to changes in viewing conditions as encountered in real-world settings. To provide a quantitative account of how space size representations emerge in neuronal circuits we used computational modeling and direct comparison to brain data. We showed that a state-of-the-art deep convolutional neural network (Fig. 1d) trained to recognize natural scene categories (scene-CNN) predicted the scene space size from pixel values better than previous models such as GIST and HMAX (Fig. 1e), and was the only model to explain away the electrophysiological scene size representation (Fig. 1f). Together our data provide a first description of an electrophysiological signal for spatial scene processing in humans, and provide a novel quantitative computational model of the dynamics of emerging visual scene space representation.

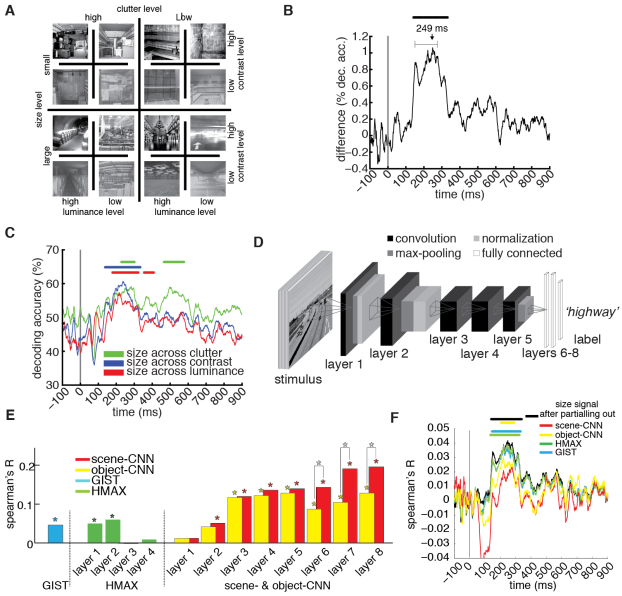


Figure 1. a) The image set consisted of 48 images of indoor scenes differing in size, luminance, contrast and clutter. **b)** Scene size was discriminated by visual representations in the MEG at ~250ms, constituting a marker of scene size perception. **c)** The scene size marker was independent of low-level image and semantic properties (i.e. luminance, contrast, clutter, semantic category). **d)** The convolutional neural network (CNN) had an 8-layer architecture, implementing biologically plausible operations such as convolution, max pooling and normalization. It was trained on scene categorization (scene-CNN) independent of scene size. **e)** The scene-CNN predicted the scene space size from pixel values better than received models such as GIST and HMAX. **f)** The scene-CNN was the only model to explain away (by partialling out) the electrophysiological scene size representation.

Disclosures: **R.M. Cichy:** None. **A. Khosla:** None. **D. Pantazis:** None. **A. Oliva:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.02

Topic: D.04. Vision

Support: NSERC Discovery

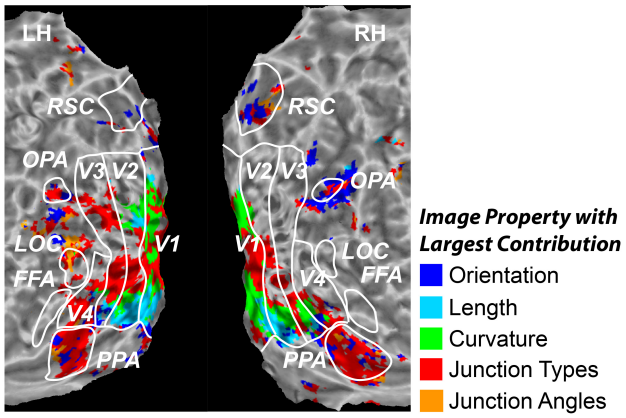
Canadian Foundation for Innovation

Ontario Research Fund

Title: Emergence of scene structure in the human brain: 2d cues to 3d shape are essential for neural representations of scene categories

Authors: *H. CHOO, D. B. WALTHER;
Psychology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Humans can quickly recognize a novel real-world environment according to its basic-level scene category. Which visual features facilitate such efficient categorical scene perception in humans? To answer this question we combine multi-voxel pattern analysis of neural representations of scene categories throughout visual cortex with computational models of scene categorization. Participants viewed line drawings of six scene categories (beaches, forests, mountains, city streets, highways, and offices) while in an MRI scanner. We decoded scene categories from locally distributed neural activity patterns. We compared decoding error patterns to the error patterns from five computational models of scenes, each relying on the statistics of only one kind of contour property: orientation, length, curvature, junction types, or junction angles. We found that statistics of junction properties exhibited the largest contribution to the neural representations of scene categories in high-level scene-selective brain regions (parahippocampal place areas, PPA; occipital place area, OPA; lateral occipital complex, LOC), followed by orientation statistics (see figure). To assess the causal involvement of these visual properties in neurally representing scene categories, we manipulated the images in such a way that junctions or orientations were disrupted. In early visual cortex, scene categories could be successfully decoded under both manipulations. In the PPA, OPA and LOC, on the other hand, disruption of junction statistics severely reduced the extent of category-specific neural activity. When orientations were disrupted, scene categories could still be decoded successfully in the PPA and LOC. Based on these results we suggest a causal role for contour junctions, which provide cues for the 3D arrangement of surfaces in a scene, in the neural mechanisms of scene categorization.



Disclosures: **H. Choo:** None. **D.B. Walther:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.03

Topic: D.04. Vision

Support: Integrative Graduate Education & Research Traineeship (National Science Foundation)

Dissertation Research Funding Award (Society for Research in Child Development)

Dissertation Research Award (American Psychological Association)

Title: Neural and behavioral sensitivity to boundary cues in Williams syndrome

Authors: *K. FERRARA, B. LANDAU, S. PARK;
Cognitive Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: Boundaries are fundamental features that define a scene and contribute to its geometric shape. For example, 4-yr-olds reorient in accord with the geometry of a layout defined by a curb that is 2 cm high, but fail to do so when the curb is replaced by a flat mat (Lee & Spelke, 2011). Our previous research using fMRI showed a similar distinct sensitivity to boundaries in scene representation by the healthy adult brain (Ferrara & Park, 2014). In the present research, we aim to determine whether the finely tuned sensitivity to boundaries may be impaired by genetic deficit. We couple behavioral (Exp. 1) and neuroimaging (Exp. 2) methods to study individuals with Williams syndrome (WS), a developmental disorder characterized by the deletion of 25 genes on chromosome 7. It is accompanied by a profile that includes severe impairment in a range of spatial functions. In Exp. 1, individuals with WS (n = 12) and typically developing (TD) age-matched controls (n = 12) were disoriented and then recovered a hidden target in 3 different types of arrays that varied in terms of boundary cue: a mat, a curb (5cm) and full walls (2m). Unlike TD controls who reoriented geometrically in all 3 arrays, people with WS only reliably used geometry in the wall condition. These data indicate that the WS reorientation mechanism is fragile, with geometric sensitivity triggered only by the full wall, but not the small curb. In Exp. 2, we measured fMRI activity in scene-selective regions for the same WS and TD participants. We used artificially-created scene stimuli that mirrored the physical boundary arrays of Exp. 1: a mat, a curb with a small addition of structure, and a full wall. Participants viewed images in blocks of 12 seconds while performing a one-back task. For TD controls, the parahippocampal place area (PPA) showed an increase in activity from the mat, to curb, to wall. This indicates impressive sensitivity to the presence of the minimal curb, even though it and the mat are visually similar. For WS participants however, PPA activity did not distinguish between the mat and curb. Multi-voxel pattern analyses using a linear classifier confirmed these qualitative differences between the two groups. Taken together, these results reveal one of the crucial aspects of scene representation that is manifested behaviorally as fine-grained sensitivity to slight boundary cues in reorientation. Using WS as a test case, we find that atypical patterns of reorientation correspond with less fine-grained distinction at the neural level in WS compared to

TD controls. By coupling behavioral and neuroimaging methods, this research sheds light on the connection between scene representation in the brain and fluid behavioral navigation.

Disclosures: K. Ferrara: None. **B. Landau:** None. **S. Park:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.04

Topic: D.04. Vision

Support: MURI (to DMB)

James S. McDonnell Award (to KDF)

Title: The good, the bad and the early: top-down influence on scene categorization

Authors: *M. KUMAR[1], Y. ZHANG[2], D. M. BECK[1,2], K. D. FEDERMEIER[1,2];
[1]Neurosci., [2]Psychology, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Humans are extraordinarily quick at processing natural scenes. Furthermore, good exemplars of natural scene categories are not only categorized more easily but are also more readily detected than bad exemplars. However, it remains unclear when and how this good exemplar advantage arises. Does the good/bad difference arise early in visual processing, due to differences in low- level visual features, or later, from differences in high level visual or semantic processing? To address this question, we measured event-related potentials (ERPs) while participants viewed (and made a delayed judgment about) good and bad exemplars of six scene categories: beaches, city streets, forests, highways, mountains and offices. Good and bad exemplars first evoked differential ERPs 250 to 350 ms after onset, with bad exemplars producing greater frontal negativity than good exemplars. This effect is consistent with the N3 complex, previously associated with processing the global structure of an image, and indicates facilitated high-level visual processing for good relative to bad scenes. Such effects could arise because of differences in the properties of the images themselves or because high-level visual processing is being affected by stored representations (e.g., templates) of the scene categories. To differentiate between these mechanisms, we next examined whether these N3 effects could be modulated by expectation. In a follow-up experiment, participants were cued ahead of each trial with a category label (e.g. 'Beach') and the subsequent image shown either matched or mismatched the cue. We replicated the good/bad difference from the earlier experiment when the

image matched the cue. Interestingly, the good/bad effect disappeared when the images were mismatched to the cue, consistent with the idea that the good/bad difference in the N3 time window may reflect a match to template. Overall, the results indicate that the good exemplar advantage may not only involve eased decision-making, but also arises in perceptual processing -- and, more specifically, higher-order visual processing -- jointly affected, as early as 250 to 350 ms, by visual properties of the image and top-down expectations.

Disclosures: **M. Kumar:** None. **Y. Zhang:** None. **D.M. Beck:** None. **K.D. Federmeier:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.05

Topic: D.04. Vision

Support: NIH Grant EY022350

NSF Grant SBE-0541957

Title: Multiple landmark codes in the human brain

Authors: ***S. A. MARCHETTE**[1], L. K. VASS[1,2], J. RYAN[1], R. A. EPSTEIN[1];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Univ. of California, Davis, Davis, CA

Abstract: Landmarks are entities that have a special status in navigation because they are associated with specific locations or directions in the world. The use of landmarks is central to many wayfinding strategies, however little is known about how they are coded in the brain. Here we use multivoxel pattern analysis of fMRI data to address this issue. Subjects were scanned while viewing photographs of the interiors and exteriors of ten familiar buildings from the University of Pennsylvania campus. Despite their visual dissimilarity, the interiors and exteriors corresponding to the same building elicited similar activity patterns in the parahippocampal place area (PPA), retrosplenial complex (RSC) and occipital place area (OPA), three regions known to respond strongly to visual scenes. We then investigated the conditions necessary for this generalization across stimuli by performing the same experiment with two additional groups of subjects: (1) Temple University students, who did not know the correspondences between interior and exterior images and (2) Penn students who performed a concurrent memory task that blocked mental imagery. Generalization across stimuli depended upon knowing the correspondences among them in PPA but not in the other two regions, suggesting that the PPA is

the key region involved in learning the different perceptual instantiations of a landmark. In contrast, generalization depended upon the ability to freely retrieve information from memory in RSC, and did not depend upon familiarity or cognitive task in OPA. Taken together, these experiments suggest a tripartite division of labor, whereby PPA codes landmark identity, RSC retrieves spatial or conceptual information associated with landmarks, and OPA processes visual features that are important for landmark recognition.

Disclosures: **S.A. Marchette:** None. **L.K. Vass:** None. **J. Ryan:** None. **R.A. Epstein:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.06

Topic: D.04. Vision

Support: NSERC Discovery Grant to J.S.C.

UTSC Research Competitiveness Fund to J.S.C.

Title: Are scene-shape and scene-texture processing mediated by shared or distinct neuronal mechanisms in the parahippocampal place area?

Authors: ***J. S. CANT**[1,2], M. X. LOWE[1,2], J. RAJSIC[2], J. P. GALLIVAN[3];
[1]Psychology, Univ. of Toronto Scarborough, Scarborough, ON, Canada; [2]Psychology, Univ. of Toronto, Toronto, ON, Canada; [3]Psychology, Queen's Univ., Kingston, ON, Canada

Abstract: It has recently been demonstrated that the scene-sensitive PPA is more active for judgments of the surface texture and material properties of objects, compared to judgments of object shape. This appears inconsistent with the view that PPA is specialized for processing scenes, since the single objects used did not invoke scene imagery. But surface texture (and the material-properties signaled by texture) is important in scene processing as it can be used to aid in image segmentation, can contribute to the recognition of scene identity, and can provide affordance-related cues relevant for navigation. Thus, the finding that attending to object texture and material activates PPA may be better interpreted as evidence that PPA utilizes multiple visual features, in addition to its well-known role in processing structural geometry, when representing scenes. In the present study we tested this hypothesis, and also examined whether the processing of these features (i.e., scene shape and material) is mediated by shared or distinct neuronal mechanisms. Using fMRI, we conducted both univariate and multivariate (i.e.,

multivoxel pattern analysis, MVPA) analyses to examine activity in PPA while participants made shape and material-property judgments of both objects and scenes (images consisted of a central object located within an indoor scene). We also examined activity in LOC, to explore if this object shape-sensitive region is involved in processing the geometry of scenes. Interestingly, judgments of object shape produced the highest activation in LOC (compared with judgments of scene shape, scene material, and object material, which did not differ), demonstrating that LOC is not a general-purpose shape-processing region. In PPA, activation was higher for judgments of object material compared with object shape, replicating previous results. But importantly, activation for both shape and material judgments of scenes, which did not differ, was higher than activation for judgments of object features. Moreover, MVPA analyses revealed that while patterns of object- and scene-related activity could be successfully decoded in PPA (and LOC), patterns for scene shape and scene material were quite similar and thus could not be distinguished from each other. Together, these results demonstrate that PPA is specialized for processing visual features of scenes, not single objects. But more interestingly, the consistency between the univariate and multivariate results suggest that the processing of multiple scene features (i.e., shape, texture/material) in PPA is mediated by shared neuronal mechanisms.

Disclosures: **J.S. Cant:** None. **M.X. Lowe:** None. **J. Rajsic:** None. **J.P. Gallivan:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.07

Topic: D.04. Vision

Support: NIH NEI F32EY021710 to M.D.L.

NIH NEI R01 EY019684 to J.L.G.

Title: Semantics, distance, and spatial frequency all describe the same representation in scene-selective areas of the human brain

Authors: *M. D. LESCROART[1], D. E. STANSBURY[2], J. L. GALLANT[2];
[1]UC Berkeley, Berkeley, CA; [2]Helen Wills Neurosci. Inst., Univ. of California, Berkeley, Berkeley, CA

Abstract: Visual scene perception activates several areas in the human brain, including the Parahippocampal Place Area (PPA), Retrosplenial Cortex (RSC), and the Occipital Place Area

(OPA). However, precisely *what* scene-related features are represented in these areas has been a subject of protracted debate. Previous studies have suggested that PPA, RSC, and/or OPA might represent at least three types of features: [1] low-level 2D features such as spatial frequency; [2] 3D spatial features such as the distance to objects in a scene; or [3] abstract semantic features such as the categories of objects in a scene. We used a voxel-wise modeling approach to determine which of these features are most likely represented in scene-selective areas. Under this approach we construct encoding models based on multiple feature spaces that reflect alternative hypotheses about which features are represented in scene-selective areas. Specifically, we used fMRI to measure brain responses to a large set of natural images, and we modeled the responses using three feature spaces: [1] A low-level feature space based on the distribution of Fourier power in each image; [2] a subjective distance feature space based on human ratings of the distance to objects in each image; and [3] a semantic category feature space based on semantic labels assigned to each image by human raters. We used linear regression to fit each feature space to the BOLD fMRI data for each voxel in the brain, and we evaluated each fit model by estimating the amount of variance it predicted in a separate data set reserved for that purpose. We found that all three models predict similar amounts of variance in PPA, RSC, and OPA. The similarity in predictions of the three models might indicate that each feature space predicts a different component of response variance. Alternatively, all three models might predict the same response variance (due to correlations inherent in natural images). To address this issue we fit all three models jointly and conducted a variance partitioning analysis. This analysis revealed that most—but not all—of the variance predicted by the semantic model was also predicted by the other two models. Additionally, neither the low-level Fourier model nor the subjective distance model predicted any variance independent of the semantic model. Thus, all three models explain much common variance, but the semantic model is marginally better than the others. We hypothesize that PPA, RSC, and OPA represent complex features that are found in natural scenes, but which are not completely semantic.

Disclosures: **M.D. Lescroart:** None. **D.E. Stansbury:** None. **J.L. Gallant:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.08

Topic: D.04. Vision

Support: NIH EY02316601

NSF BCS 025149

NIH RO1 MH64043

Title: Mapping of scene category, exemplar, and image format representations across the visual system

Authors: *J. G. KIM[1], N. KRIEGESKORTE[3], S. KASTNER[2];
[1]Princeton Neurosci. Inst., [2]Princeton Univ., Princeton, NJ; [3]Cognition and Brain Sci. Unit, Med. Res. Council, Cambridge, United Kingdom

Abstract: Recent neuroimaging studies have shown that different categories of scenes elicit distinct patterns of fMRI responses in scene-selective areas such as the parahippocampal place area (PPA). In a series of behavioral experiments, we demonstrated that higher-order image statistics extracted from natural scenes provide meaningful category information, suggesting these features as the basis for the neuroimaging findings. Here we used intact and synthesized texture scenes that have preserved higher-order image statistics as the intact scenes (Portilla & Simoncelli, 2000) to test if stimuli with matched image statistics but are perceptually distinct, elicit similar fMRI response patterns across the visual hierarchy. Using a representational similarity analysis, we examined the amount of within category scene exemplar information (beach 1 vs. beach 2), scene category information (beach vs. city), and image format information (intact beach vs. texture beach) across 27 functionally defined regions of interests including early visual, category-selective and topographically organized fronto-parietal attention areas under two different tasks: passive viewing and scene categorization. Early visual areas (e.g., V2) elicited distinct patterns of responses to different exemplars, categories and image formats and the degree of the pattern separability across them were comparable (e.g., the degree of response separability between beach 1 vs. beach 2 was just as much as that for beach vs. city and intact beach vs. texture beach). Responses in scene-selective areas (e.g., PPA) showed the strongest separability to differences in image format, followed by scene categories and within category exemplars. While this order remained the same, the exemplar, category and image format information was greater under the categorization task than passive viewing. Responses in fronto-parietal areas (e.g., precentral cortex) did not elicit different patterns of responses to different exemplars, scene categories or image formats under passive viewing. However, under the categorization task, these regions showed distinct patterns of responses to image format and scene categories. Together our results demonstrate a gradual transformation of the representations of exemplar, scene category and image format information across the visual hierarchy that is dynamically represented under different task demands.

Disclosures: **J.G. Kim:** None. **N. Kriegeskorte:** None. **S. Kastner:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.09

Topic: D.04. Vision

Support: NIMH Intramural Research Program

Title: Comparing conceptual and cortical visual representations of multidimensional naturalistic images

Authors: M. L. KING[1], D. J. KRAVITZ[2], *C. I. BAKER[1];
[1]Lab. Brain and Cognition, NIH, Bethesda, MD; [2]The George Washington Univ., Washington, DC

Abstract: We can judge image similarity on many different dimensions such as visual properties, semantics, or emotional quality. However, how these rich multi-dimensional representations emerge from cortical representations remains unclear. Regions in occipitotemporal cortex (OTC) exhibit category-selectivity (e.g. faces), and it has been reported that OTC represents stimuli according to underlying organizational principles such as animate vs. inanimate and real-world object size. Human object-similarity judgments are reflected in OTC representations and it may thus provide a substrate for perceptual and/or conceptual mental spaces. However, prior studies have often focused on isolated objects from a small set of categories with no context, and the generalizability across image sets is unclear. Here, we investigated the relationship between behavioral representations of naturalistic scenes (objects in context) and cortical representations throughout OTC. To characterize behavioral representations, two groups of participants (each n = 10) viewed independent sets of 144 unique scenes. Each set contained 48 categories (e.g. adults, pets, food, kitchens, dolls) with 3 exemplars per category. Participants arranged the stimuli on a computer screen according to their perceived similarity (Mur et al., 2013). Representational similarity analyses revealed that subjects organized the stimuli in broad clusters of people, animals, household items, natural outdoor scenes, manmade outdoor scenes, and transportation with high correlation across image sets and subjects ($r = .77$, $p < .0001$), indicating stable representational structure. Importantly, these groupings appear to reflect a rich conceptual structure that goes beyond any simple organizational principles. A subset of participants (n = 5 for each set) also viewed the images during an fMRI scan at 7T prior to performing the behavioral task. Analyses on the patterns of response at both local (e.g. category-selective regions) and global (all of OTC) scales revealed a representational structure primarily distinguishing scenes containing faces and bodies from all other images, with high concordance across subjects. However, this did not readily map onto the

conceptual structure observed in behavior. Our findings suggest that representations in OTC primarily reflect its large-scale spatial organization, with regions selective for faces and bodies, and do not capture conceptual representations that extend beyond simple dimensions readily captured in visual areas. These conceptual representations must emerge from highly distributed responses across brain regions, both within and outside OTC.

Disclosures: **M.L. King:** None. **D.J. Kravitz:** None. **C.I. Baker:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.10

Topic: D.04. Vision

Support: NSERC Discovery

Canadian Foundation for Innovation

Ontario Research Fund

Title: Conceptual representations of scene categories in prefrontal cortex transcend sensory modalities

Authors: ***Y. JUNG**[1], B. LARSEN[2], D. B. WALTHER[1];
[1]Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada; [2]Dept. of Psychology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: People typically perceive their natural environment as rich tapestries of sights and sounds. How does visual and auditory information contribute to forming a mental representation of a particular type of environment? In the visual domain, neural representations of scene categories, global scene properties, scene content as well as relations between objects and scenes have been identified and characterized in early visual cortex as well as higher-level visual areas, such as the parahippocampal place area (PPA), the retrosplenial cortex (RSC), the occipital place area (OPA), and the lateral occipital complex (LOC). The representations of scenes in these brain regions are largely driven by regularities in visual properties of scenes. Here we ask how and where in the brain more general concepts of natural environments are represented. We presented, in separate blocks, images and sounds associated with four scene categories (beaches, forests, cities, and offices) to participants inside an MRI scanner. It was possible to decode visually presented scene categories in early visual cortex as well as the PPA, RSC, OPA and LOC.

Analysis of patterns of decoding errors allowed us to characterize the extent to which neural codes are related to low-level visual features or to patterns of human behavior based on scene images. Low-level image properties provided a good explanation for error patterns in V1, whereas error patterns from behavioral scene categorization provided a good match with neural codes in the PPA and OPA. Sound categories could be decoded from five anatomically defined sub-regions of primary auditory cortex (A1) and adjacent parts of the superior temporal gyrus (STG). Errors from a behavioral categorization experiment with sounds matched well with decoding errors in A1, especially directly on Heschl's Gyrus. Finally, we identified regions in the prefrontal cortex with neural representations of scene categories that generalize between images and sounds of scenes. Since scene images and sounds share no low-level sensory features, the category-specific activation patterns in these brain regions reflect a more abstract, conceptual representation of real-world environments. Moreover, error patterns in prefrontal regions could not be related to stimulus properties or behavior based on any one sensory modality alone. In conclusion, we found neural representations of scene categories triggered by images in visually active regions and those triggered by sounds in auditory cortex. Additionally, we identified conceptual representations of scene categories, which transcend sensory modalities, in prefrontal cortex.

Disclosures: **Y. Jung:** None. **B. Larsen:** None. **D.B. Walther:** None.

Nanosymposium

196. Cortical Visual Representations of Scenes

Location: S102

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 196.11

Topic: D.04. Vision

Support: NSF GRFP DGE-0645962

ONR MURI N000141410671

HCP 1U54MH091657

Title: Two distinct scene processing networks connecting vision and memory

Authors: ***C. BALDASSANO**[1], A. ESTEVA[2], D. M. BECK[4], L. FEI-FEI[3];
[1]Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Electrical Engin., [3]Computer Sci., Stanford Univ., Stanford, CA; [4]Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Research on visual scene understanding has identified a number of regions involved in processing natural scenes, but has lacked a unifying framework for understanding how these different regions are organized and interact. We propose a new organizational principle, in which scene processing relies on two distinct networks that split the classically defined Parahippocampal Place Area (PPA). The first network consists of the Transverse Occipital Sulcus (TOS, or the Occipital Place Area) and the posterior portion of the PPA (pPPA). These regions have a well-defined retinotopic organization and do not show strong memory or context effects, suggesting that this network primarily processes visual features from the current view of a scene. The second network consists of the caudal Inferior Parietal Lobule (cIPL), Retrosplenial Cortex (RSC), and the anterior portion of the PPA (aPPA). These regions are involved in a wide range of both visual and non-visual tasks involving episodic memory, navigation, and imagination, and connect information about a current scene view with a much broader temporal and spatial context. We provide evidence for this division from a diverse set of sources. Using a data-driven approach to parcellate resting-state fMRI data, we identify coherent functional regions corresponding to scene-processing areas. We then show that a network clustering analysis separates these scene-related regions into two adjacent networks, which show sharp changes in connectivity properties. Additionally, we argue that the cIPL has been previously overlooked as a critical region for full scene understanding, based on a meta-analysis of previous functional studies as well as diffusion tractography results showing that cIPL is well-positioned to connect visual cortex with other cortical systems. This new framework for understanding the neural substrates of scene processing bridges results from many lines of research, and makes specific predictions about functional properties of these regions.

Disclosures: **C. Baldassano:** None. **A. Esteva:** None. **D.M. Beck:** None. **L. Fei-Fei:** None.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.01

Topic: D.10. Spinal Cord Injury and Plasticity

Support: RFBR grant № 13-04- 01091

Russian Scientific Fund project № 14-45-00024

Start-up funds allocated to PS by the Stony Brook University

Title: Striking functional characteristics of the lumbar and sacral neuronal circuitries for stepping in the *in vivo* adult spinal rat

Authors: *P. SHAH[1], C. PRESTON[1], H. ZHONG[2], R. R. ROY[2], V. R. EDGERTON[2], Y. P. GERASIMENKO[3];
[1]Stony Brook Univ., Stony Brook, NY; [2]Univ. of California Los Angeles, Los Angeles, CA; [3]Pavlov Inst. of Physiol., St Petersburg, Russian Federation

Abstract: We recently demonstrated that electrically enabling motor control (eEmc) simultaneously at lumbar (L2) and sacral (S1) segments of the spinal cord influence the excitability of the spinal networks to evoke a much stronger stepping response in spinal rats than when stimulating at either segment alone. An L2 pulse applied at specific times after an S1 pulse evokes a variable stepping pattern, i.e., poor to coordinated stepping depending on the time of onset of the L2 pulse relative to the S1 pulse. In contrast, an L2 pulse prior to an S1 pulse consistently generates robust stepping. In all scenarios, the S1 pulse consistently amplifies the EMG bursting activity in the hindlimb muscles. These results suggest that in spinal rats L2 serves to generate a locomotor rhythm, whereas S1 functions as a potent 'modulator' of sensory input to modulate the amplitude of the response. To test this idea, we hypothesized that a re-transection at L2 would dramatically impede stepping, whereas re-transection at S1 would retain the pattern generation and formation features of the more rostral cord, but attenuate the EMG bursting and kinematics features of stepping. Adult rats (n=8) underwent a mid-thoracic spinal cord transection (ST) at T10. The rats then were divided into two groups: one group had a re-transection at L2 and the other group had a re-transection at S1. The rats were tested for stepping ability (kinematics motion analysis and EMG) before and after the re-transection with eEmc at L2 or S1. Stimulation at L2 in the absence of S1 (transections at T10 and S1) facilitated bilateral and rhythmic, albeit irregular, stepping, whereas stimulation at S1 in the absence of L2 (transections at T10 and L2) elicited a very weak stepping pattern. EMG burst characteristics and patterns in hindlimb flexor and extensor muscles were consistent with the kinematics data. The data provide the first in-vivo evidence that the rostral segments of the lumbar spinal cord play a predominant role in the initiation and generation of rhythmic activation patterns necessary for locomotion in the adult spinal rat. The data further suggest that the sacral spinal cord participates modestly in rhythm initiation and generation, but provides a strong facilitatory influence.

Disclosures: P. Shah: None. **C. Preston:** None. **H. Zhong:** None. **R.R. Roy:** None. **V.R. Edgerton:** None. **Y.P. Gerasimenko:** None.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.02

Topic: D.10. Spinal Cord Injury and Plasticity

Support: DoD W81XWH1110707

Title: Enhancing cortical representational plasticity with non-invasive direct current stimulation to accelerate upper limb recovery in quadriplegia

Authors: *K. A. POTTER-BAKER[1], D. P. JANINI[2], N. M. VARNERIN[2], D. A. CUNNINGHAM[2], V. SANKARASUBRAMANIAN[2], K. E. SAKAIE[3], F. S. FROST[4], E. B. PLOW[2];
[2]Dept. of Biomed. Engin., [3]Dept. of Diagnos. Radiology, [4]Dept. of Physical Med. and Rehabil., [1]Cleveland Clin. Fndn., Cleveland, OH

Abstract: Current published work suggests that a minimum of 9 months of rehabilitation is required to elicit significant improvement in upper limb function following incomplete spinal cord injury (iSCI). With over 12,500 new cases and a prevalence of 337,000 in the U.S. alone, however, such extensive rehabilitation programs are impractical. Here, we tested the hypothesis that the brain and its residual descending pathways represent the most spared, and hence ideal, innovative targets for maximizing and accelerating upper limb recovery in iSCI. In particular, since loss of representation of weaker muscles in the motor cortex exaggerates muscle weakness and limits recovery following iSCI, we aimed to boost inherent adaptive plasticity of weak representations using transcranial direct current stimulation (tDCS). We hypothesized that tDCS would accelerate increases in weak muscle cortical representational plasticity while also enhancing excitability of their descending pathways to paretic limbs to ultimately maximize functional outcomes following rehabilitation. To test our hypothesis, eight patients with chronic iSCI received either upper limb rehabilitation with tDCS (2 mA anodal) to motor cortical representations of weak muscles or rehabilitation alone. Representational plasticity was measured using TMS before and after treatment and diffusion tensor magnetic resonance imaging (DTI) quantified sparing of descending tracts. Functional recovery and muscle strength was assessed before and after treatment. We found that patients who received tDCS plus rehabilitation demonstrated significant focal increases in the cortical representation of their weaker muscle, where its excitability increased by 60% ($p<0.05$). Representational plasticity changes were associated with gains in motor function and muscle strength. In addition, level of recovery was related to cortical tract integrity, wherein patients that demonstrated the most recovery had greatest tract sparing following their iSCI ($r=0.97$; $p<0.0001$). Our results suggest that long-term pairing with tDCS applied to the motor cortex could result in significant functional improvements by facilitating more permanent plasticity of weaker cortical representations. Further, descending tract integrity, as measured with DTI, may serve as a valuable prognostic marker of impairment and functional recovery potential.

Disclosures: **K.A. Potter-Baker:** None. **D.P. Janini:** None. **N.M. Varnerin:** None. **D.A. Cunningham:** None. **V. Sankarasubramanian:** None. **K.E. Sakaie:** None. **F.S. Frost:** None. **E.B. Plow:** None.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.03

Topic: D.10. Spinal Cord Injury and Plasticity

Support: UCLA CTSI Grant UL1TR000124

NIH NIBIB Grant U01EB015521

Title: A novel method for recording long term EMG activity in the laboratory and at home in individuals with cervical SCI

Authors: ***P. HAAKANA**[1], D. SAYENKO[2], A. J. PESOLA[4], T. FINNI[4], V. R. EDGERTON[3], D. C. LU[1];
[1]UCLA Neurosurg., Los Angeles, CA; [2]Integrative biology and physiology, [3]Physiological science, UCLA, Los Angeles, CA; [4]Biol. of physical activity, Univ. of Jyvaskyla, Jyvaskyla, Finland

Abstract: We have previously recorded long term EMG activity using shorts with embedded electromyography (EMG) sensors on healthy subjects (Finni et al. 2007) and office workers (Pesola et al. 2014). However, we do not have detailed information about long term muscle activity in the spinal cord injury (SCI) population. Such information allows us to have specific details on the normal and abnormal patterns of muscle activity during an individual's daily life outside of the laboratory and see the changes in activation patterns after rehabilitation interventions. EMG was recorded from eight upper limb muscles using a custom-made shirt with embedded EMG electrodes. Data was stored into a data collection module attached to the shirt. Five participants (injury levels C5-7) were asked to come in to the laboratory to perform exercises such as handgrip tasks, relaxation, and wheeling in the corridor with a wheelchair. After the testing the participants went home and wore the shirt for the rest of the day (mean 7hrs, range 3-13hrs). EMG was analyzed as mean values during exercises in the laboratory. Home recordings were analyzed using burst analysis modified from Kern et al. 2001 and Tikkanen et al. 2013. Average burst time when muscles were considered active was 52±10.8 % of the recording time. Average burst duration was 0.4 ±0.1 sec and average burst rate 1.8±0.5 bps.

Average duration of the longest period of inactivity was 2.9±2.7 min, and average amplitude during daily testing was 50.8±4.8 % (36.7-68.6 %) of the activity level during wheeling. Wearable EMG recording system allows us to access more detailed information about rehabilitation progress outside of the laboratory. Because all wires are integrated into the shirt, no additional devices are needed, and patients experience no restriction in their movements. We believe that this novel wearable EMG system could be used in the future as a tool to assess spasms, daily physical activity levels, muscle coordination, and changes in activation patterns in individuals with neurological disorders.

Disclosures: **P. Haakana:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lu Daniel C, Edgerton Reggie V. **D. Sayenko:** None. **A.J. Pesola:** None. **T. Finni:** None. **V.R. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Victor R Edgerton. **D.C. Lu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Daniel C Lu.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.04

Topic: D.10. Spinal Cord Injury and Plasticity

Support: NIH Grant R01HD059895

Craig H Neilson Foundation

Title: The relationship between gait function and reflex-mediated hypertonia in people with incomplete spinal cord injury

Authors: *L. D. DUFFELL[1], M. M. MIRBAGHERI[2];
[1]Univ. Col. London, London, United Kingdom; [2]Rehabil. Inst. Chicago, Chicago, IL

Abstract: An incomplete spinal cord injury (SCI) results in the partial loss of motor and sensory function below the level of the injury. One secondary consequence is neuromuscular abnormalities causing hypertonia of muscle groups, which are thought to be the result of a combination of intrinsic and reflex-mediated muscle stiffness. Hypertonia commonly affects ankle-joint muscles, which have important roles during gait, however the relationship between

hypertonia and gait function remains controversial in people with SCI. Clinical indications of spasticity have been proposed to be unrelated to gait impairment, however these tests do not provide information regarding the origin of spasticity. This study aimed to compare gait function of people with SCI, with and without reflex-mediated hypertonia. This study had IRB approval and 45 subjects with chronic, incomplete SCI were recruited. Neuromuscular properties were assessed with subjects seated in an isokinetic dynamometer with one ankle strapped to a footplate. Ankle position, torque and electromographic (EMG) activity of ankle muscles were measured during a series of passive isokinetic movements to maximum dorsi-flexion (DF) at two velocities: 5 and 100°/sec. Maximum voluntary isometric contractions (MVICs) and active range of motion (AROM) at the ankle joint were also measured. Functional scores (WISCI II) and clinical measures of walking speed (10 meter walk test), endurance (6 minute walk test) and mobility (timed up and go) were assessed. Based on EMG activity during isokinetic DF at 100°/sec, 19 subjects were classified as having reflex-mediated hypertonia (reflex on) and 26 without (reflex off). Subjects classified as reflex on had significantly higher peak torque and stiffness during fast movements ($p<0.001$), and torque dynamic gain ($p<0.001$), than those classified as reflex off. There were no significant differences between groups in terms of age, gender, WISCI II scores, AROM and MVICs. Walking speed, endurance and mobility were similar between subjects that did and did not have reflex-mediated hypertonia. Our data suggest that gait function may not relate to the presence of reflex-mediated hypertonia in people with chronic, incomplete SCI. It has been suggested that while inhibitory mechanisms are reduced in spastic muscles under passive conditions, inhibition is similar between people with SCI and healthy subjects during voluntary contractions, which may explain our findings, although this issue remains controversial. Gait function may still be affected by intrinsic muscle stiffness, and the positive or negative effects of reflex-mediated hypertonia on gait function may be subject-specific.

Disclosures: **L.D. Duffell:** None. **M.M. Mirbagheri:** None.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.05

Topic: D.10. Spinal Cord Injury and Plasticity

Title: Analysis of cortical plasticity after spinal cord injury using resting state-fMRI

Authors: *K. MATSUBAYASHI[1], A. IWANAMI[1], J. KOHYAMA[2], Y. KOMAKI[3], M. MATSUMOTO[1], H. OKANO[2], M. NAKAMURA[1];
[1]Orthopaedic Surgery, [2]Physiol., Keio Univ. Sch. of Med., Tokyo, Japan; [3]Central Inst. for Exptl. Animals, Kawasaki, Japan

Abstract: [Purpose] We have reported the effectiveness of cell transplantation therapy for spinal cord injury (SCI) using neural stem cells (NS cells) and induced pluripotent stem cells (iPS cells). However, the mechanisms of functional recovery as well as reconstruction of neuronal network remain to be elucidated. Recent studies have demonstrated that SCI changed the state of large cortical networks. SCI leads to atrophy of primary motor and sensory cortex, and then reorganization of the sensorimotor system occurs(Freund P. Brain 2011), which was detected by the functional magnetic resonance imaging (fMRI). However, few studies have reported SCI-related functional changes of the cortex in detail. Here we analyze the relations between the cortical plasticity and the functional improvement after SCI using resting state- fMRI. [Method]Four C57BL6 female mice were subjected to resting-state fMRI. After careful acclimation to environmental stress, MRI was performed using a 7.0-Tesla MRI apparatus equipped with actively shielded gradients at maximum strength of 700mT/m (Biospec ; 70/16 Brucker Biospin) with CryoProbe (Brucker BioSpin AG). Mice received complete spinal cord transections at the Th9/10 level using a surgical blade. The severed ends of the cord were inspected under a surgical microscope carefully to ensure complete transection. MRI was performed before and two weeks after SCI. MRI data analysis was performed using SPM12 software and CONN toolbox. This consisted of head movement correction, adjustments of acquisition timing across slices, and smoothing. Structural and functional images were spatially normalized to a standard structural brain averaged from C57BL6 mice (n=20). Functional connectivity was analyzed based on the AMBMC labels (Ulmann, JFP,et al. Neuroimage 2013). [Result] First we successfully detected the normal functional brain network connectivity (FBNC) using fMRI in the mice before SCI. Then we compared the change of FBNC before and after SCI. The bilateral primary somatosensory area changed the synchronicity after SCI. In addition, the bilateral primary motor cortex has connected with contralateral cingulate area strongly in the normal mice, but the primary motor cortex has connected strongly with another area in the mice after SCI. [Conclusion] These results demonstrate that it is feasible to analyze FBNC of mice using fMRI. Our findings also provide the evidence that SCI induced FBNC alterations in the brain cortex. In the future, we would like to take fMRI in various degree of SCI model to explore the specific spatial and temporal pattern of brain functional changes after SCI.

Disclosures: K. Matsubayashi: None. **A. Iwanami:** None. **J. Kohyama:** None. **Y. Komaki:** None. **M. Matsumoto:** None. **H. Okano:** None. **M. Nakamura:** None.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.06

Topic: D.10. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS076976

Title: Spinal cord epidural stimulation and climb training enhance axon regeneration in rats transplanted with olfactory ensheathing cells after a complete spinal cord transection

Authors: A. K. YEUNG, G. GARCIA-ALIAS, K. G. GRIFFIS, R. R. KHANKAN, H. ZHONG, *R. R. ROY, P. E. PHELPS, V. EDGERTON;
Integrative Biol. and Physiol., UCLA, Los Angeles, CA

Abstract: Implantation of olfactory ensheathing cells (OECs) after a spinal cord lesion has been shown to promote axon regeneration across the lesion site and to promote some functional recovery. In addition, a regimen of rehabilitative motor training facilitates the extent of functional recovery. The spinal cords of 20 adult Sprague Dawley rats were completely transected at ~T8 and randomly assigned to 4 groups (n=5/group). The rats received a transplantation of either OECs or skin fibroblasts (FBs) immediately after the spinal cord transection and were either trained to climb a grid or not trained. Two groups (OEC-Trained, and FB-Trained) began training 2 weeks post-injury. The rats were trained to climb up a grid (1-inch spacing) inclined at 60 degrees for 20 min/day, 3 days/week. During training, the rats received sub-threshold epidural stimulation (40 Hz at L2 and S1). Two other groups (OEC-CSA and FB-CSA) were immunosuppressed with cyclosporine A (CSA) for the duration of the study but did not receive any training or epidural stimulation. Transcranial electrical stimulation (TES, singular monophasic pulse, 0.2 Hz) was performed in a non-anaesthetized state to electrophysiologically assess connectivity across the lesion site. Two months post-injury, TES elicited more early responses (ERs) and silent period responses (SPRs) in the hindlimb muscles of trained than non-trained rats. The greatest number of ERs was observed in the OEC-Trained group. At 7 months post-injury, TES was performed after the rats were given a dose of strychnine (0.5 mg/kg body weight, i.p.), a glycine receptor antagonist. Under these conditions, the majority of trained rats showed ERs, whereas only one untrained rat had an ER. TES after strychnine administration also elicited spontaneous bursting responses (SBRs) in the majority of untrained rats but in only 1 trained rat. The variety of responses elicited highlights the advantages of performing TES in awake rats and in rats under the influence of strychnine. These methods allow for the detection of changes in a range of networks projecting to specific muscles. These data also suggest that using strychnine can maximize evidence of supraspinal connectivity by exposing networks that would not be observed without systemic disinhibition. Overall, these

results suggest that a training regimen involving grid climbing with epidural stimulation can enhance the regenerative effects of OEC transplantation.

Disclosures: **A.K. Yeung:** None. **G. Garcia-Alias:** None. **K.G. Griffis:** None. **R.R. Khankan:** None. **H. Zhong:** None. **R.R. Roy:** None. **P.E. Phelps:** None. **V. Edgerton:** None.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.07

Topic: D.10. Spinal Cord Injury and Plasticity

Support: Russian Scientific Fund project № 14-45-00024

NIH U01EB15521,

NIH R01EB007615

Title: Non-invasive approaches of neural locomotor network activation in non-injured subjects placed in vertical suspended position

Authors: ***P. GAD**[1], D. SAYENKO[2], Z. MCKINNNEY[2], R. GORODNICHEV[3], T. MOSHONKINA[4], I. KOZLOVSKAYA[5], V. EDGERTON[2], Y. GERASIMENKO[2,4];
[1]Univ. Of California Los Angeles, Woodland Hills, CA; [2]Univ. Of California Los Angeles, Los Angeles, CA; [3]Vehlie Lukie Sports Inst., Vehlie Lukie, Russian Federation; [4]Pavlov Inst. of Physiol., St. Petersburg, Russian Federation; [5]Inst. of Biomed. Problems, Moscow, Russian Federation

Abstract: The mammalian lumbar spinal cord has the capability to generate locomotor activity in the absence of input from the brain. Previously, we reported that transcutaneous electrical stimulation of the spinal cord at vertebral level T11 can activate the locomotor circuitry in non-injured subjects when their legs are placed in a gravity neutral position using horizontal suspension device. In this conditions the mechanical stimulation to the soles of the feet could induce the locomotor like activity as well. The objective of this study was to evaluate the effect of non-invasive activation of the neural networks on the spinal cord via transcutaneous stimulation and/or sensory mechanical stimulation of the foot while normal subjects were suspended in vertical position with 100% body weight support over a treadmill with no contract with the treadmill surface. We observed that multi-site independent spinal cord stimulation at T11, T12, and L1 at 30 Hz can activate the neural locomotor networks to generate alternating

movements of the two legs with well coordinated EMG patterns in proximal and distal muscles. Sensory stimulation on the other hand resulted in lower excursions in the various joints with less robust EMG patterns. The overall integrated EMG was lower in all muscles except the ankle extensors during sensory stimulation compared to spinal cord stimulation. The best results were observed in all subjects during simultaneous sensory stimulation and spinal cord stimulation with significantly higher EMG levels, robust excursion of various joints and activation patterns. This synergistic effect suggest the convergence of sensory afferent inputs from foot receptors and transcutaneous spinal cord stimulation on similar neuronal networks. This phenomenon has high impact as a strategy to neuromodulate the spinal circuitry and to regain motor functions after a severe SCI.

Disclosures: **P. Gad:** None. **D. Sayenko:** None. **Z. McKinnney:** None. **R. Gorodnichev:** None. **T. Moshonkina:** None. **I. Kozlovskaya:** None. **V. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovery Technologies. **Y. Gerasimenko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovery Technologies.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.08

Topic: D.10. Spinal Cord Injury and Plasticity

Support: NIH Grant U01EB015521

Title: Buspirone treatment promotes forelimb functional recovery in cervical spinal cord injured rats

Authors: B. JIN[1], M. ALAM[2], G. GARCIA-ALIAS[1], Y. GERASIMENKO[1], H. ZHONG[1], R. ROY[1], D. LU[2], *V. EDGERTON[1];
[1]Dept Integrative Biol. & Physiol., [2]Dept Neurosurg., UCLA, Los Angeles, CA

Abstract: Serotoninergic agonists have been shown to improve the recovery of stepping ability in spinal animals by modulating the excitability of the locomotor circuits in the lumbosacral spinal cord. In the present study we tested whether or not buspirone, a partial serotonin 5-HT1A receptor partial agonist, would facilitate fine forelimb motor recovery, such as reaching and grasping, after a cervical spinal cord injury in rats. Adult Long-Evans rats were trained and then

tested to reach and grasp sugar pellets. Intramuscular EMG electrodes were implanted in forelimb muscles and epidural stimulation electrodes were implanted at cervical spinal cord segments C6 and C8. Spinal motor evoked potentials (sMEPs) were elicited by stimulating the C6-C8 spinal segments. sMEP latencies and amplitudes were determined in each muscle implanted with EMG electrodes. After baseline testing the rats received a bilateral dorsal funiculi crush injury at spinal cord level C4. At 4 weeks post-injury, five rats were tested electrophysiologically and behaviorally with and without the administration of buspirone (5 gm/kg, ip.). The success rate for reaching and grasping 4 weeks post injury was greater with than without buspirone administration for all rats except one ($p = 0.0339$; paired t-test). After buspirone administration, the sMEPs increased in the number and amplitude of late responses, suggesting an increased activation state of the cervical interneuronal motor network. The improved success rates of reaching and grasping and the increase in sMEPs reflect a recovery of motor function and improved forelimb motor circuit activity throughout the spinal cord-muscle pathway. Combined these data suggest that buspirone treatment has therapeutic potential for motor recovery after a cervical spinal cord injury.

Disclosures: **B. Jin:** None. **M. Alam:** None. **G. Garcia-Alias:** None. **Y. Gerasimenko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroRecovery Technologies. **H. Zhong:** None. **R. Roy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroRecovery Technologies. **D. Lu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroRecovery Technologies. **V. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroRecovery Technologies.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.09

Topic: D.10. Spinal Cord Injury and Plasticity

Support: NIH Grant U01EB015521

Title: Epidural spinal cord stimulation improves forelimb reaching and grasping in cervical spinal cord injured rats

Authors: *M. ALAM[1], B. JIN[2], G. GARCIA-ALIAS[2], Y. GERASIMENKO[2], H. ZHONG[2], R. ROY[2], D. LU[1], R. EDGERTON[2];
[1]Dept. of Neurosurg., [2]Dept. of Integrative Biol. and Physiol., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Electrically enabling motor control (eEmc) via epidural stimulation of spinal cord is a promising therapeutic technique for the recovery of motor function after spinal cord injury. In the present study, we tested whether electrical stimulation delivered epidurally in the cervical spinal cord would facilitate the recovery of fine forelimb motor function after a dorsal funiculi crush (DFC) injury at C4. Adult Long-Evans rats were trained to reach and grasp sugar pellets. Intramuscular EMG electrodes were implanted in forelimb muscles and epidural stimulation electrodes were implanted at cervical spinal cord segments C6 and C8. Immediately after the spinal cord injury, the rats demonstrated significant deficits in forelimb fine-motor function of reaching and grasping. The rats were tested to reach and grasp sugar pallets with and without eEmc during 10 weeks post-injury. To determine the best stimulation parameters to activate the cervical spinal networks involved in fine forelimb motor function, monopolar and bipolar pulses were delivered at varying frequencies (20, 40, and 60Hz) concomitant with the reaching and grasping task. Video and forelimb EMG were recorded during this behavioral task. The DFC injury resulted in a significant drop in the success rates for reaching and grasping scores. Bipolar stimulation (C6- C8+ and C6+ C8-) resulted in a better success rate compared to monoplar stimulation (C6- Ref+ and C8- Ref+). Lower frequency stimulation (20 Hz) had a better effect in improving forelimb function compared to higher frequencies (40 and 60Hz). Interestingly, the reaching and grasping scores remained elevated after cessation of the stimulation, suggesting that eEmc had a durable effect beyond the stimulation period. Video analyses revealed improved movement trajectories during forelimb reaching and grasping with eEmc compared to without. Combined, these data suggest that eEmc has therapeutic potential for rehabilitation after a cervical SCI.

Disclosures: M. Alam: None. **B. Jin:** None. **G. Garcia-Alias:** None. **Y. Gerasimenko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroRecovery Technologies. **H. Zhong:** None. **R. Roy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroRecovery Technologies. **D. Lu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroRecovery Technologies. **R. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroRecovery Technologies.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.10

Topic: D.10. Spinal Cord Injury and Plasticity

Title: Ankle Foot Orthosis: Effects on the gait of children with myelomeningocele under a dual task paradigm

Authors: N. PIROUZ[1], *T. KARAKOSTAS[3,2,4], B. MALAS[1];
[1]Prosthetics & Orthotics, [2]Rehabil., Lurie Children's Hosp. of Chicago, Chicago, IL; [3]Motion Analysis Ctr., Rehabil. Inst. of Chicago, Chicago, IL; [4]Sch. of Medicine, Orthopaedics, Northwestern Univ., Chicago, IL

Abstract: Ankle foot orthoses (AFOs), a common intervention to improve the gait of children with myelomeningocele (MMC), facilitate balance, stability and efficiency of gait. Evidence suggests that walking involves a cognitive component. As one walks there may be the need to concurrently allocate attentional resources to the motor component of gait and to cognitive tasks such as conversing. Clinical observations suggest that walking aids may improve performance of cognitive tasks and gait. The purpose of this study was to assess the effects of AFOs while walking and performing a cognitive task. Eighteen children with MMC (7-13 years old, GMFCS I-III) were assessed in two visits. During the first visit children walked at self selected speeds on a GAITRite instrumented walkway with shoes, but no AFOs, under two conditions: a dual task involving walking while counting (WC) and walking only (W). During the second visit, 2 weeks later, WC and W were performed with the AFOs. The order of tasks was randomized. Repeated measures analysis of variance was performed on walking velocity, cadence, stride length, rate of responses and rate of correct responses ($a<0.05$). Data were analyzed for 16 subjects. Table 1 shows the statistically significant variables. Velocity and stride length significantly increased with the use of AFOs in W. During WC only velocity significantly increased. Rate of responses and rate of correct responses significantly improved with the use of AFOs during WC. This is, to our knowledge, the first study examining the effect of AFOs under a dual task paradigm in this population. Our data support previous findings that AFOs improve the gait of children with MMC during W. The use of AFOs also allowed concurrent improvements in gait and the performance of the cognitive task. This is most likely due to the AFOs decreasing the attentional demands on ambulation. These resources then can be used to facilitate performance of the cognitive task. It appears, therefore, that ambulatory aids do facilitate performance of concurrent motor and cognitive tasks. Table 1. Gait data and Verbal responses. Velocity (V), Stride length (SL), Rate of responses (R), Rate of Correct Responses (RC) with (AFO) and without (NAFO) AFO during single walking (W) and dual, walking and counting (WC) tasks.

Variable	Mean	SD	p
W NoAFO V	65.9	29.5	.00
W AFO V	77.3	27.6	
W NoAFO SL	79.6	17.4	.00
W AFO SL	94.2	38.3	
WC NoAFO V	43.8	24.6	.00
WC AFO V	55.8	24.4	
WC NoAFO R	0.4	0.3	.02
WC AFO R	0.5	0.3	
WC NoAFO RC	0.3	0.3	.00
WC AFO RC	0.4	0.3	

Disclosures: **N. Pirouz:** None. **T. Karakostas:** None. **B. Malas:** None.

Nanosymposium

197. Advances in Spinal Cord Injury Research

Location: S403

Time: Sunday, October 18, 2015, 1:00 PM - 3:45 PM

Presentation Number: 197.11

Topic: D.10. Spinal Cord Injury and Plasticity

Title: Effects of varying bone marrow-derived MSC concentrations and transplant locations for reducing motor and morphological deficits in a rat model of spinal cord injury

Authors: ***J. J. MATYAS**[1], A. STEWART[2], A. GOLDSMITH[3], S. ZEILER[3], Z. NAN[3], J. ROSSIGNOL[4], G. DUNBAR[2];
[1]Field Neurosciences Inst. Lab. for Resto, Mount Pleasant, MI; [2]Program in Neurosci., [4]Col. of Med., [3]Field Neurosciences Inst. for Restorative Neuroscence, Mt Pleasant, MI

Abstract: Spinal cord injury (SCI) is widely considered to be a permanently disabling condition, constraining those affected by it to wheelchairs and requiring intense daily care and assistance. Spontaneous recovery is limited, and most current therapies have been inadequate in fully restoring function. Strategies targeting regeneration and protection of cells in the injured cord are currently gaining momentum in the field of SCI research, particularly those of cell replacement

therapies. Human trials involving the transplantation of autologous stem cells have been conducted in several countries. However, determining the types of cells and the concentrations which are most efficacious is still widely debated. Therefore, it is important to determine what cell types, concentrations, and locations would provide the maximum benefit in functional recovery. The current study explored the optimization of bone marrow-derived mesenchymal stem cells (MSCs) by transplanting various concentrations of them into the injured rat spinal cord, and testing various transplant locations. No significant differences between MSC-treated animals and lesioned controls in measures of locomotor assessment and the horizontal ladder task were observed, though there were trends toward a therapeutic effect. Footprint analysis revealed mild sparing on the measure of base of support in animals receiving cells of any concentration, but not in those receiving transplants to the lesion penumbra. Histological assessment for myelin content and glial scarring indicated that MSCs may provide a potential protective effect against progressive demyelination following SCI, and may also reduce the density of fibrotic scar tissue. Collectively, results indicate that MSCs may provide a modest therapeutic effect, especially at concentrations approaching 50,000 cells/μL, and when transplanted in and rostral to the lesion epicenter, though further work is needed to elucidate the optimum transplant locations and cell concentrations necessary to provide maximum benefits towards functional recovery. Support for this study was provided by the Office of Research and Sponsored Programs at CMU, the College of Humanities and Social Behavioral Sciences, the College of Medicine, and the Field Neurosciences Institute and John G. Kulhavi Professorship, as well as the Jeff Lichon Spinal Cord Injury Foundation and the James & Catherine Steinmetz Graduate Scholarship.

Disclosures: J.J. Matyas: None. **A. Stewart:** None. **A. Goldsmith:** None. **S. Zeiler:** None. **Z. Nan:** None. **J. Rossignol:** None. **G. Dunbar:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.01

Topic: E.02. Neuroimmunology

Support: NIH Grant P30 GM103328

Title: Hypertension and peripheral inflammation during pregnancy is associated with postpartum depression and anxiety-like behavior in rats

Authors: *K. L. WALLACE, T. BOWLES, S.-K. SPENCER, C. BEAN;
Univ. MS Med. Ctr., Jackson, MS

Abstract: Up to 10% of women with hypertension during pregnancy develop hemolysis elevated liver enzyme low platelet (HELLP) syndrome, which is a life threatening syndrome with high maternal mortality and morbidity. As women with a history of HELLP syndrome are reported to be at an increased risk of developing postpartum depression or post-traumatic stress disorder (PTSD) we set out to determine if we could detect PTSD and depressive like behavior in an animal model of HELLP syndrome. On gestational day (GD) 12, mini-osmotic pumps infusing sFlt-1 and sEng are placed into rats to induce HELLP syndrome and were not removed until 12-24hrs post-delivery. All pups were permanently removed at the time of pump removal. On post-partum day (PPD) 10 rats were subjected to a single marble burying test followed by sucrose preference test for 5 consecutive days on PPD17. In a different group of rats, at GD19 mean arterial pressure was significantly increased in HELLP rats compared to NP rats (124+3.34 vs. 108+2mmHg; p=0.04), as were brain concentrations of interleukin-1beta in the posterior cortex (384.74+74 vs. 119.7pg/mg/mL; p=0.03; n=6/group). At PPD3 dams in the HELLP groups displayed sickness behavior as there was a significant (p=0.05)reduction in conspecific contact grooming and investigatory sniffing over a three day period compared to NP dams. Dams in the HELLP group buried significantly more marbles (56+4.3%, p=0.006) compared to NP (30.2+6.3%) dams at PPD10. A separate group of dams was tested at PPD 17 and HELLP rats also had a significant increase in marble burying (61.1+11%, p=0.03) compared to NP rats (30.2+7.38%). Texas red dextran infusion at PPD30 into revealed a trend towards an increase in BBB leakage in the posterior region compared to NP rats (n=3/group). These results suggest that hypertension and peripheral inflammation during pregnancy contributes to an increase in blood brain barrier permeability and neuroinflammation which previous studies have shown to be accompanied by alterations in behavior. Current studies are ongoing to determine if sucrose preference tests are altered in response to HELLP syndrome during pregnancy. The results from the current study suggest that this might be one mechanism of PTSD and post-partum depression in women with hypertension and inflammation during pregnancy.

Disclosures: K.L. Wallace: None. **T. Bowles:** None. **S. Spencer:** None. **C. Bean:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.02

Topic: E.02. Neuroimmunology

Title: Activation of the brain's reward system attenuates tumor growth in mice

Authors: *F. HAKIM[1,2], T. BEN SHANNAN[3], M. SCHILLER[2], H. AZULAY-DEBBY[2], J. SHAKYA[2], M. RAHAT[2], A. ROLLS[2];
[1]Pediatric Pulmonary Div., Rambam Hlth. Care Campus, Haifa, Israel; [2]Immunol., [3]Neurosci., Tecnion, Israel Inst. of Technol., Haifa, Israel

Abstract: A diagnosis of cancer is a life-changing event, which impacts the patient's mental well-being. Mood characteristics and the quality of life of subjects receiving treatment for cancer have been recently highlighted as one of the main components determining the success of cancer therapy. Previous studies have linked psychological and cognitive factors with the regulation of the immune response, which is known to play a key role in tumor progression, angiogenesis and metastasis. However, mechanistic studies into this association have primarily focused on the effects of stress on immunity. Increasing evidence indicates that a positive emotional state also affects immunity. A key component in the formation of a positive effect is the brain's reward system. We used a pharmacogenetic approach (Designer Receptors Exclusively Activated by Designer Drugs-DREADDs) to activate the dopaminergic neurons in the ventral tegmental area (VTA), a key component of the brain reward system. We found that the activation of the VTA in tumor-bearing mice (Lewis lung carcinoma; LLC) affects tumor growth. We found that repeated stimulations of the VTA significantly reduced the size of the tumor ($p=0.0064$). We attribute these effects to changes in the anti-tumor immune response, specifically, CD11b+Gr1+Ly6+ myeloid cells (G-MDSCs), which were significantly reduced in the tumor microenvironment of the VTA-activated mice compared to controls. We further demonstrated that these effects were mediated, at least in part, via the sympathetic nervous system (SNS). Taken together, our data indicates that the reward system can affect tumor progression by enhancing the anti-tumor immune response. These findings highlight the potential involvement of mood-regulating circuits in the organism's ability to fight cancer.

Disclosures: F. Hakim: None. **T. Ben Shannan:** None. **M. Schiller:** None. **H. Azulay-Debby:** None. **J. Shakya:** None. **M. Rahat:** None. **A. Rolls:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.03

Topic: E.02. Neuroimmunology

Support: CFR

Title: Ganciclovir modulates microglia using the innate immune adaptor STING

Authors: *V. MATHUR[1,2], D. DO[1], J. SHEN[1,2], R. BURAI[3], H. LASHUEL[3], T. WYSS-CORAY[1,2];
[1]Neurol. and Neurosci., Stanford Univ., Palo Alto, CA; [2]Palo Alto Veterans Inst. for Res., Palo Alto, CA; [3]Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Abstract: Microglia, the immune cells of the CNS, are implicated in a variety of neurodegenerative diseases. In some diseases (e.g. Alzheimer's), they clear the brain of debris and amyloid deposits, while in others (e.g. Huntington's), microglia are pro-inflammatory and may contribute to neuronal death. In our recent work, we showed a profound activation of microglia in the brains of mice with experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis, and that the FDA approved drug Ganciclovir (GCV) rescued symptoms of EAE by selectively inhibiting the proliferation of microglia. We now show that GCV and its derivatives remarkably reduce inflammation in microglia via the anti-viral innate immune response. Unbiased profiling of the microglial secretome showed that GCV modulates the secretion of several proteins induced as a part of the anti-viral response. GCV and its derivatives mimic cyclic dinucleotides to induce the production of IFNβ and the chemokine CXCL10 (or IP10). This activity is dependent on the presence of the innate immune adaptor STING and the transcription factor Stat1. In microglia lacking STING, GCV and its derivatives are unable to induce IFNβ, CXCL10 or reduce inflammation. Blocking IFNβ further reduced the induction of CXCL10 by GCV suggesting IFNβ is upstream of CXCL10. Finally, CXCL10 production by GCV was reduced upon inhibition of Jak/Stat signaling. Together, these results elucidate the molecular mechanism for reduction of microglial inflammation by the antiviral drug GCV.

Disclosures: V. Mathur: None. **D. Do:** None. **J. Shen:** None. **R. Burai:** None. **H. Lashuel:** None. **T. Wyss-Coray:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.04

Topic: E.02. Neuroimmunology

Support: R01AA12882

Title: Prenatal exposure to ethanol increases ethanol intake in pubertal offspring: Possible role of CCL2/CCR2 chemokine system in stimulating neurogenesis of orexigenic peptide-expressing neurons

Authors: G.-Q. CHANG, O. KARATAYEV, *S. F. LEIBOWITZ;
Rockefeller Univ., New York, NY

Abstract: Background: Clinical studies show maternal consumption of alcohol during pregnancy to increase alcohol drinking in the offspring, and in animal studies, prenatal exposure to ethanol stimulates neurogenesis and density of neurons expressing orexigenic peptides known to increase ethanol intake. With studies showing ethanol drinking to activate the peripheral immune system, we investigated in male rats whether prenatal ethanol also stimulates neuroimmune function in the hypothalamus, by examining: 1) weanling offspring for changes in the chemokine CCL2 and its receptor CCR2 as they relate to the development of peptide-expressing neurons; and 2) pubertal offspring for changes in consumption of and preference for alcohol. This study focused on the orexigenic peptide, melanin-concentrating hormone (MCH) in the perifornical lateral hypothalamus (PFLH), which has an important role in the ingestion and rewarding properties of ethanol and colocalizes with CCL2 which acts through CCR2 to stimulate neuronal development. Methods: The offspring of Sprague-Dawley dams, given ethanol (2-4 g/kg/day) or water intraorally from gestational day 11-15, were either sacrificed on postnatal day 25 for brain analyses using multi-label immunohistochemistry or examined behaviorally on postnatal days 40-70 for measurements of ethanol intake and preference with a two-bottle choice. Results: Prenatal ethanol exposure compared to water control increased circulating levels of CCL2 in the dam and density of MCH- and CCR2-positive neurons in the PFLH of the offspring. Double-labeling studies showed that CCR2 co-exists with MCH in 20% of the peptide neurons in control rats and ethanol markedly increases to 60% the density of these CCR2/MCH co-labeled neurons. Further analyses of the offspring of dams injected with BrdU, a marker of cell proliferation, demonstrated that *in utero* exposure to ethanol during the period of hypothalamic neurogenesis stimulates the birth of new neurons that co-express CCR2 and MCH, as revealed by a significant increase in triple-labeled BrdU/CCR2/MCH neurons in the PFLH. This increased proliferation of CCR2/MCH neurons in weanling offspring was accompanied by a behavioral change in pubertal offspring, a two-fold increase in the drinking of and preference for ethanol. Discussion: These results demonstrate a strong stimulatory effect of prenatal ethanol on the hypothalamic CCL2/CCR2 chemokine system in association with MCH neurons and link this increase in neuronal development to greater alcohol intake, consistent with other evidence showing knockout of the CCR2 receptor to reduce ethanol intake and PFLH injection of MCH to increase ethanol intake.

Disclosures: G. Chang: None. **O. Karatayev:** None. **S.F. Leibowitz:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.05

Topic: E.02. Neuroimmunology

Support: S.L.E. Lupus Foundation

Title: Effect of maternal AQP4-IgG antibody transfer in Neuromyelitis optica pregnancies

Authors: *S. MADER[1], L. BRIMBERG[1], J. M. CRAWFORD[2], A. BONNIN[3], J. L. BENNETT[4], P. HUERTA[1], B. T. VOLPE[1], B. DIAMOND[1];
[1]Dept. of Autoimmunity, The Feinstein Inst. For Med. Res., Manhasset, NY; [2]Dept. of Pathology and Lab. Medicine,, Hofstra North Shore–LIJ Sch. of Med., Hempstead, NY; [3]Zilkha Neurogenetic Inst. and Dept. of Cell and Neurobio., Keck Sch. of Med. of the Univ. of Southern California, Los Angeles, Los Angeles, CA; [4]Departments of Neurol. and Ophthalmology, Univ. of Colorado Sch. of Med., Denver, CO

Abstract: Antibodies to astrocytic aquaporin-4 (AQP4-IgG) are a highly specific biomarker in Neuromyelitis Optica Spectrum Disorders (NMOSD), which is comprised of astrocytic diseases of the Central Nervous System (CNS) and can result secondarily in demyelination. *In vivo* models showed that AQP4-IgG contributes to the disease pathogenesis. However, those studies required either direct injection of AQP4-IgG into the brain together with human complement or prior blood brain barrier disruption by lipopolysaccharide (LPS). Recently, it was suggested that AQP4-IgG results in an increased frequency of miscarriages in NMOSD, raising the possibility that AQP4-IgG affects either the placenta or the developing fetus. To address this possibility, we injected intravenously different concentrations (60 to 200 ug) of human monoclonal AQP4-IgG or an isotype matched control antibody to pregnant mice at embryonic day E14.5. qPCR results show that AQP4 is expressed at significantly higher levels in the fetal brain compared to the placenta throughout all gestational stages and Western blot analysis suggests a novel AQP4 isoform in the developing brain. At high concentrations, maternal AQP4-IgG resulted in death of the offspring. Prenatal exposure to AQP4-IgG at lower concentrations resulted in living offspring. Behavioral analysis of those offspring showed that mice born to pregnant dams injected with AQP4-IgG exhibit an impairment in flexible learning. This behavioral phenotype was observed in male mice only and was associated with alterations in the astrocytes in the hippocampus. This animal model will help us to understand the immediate and long term consequences of maternal AQP4-IgG antibody on the offspring.

Disclosures: S. Mader: None. **L. Brimberg:** None. **J.M. Crawford:** None. **A. Bonnin:** None. **J.L. Bennett:** None. **P. Huerta:** None. **B.T. Volpe:** None. **B. Diamond:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.06

Topic: E.02. Neuroimmunology

Support: European Research Council (E.R.C.) advanced grant (232835)

EU Seventh Framework Program (FP7) grant (279017)

Title: Breaking immune tolerance by targeting Foxp3+CD4+ regulatory T cells mitigates Alzheimer's disease pathology

Authors: *K. BARUCH, N. ROSENZWEIG, A. KERTSER, A. DECZKOWSKA, M. SCHWARTZ;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder in which chronic neuroinflammation plays an active part in disease progression. Nevertheless, whereas immunosuppressive drugs have repeatedly failed in treating this disease, boosting recruitment of immune cells to the CNS under chronic neurodegenerative conditions in general, and in AD in particular, was associated with attenuation of pathology. Our group has recently pointed to choroid plexus (CP), an epithelial layer that forms the blood-cerebrospinal fluid-barrier (B-CSF-B), as a selective gateway for leukocyte entry to the CNS in homeostasis and following injury, and showed that boosting CP-mediated inflammation-resolving immune cell recruitment to the CNS, can facilitate the resolution of the neuroinflammatory response. Here, we hypothesized that in AD, suboptimal recruitment of immune cells to the brain is an outcome of systemic immune failure, involving CP gateway dysfunction. Examining the CP of 5XFAD AD transgenic (AD-Tg) mice along disease progression, we found dysfunction of CP gateway activity, which was associated with local CP deficiency in interferon (IFN)-γ levels, and reduced epithelial NFκB/p65 signaling. We show that breaking systemic immune tolerance by transient conditional depletion of Foxp3+ regulatory T cells (Tregs), or pharmacological inhibition of their activity, in AD-Tg mice, augmented IFN-γ-dependent CP-gateway activity for leukocyte trafficking. The activation of this immune-brain axis was followed by accumulation of immunoregulatory cells at cerebral sites of amyloid-β pathology, plaque clearance, and mitigation of cognitive decline. Conversely, augmenting systemic Treg levels in AD-Tg mice was associated with accelerated disease pathology. Collectively, our findings identify Treg-mediated immune suppression in AD

as an obstacle to mounting a systemic immune response for the resolution of neuroinflammation, and suggest a novel therapeutic approach for treating AD.

Disclosures: K. Baruch: None. **N. Rosenzweig:** None. **A. Kertser:** None. **A. Deczkowska:** None. **M. Schwartz:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.07

Topic: E.02. Neuroimmunology

Support: Emory ADRC

Alzheimer's Disease Drug Discovery Foundation

NIH Training Grant Fellowship in Translational Neurology (5T32NS007480

Title: Modulation of soluble TNF signaling alters CNS immune cell populations and rescues impaired synaptic plasticity in 5xFAD mice

Authors: *K. P. MACPHERSON[1], P. SOMPOL[2], G. T. KANNARKAT[1], J. CHANG[1], C. NORRIS[2], M. G. TANSEY[1];
[1]Emory Univ., Atlanta, GA; [2]Univ. of Kentucky Col. of Med., Lexington, KY

Abstract: Recent evidence supports a role for peripheral inflammation and immune responses in the pathophysiology of Alzheimer's disease (AD). Conditions of chronic peripheral inflammation, such as metabolic syndrome and diabetes, and markers of inflammation, such as tumor necrosis factor (TNF), are associated with increased risk for development of AD. TNF is elevated in AD patients both in the plasma and associated with plaque pathology. Altered peripheral immune cell trafficking is evident in the brains of AD patients by the presence of T cells, which circulate in the CSF of healthy adults. TNF is known to have many functions including altering BBB permeability and modulation of glutamate receptor physiology. Transmembrane TNF (tmTNF) binds primarily TNFR2 and induces pro-survival signaling that plays a role in immunity of infection, remyelination, and is neuroprotective. Soluble TNF (sTNF) binds primarily TNFR1 and induces proinflammatory signaling that plays a role in microglial activation and neurodegeneration. Systemic XPro1595, a novel biologic that selectively neutralizes sTNF without immunosuppression and spares tmTNF signaling may ameliorate AD-like pathology induced by inflammation and/or regulate immune cell traffic across the BBB. In

the 5xFAD transgenic (Tg) mouse model we assessed changes in immune cell populations in the CNS flowing peripheral dosing of XPro1595. We report that XPro1595 alters immune cell populations in both the myeloid and T cell compartments within the brain, as well as peripheral lymphoid organs. In the brain, XPro1595 alters immune cell populations in a genotype-independent manner. XPro1595 reduces microglial activation representative of a shift towards quiescent microglia. The MHCII+ CD45high CD11b+ population is significantly decreased in non-Tg mice only, potentially due to a floor effect in Tg mice that have a reduced baseline MHCII+ CD45high population. To investigate the synaptoprotective properties of XPro1595 long-term potentiation (LTP) was assessed in slices of CA1 of the hippocampus in Tg mice following peripheral dosing of XPro1595. Slices from 5xFAD mice exhibited significant reductions in LTP, as compared to non-Tg mice, that was significantly increased with XPro1595 to near non-Tg levels. Experiments are ongoing to determine if these TNF-mediated changes in LTP and immune cell populations correlate with changes in synaptic proteins, amyloid burden and cognitive function. [Funding support from the Emory ADRC, the Alzheimer's Disease Drug Discovery Foundation and a Training Grant Fellowship in Translational Neurology (5T32NS007480].

Disclosures: K.P. Macpherson: None. **P. Sompol:** None. **G.T. Kannarkat:** None. **J. Chang:** None. **C. Norris:** None. **M.G. Tansey:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.08

Topic: E.02. Neuroimmunology

Support: NIH IRP

Title: Elucidating adaptive roles of microglia in chronically stressed mice

Authors: *M. L. LEHMANN, H. A. COOPER, M. A. HERKENHAM;
Natl. Inst. of Mental Hlth., NIH, Bethesda, MD

Abstract: We hypothesized that chronic psychosocial stress can precipitate an immune reaction in the brain directly through activation of resident microglia and that the degree and kind of activation are dependent on the psychological status of the animal following the stress. To model psychosocial stress in rodents, we used chronic social defeat (CSD). Mice exposed to CSD become subordinate, and mice susceptible to CSD (CSD-S) show enduring deleterious

psychological and physiological consequences. However, a subset avoids this outcome, which we call resilient (CSD-R). We first performed a microarray analysis on microglia isolated from CSD-S and CSD-R mice to understand how these cells differentially respond to and perhaps contribute to stress adaptability. Gene expression profiles revealed that microglia from CSD-S relative to CSD-R mice are more phagocytic and promote a permeable blood brain barrier (BBB) that might support entry of peripheral monocytes into the brain. A series of ex-vivo and in-vivo experiments was performed to test the array results. First, cultured microglia from CSD-S and CSD-R brains were exposed to fluorescently labeled apoptotic cells and assayed for phagocytic activity. Microglia from CSD-S mice were significantly more phagocytic compared to CSD-R mice, and they contained higher levels of labeled debris. Second, BBB permeability was quantified in CSD-S and CSD-R mice using i.v.-injected sodium fluorescein and, in addition, visualized using i.v.-injected fixable FITC-dextran. CSD-S brains showed substantial increases in BBB permeability compared to brains from CSD-R and non-stressed mice. Third we tested cellular extravasation by injecting mice previously exposed to two weeks of CSD with peripheral blood mononuclear cells (PBMCs) isolated from ubiquitous cell GFP reporting mice. Stressed mice were exposed to three further days of CSD after adoptive transfer, and then brains and spleens were examined for GFP+ cells. Although spleens from all groups showed colonization of GFP+ cells, neither FACS analysis nor immunohistochemistry showed the presence of GFP+ cells in brain in any condition, suggesting that CSD does not cause extravasation of PBMCs into brain. Together these results demonstrate that CSD-S microglia are more phagocytic and secrete molecules that break down the BBB, though at the time point examined, peripheral cells do not enter the brain. We hypothesize that these kinds of activities represent a CNS-centric inflammatory state that contributes to the susceptible phenotype. Causal relationships between microglia phenotype and behavioral phenotype are under current investigation.

Disclosures: **M.L. Lehmann:** None. **H.A. Cooper:** None. **M.A. Herkenham:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.09

Topic: E.02. Neuroimmunology

Support: Lady Tata Memorial Trust Grant

Indian Council of Medical Research, Government of India

Title: Acute and long-term neurological consequences of non-cerebral mild murine malarial infection

Authors: *S. K. GUHA, R. TILLU, I. SARKAR, A. SOOD, M. PATGAONKAR, A. SENGUPTA, I. NANAVATY, S. SHARMA, V. A. VAIDYA, S. PATHAK;
Dept. of Biol. Sci., Tata Inst. of Fundamental Res., Mumbai, India

Abstract: Neurological implications of malarial infection are almost always studied in the context of cerebral malaria. However, the neurological repercussions of mild malarial infection, the most prevalent form of the disease, remain poorly understood. Using a self-limiting non-cerebral mild murine malaria model of *Plasmodium Chabaudi adami*, we investigated the behavioural, cellular, and molecular effects of malarial infection. The infection induced proinflammatory cytokines in the serum and the brain. At the peak of parasitemia, the infection selectively impaired social interaction and induced anxiety-like behaviour; but did not alter depression-like, locomotor, or cognitive behavior. Correlated with these behavioural alterations, hippocampal neuroinflammation and a concomitant decline in adult hippocampal neurogenesis was also observed. Although these cellular and behavioural effects of the infection were transient and disappeared post-parasite clearance, the serum and the brain cytokine profile remained altered even two weeks post parasite clearance. These results suggest that even a history of mild malarial infection may result in an altered CNS immune milieu that persists post infection. Further experiments revealed that a history of mild malarial infection in juvenile animals resulted in enhanced susceptibility to the anxiogenic consequences of chronic mild stress in adulthood. Taken together, our findings suggest that even a single episode of mild malarial infection has both immediate and relatively persistent neurological implications.

Disclosures: **S.K. Guha:** None. **R. Tillu:** None. **I. Sarkar:** None. **A. Sood:** None. **M. Patgaonkar:** None. **A. Sengupta:** None. **I. Nanavaty:** None. **S. Sharma:** None. **V.A. Vaidya:** None. **S. Pathak:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.10

Topic: E.02. Neuroimmunology

Support: Vinnova

KAW

KCAP

SciLifeLab

Title: Anoctamin 2 as an autoimmune target in multiple sclerosis

Authors: *P. NILSSON[1,2], B. AYOGLU[2], N. MITSIOS[3], M. KHADEMI[4], I. KOCKUM[4], M. UHLEN[2], J. MULDER[3], J. SCHWENK[2], T. OLSSON[4];
[2]SciLifeLab, [1]KTH - Royal Inst. of Technol., Stockholm, Sweden; [3]Neurosci., [4]Clin. Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: Background: The increasing availability of recombinant components of the human proteome and multiplex array platforms provide unique opportunities for both targeted and discovery-driven analyses of autoantibody repertoires. We previously identified enriched affinity for 51 out of 11,520 human protein fragments by plasma IgG of individuals with multiple sclerosis (MS). Almost all of these antigens were novel autoantibody targets not previously described in the context of MS. Methods: Here, we present an in-depth analysis and further characterization of these previously identified targets together with targets suggested in literaure (e.g. KIR4.1), using an independent cohort of 2,169 plasma samples from MS cases and population-based controls on bead-based antigen arrays. Findings: We confirmed and strengthened the presence of autoantibodies against one of our previously proposed targets, a calcium-activated chloride channel protein called anoctamin 2 (ANO2), in ~15% of MS cases. Here, autoantibodies against AN02 revealed the most prominent difference within the IgG repertoire between MS cases and controls. These results were reproduced for a subset of samples in independent assays performed at a different laboratory. Using peptide arrays, ANO2 autoantibody epitopes were mapped with higher amino acid resolution. Additionally, we found that the conspicuous HLA complex MS-associated risk genes interacted strongly with the presence of ANO2 autoantibodies, reinforcing a potential role of the ANO2 auto-reactivity in MS ethiopathogenesis. Further immunofluorescence analysis on human MS brain tissue revealed a clear increase in ANO2 staining as small cellular aggregates near and inside MS lesions. Interpretation: These findings demonstrate the potential for the existence of an ANO2 autoimmune sub-phenotype in MS. They lay the ground for further studies focusing on this particular target with regard to its pathogenic role in MS, either directly or as an epiphenomenon

Disclosures: **P. Nilsson:** None. **B. Ayoglu:** None. **N. Mitsios:** None. **M. Khademi:** None. **I. Kockum:** None. **M. Uhlen:** None. **J. Mulder:** None. **J. Schwenk:** None. **T. Olsson:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.11

Topic: E.02. Neuroimmunology

Support: NIH 1P01AI073693

Title: Lupus antibodies to the NMDA receptor cause structural and functional neuronal changes

Authors: *B. T. VOLPE[1], E. CHANG[1], M. MACKAY[1], C. KOWAL[1], C. ARANOW[1], P. WATSON[2], J. STORBECK[3], P. MATTIS[1], P. HUERTA[1], B. DIAMOND[1];
[1]Feinstein Inst. For Med. Res., Manhasset, NY; [2]Zucker Hillside Hosp., Glen Oaks, NY; [3]Queens Col., Flushing, NY

Abstract: We have previously identified a subset of anti-DNA antibodies that cross-reacts with the GluNR2A and GluNR2B subunits of the NMDA receptor. When these antibodies penetrate the blood brain barrier in the hippocampus, they cause an immediate loss of neurons. Surprising, surviving neurons are both structurally and functionally impaired. They exhibit decreased dendritic complexity. Electrophysiologic studies reveal an increased place field size in hippocampal neurons which translates into a deficit in spatial memory. These changes are not seen at two weeks after blood brain barrier breach but can be seen at 4 weeks after antibody penetrates the hippocampus and persist for an additional several weeks until the experiment was terminated; thus, this pathology arises after antibody is no longer present in the hippocampus. Interestingly, SLE patients with these antibodies also exhibit an impairment in spatial memory. Together, these studies suggest a longer therapeutic window for protecting memory function.

Disclosures: B.T. Volpe: None. **E. Chang:** None. **M. Mackay:** None. **C. Kowal:** None. **C. Aranow:** None. **P. Watson:** None. **J. Storbeck:** None. **P. Mattis:** None. **P. Huerta:** None. **B. Diamond:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.12

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 5K08NS07940503

Title: The astrocyte circadian clock regulates neuroinflammation and neuronal injury

Authors: *B. V. LANANNA[1], D. D. XIONG[1], M. IZUMO[2], A. CAMMACK[1], J. S. TAKAHASHI[2], E. H. HERZOG[1], E. S. MUSIEK[1];
[1]Washington Univ. in St Louis, Saint Louis, MO; [2]UT Southwestern, Dallas, TX

Abstract: Sleep disruption and circadian dysfunction are common symptoms of several neurodegenerative diseases, including Alzheimer Disease. The mechanisms by which these processes influence disease pathogenesis are still under investigation. Circadian clock genes mediate cell-autonomous oscillations in gene transcription and cellular function. We have recently shown that disruption of clock gene function in the mouse brain causes gliosis, synaptic damage, oxidative stress, and exacerbates neurodegeneration, but the cellular and molecular mechanisms remain unclear. Here, we report that neuron-specific deletion of *Bmal1* only partially recapitulates the neuropathological astrogliosis phenotype observed in global *Bmal1* KO mice, suggesting a cell-autonomous role for *Bmal1* in astrocyte activation. Accordingly, *Bmal1* deletion induces pronounced astrocyte activation in isolated astrocyte cultures with robust upregulation of transcripts including *Gfap, Aqp4*, and *ApoE*, and alters the astrocytic response to inflammatory stimuli. *Bmal1* deletion in astrocytes causes widespread transcriptional changes consistent with astrocyte activation, with markedly diminished expression of certain critical inflammatory suppressors, including *Chi3L1* (YKL-40). Accordingly, *Chi3L1* (YKL-40) deficient mice exhibit exaggerated neuroinflammatory responses, suggesting that BMAL1-mediated regulation of *Chi3L1* regulates neuroinflammation. Similar changes in astrocyte activation markers and inflammatory transcripts are present in cortex tissue from *Bmal1* -/- mice. Finally, co-culture of wild-type primary neurons with *Bmal1*-deficient astrocytes impairs neuronal survival and neurite outgrowth, and increases neuronal sensitivity to oxidative stress. Our results demonstrate a novel role for circadian clock genes in the regulation of astrocyte activation and neuroinflammation, and suggest that disruption of astrocyte circadian signaling could exacerbate neuronal injury in neurodegenerative diseases.

Disclosures: **B.V. Lananna:** None. **D.D. Xiong:** None. **M. Izumo:** None. **A. Cammack:** None. **J.S. Takahashi:** None. **E.H. Herzog:** None. **E.S. Musiek:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.13

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AA18834

NIH Grant AA18839

NIH Grant AA19108

NIH Grant AA23723

Title: MyD88 signaling regulates ethanol-induced immune response in the CNS of adult mice

Authors: *P. D. DREW, K. D. PHELAN, J. C. DOUGLAS, J. JOHNSON, C. J. M. KANE; Neurobio. and Developmental Sci., Univ. Arkansas Med. Sci., Little Rock, AR

Abstract: A spectrum of alcohol use disorders exist which include alcohol abuse and alcohol dependence. Approximately 7-10% of the population of the United States exhibits some form of alcohol use disorder and this results in an economic health burden of greater than $225 billion per year. It has previously been demonstrated that excessive alcohol consumption can result in brain inflammation. Interestingly, Toll-like receptor (TLR) 4 has been shown to modulate ethanol-induced inflammation in the CNS. TLR4 has been demonstrated previously to control inflammation through two downstream signaling pathways termed the MyD88-dependent or the TRIF-dependent pathways. The present studies were designed to determine if the MyD88-dependent signaling pathway controls ethanol induced inflammation in the CNS. We demonstrate that in adult wild-type C57BL/6 mice, ethanol (6 g/kg, 15% w/v, split dose) increased the expression of mRNA encoding the chemokine CCL2 (MCP-1) in the hippocampus, cerebellum, and cerebral cortex. Furthermore, IL-6 mRNA was increased in the cerebellum of these mice. Importantly, we demonstrated a critical role for the MyD88-dependent signaling pathway in ethanol-induced CNS inflammation since the expression of CCL2 and IL-6 mRNA were not stimulated by ethanol treatment in MyD88 knockout mice. These findings have implications for alcohol use disorders given clear evidence of a link between CNS inflammation and alcohol addiction. Therefore, defining the mechanisms by which ethanol induces neuroinflammation may result in development of therapies to suppress alcohol mediated neuropathology and alcohol use disorders. Supported by AA18834, AA18839, AA19108, AA023723.

Disclosures: P.D. Drew: None. **K.D. Phelan:** None. **J.C. Douglas:** None. **J. Johnson:** None. **C.J.M. Kane:** None.

Nanosymposium

198. Neuroinflammation and Diseases

Location: S404

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 198.14

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIAAA AA011605

Title: Neuronal SH-SY5Y cells display different innate immune response to ethanol and TLR3/4 stimulation compared to microglial BV2 cells

Authors: *C. J. LONERGAN, F. T. CREWS;
UNC Chapel Hill, Chapel Hill, NC

Abstract: Introduction: Binge ethanol (EtOH) consumption increases neuro-immune gene expression and neurodegeneration. Although glia are known to participate in neuroimmune signaling in brain, recent data from the Crews and other labs suggest that neurons also express immune signaling molecules (ISMs). In order to investigate the respective neuroimmune response of neurons and microglia, we examined ISMs in BV2 (mouse microglia cell line) and SH-SY5Y (human neuronal cell line) after treatment with EtOH, lipopolysaccharide (LPS), and PolyI:C. Methods: BV2 and neuroblastoma-derived SH-SY5Y were grown to 85-90% confluence prior to treatment. SH-SY5Y cells were differentiated into mature neuronal phenotype using retinoic acid for 4-5 days. Cells were treated with either TLR3 agonist PolyI:C (50ug/mL), TLR4 agonist LPS (100ng/mL), or EtOH (150mM) for 24hr. ISMs were analyzed in cell lysates and media by ELISA, Western blot (WB), and RT-PCR. Gene expression data is shown as % control for respective cell-type. Results: ISM mRNA expression (TLR2-4;7-8, CD14, RAGE, HMGB1, TNFα) and protein expression (RAGE, HMGB1, TLR4) was present in both SH-SY5Y and BV2. In neuronal SH-SY5Y cells, EtOH increased mRNA expression of TLR3 (398±80%,$p<0.05$), TLR7 (575±100%,$p<0.05$), TLR8 (320±17%,$p<0.05$), RAGE (170±15%,$p<0.05$) and HMGB1 release in media (31±2.5ng/mL[CON]vs.83±5.2ng/mL). PolyI:C increased mRNA expression of TNFα (10427±2133%,$p<0.05$), HMGB1 (126±2.9%,$p<0.05$), and TLR3 (921±260%,$p<0.05$) in SH-SY5Y. LPS had no measurable effect on SH-SY5Y. In microglial BV2 cells, EtOH increased mRNA expression of TNFα (204±15,$p<0.05$), TLR2 (170±15,$p<0.05$), TLR7 (158±8.4%,$p<0.05$), TLR8 (194±9.5%,$p<0.05$), and HMGB1 release in media (30±1.5ng/mL[CON]vs.43±0.4ng/mL,$p<0.05$). PolyI:C increased mRNA expression of TNFα (217±30%,$p<0.05$) in BV2. LPS increased mRNA expression of TNFα (440±27%,$p<0.05$) and CD14 (242±21,$p<0.05$) and HMGB1 release in media (53±4.6ng/mL[CON]vs.78±4.5ng/mL,$p<0.05$) in BV2. Conclusions: Our results indicate that neuronal cell line SH-SY5Y expresses innate immune signals following EtOH stimulation. Responsiveness of SH-SY5Y to TLR3 but not TLR4 stimulation suggests an alternative innate immune signal pathway in neurons compared to microglia. Future studies will examine signaling in primary cells and *in vivo*.

Disclosures: C.J. Lonergan: None. **F.T. Crews:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.01

Topic: E.08. Biological Rhythms and Sleep

Support: 1R01NS091070-01

Title: Generation of homeostatic sleep signals in segregated synaptic microcircuits of the *Drosophila* mushroom body

Authors: *D. SITARAMAN[1], Y. ASO[2], N. CHEN[2], G. RUBIN[2], M. NITABACH[3];
[1]Psychological Sci., Univ. of San Diego, San Diego, CA; [2]Janelia Res. Campus, HHMI, Ashburn, VA; [3]Yale Univ., New Haven, CT

Abstract: The *Drosophila* mushroom body (MB) is a key associative memory center that has also been implicated in the control of sleep. However, the identity of MB neurons underlying homeostatic sleep regulation, as well as the types of sleep signals generated by specific classes of MB neurons, has remained poorly understood. We recently identified two MB output neuron (MBON) classes whose axons convey sleep control signals from the MB to converge in the same downstream target region: a cholinergic sleep-promoting MBON class and a glutamatergic wake-promoting MBON class. Here we deploy a combination of neurogenetic, behavioral, and physiological approaches to identify and mechanistically dissect sleep-controlling circuits of the MB. Our studies reveal the existence of two segregated excitatory synaptic microcircuits that propagate homeostatic sleep information from different populations of intrinsic MB "Kenyon cells" (KCs) to specific sleep-regulating MBONs: sleep-promoting KCs increase sleep by preferentially activating the cholinergic MBONs, while wake-promoting KCs decrease sleep by preferentially activating the glutamatergic MBONs. Importantly, activity of the sleep-promoting MB microcircuit is increased by sleep deprivation and is necessary for homeostatic rebound sleep. These studies reveal for the first time specific functional connections between subsets of KCs and particular MBONs and establish the identity of synaptic microcircuits underlying generation of homeostatic sleep signals in the MB.

Disclosures: D. Sitaraman: None. **Y. Aso:** None. **N. Chen:** None. **G. Rubin:** None. **M. Nitabach:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.02

Topic: E.08. Biological Rhythms and Sleep

Support: F32 HL116077-01A1

R01 NS078410

R01 AR066082

Title: Inducible knockout of Bmal1 in skeletal muscle alters both circadian and sleep homeostatic processes

Authors: *A. J. BRAGER[1], E. OLIVER[1], J. EHLEN[1], K. ESSER[2], K. PAUL[1];
[1]Neurobio., Morehouse Sch. of Med., Atlanta, GA; [2]Ctr. for Skeletal Muscle Biol., Univ. of Kentucky Col. of Med., Lexington, KY

Abstract: In recent years, there has been a focus on peripheral regulation of central sleep and circadian processes. Many of these studies have focused on highly metabolic tissues such as the liver and pancreas. Here, we add to this existing literature by investigating how the circadian clock of the skeletal muscle alters wheel running rhythms and the ability to recover from short-term sleep deprivation. These experiments utilized an inducible Cre recombinase mouse driven by a human α-skeletal actin promoter. With this model, Bmal1 which is part of the positive limb of the transcriptional-translational feedback loop could be knocked out following a 5 d regimen of i.p. tamoxifen (10 mg/kg; n=8), an estrogen receptor antagonist. In experiment 1, wheel running rhythms were measured across 2 wk of a 12:12 light-dark cycle (LD) and constant darkness (DD) in tamoxifen-treated and vehicle-treated flox/cre mice and C57 wild-types. Under LD, there were no differences in nighttime activity onset and duration (alpha) between genotypes ($p=0.05$). Under DD, tamoxifen-treated flox/cre mice had significantly shorter free-running rhythm (23.2+0.1 h) compared to vehicle-treated flox/cre mice and C57 wild-types (23.7+0.2 and 23.8+0.2 h, respectively; $p<0.001$). In experiment 2, flox/cre mice received EEG/EMG implants. Following a 24 h baseline recording, mice were sleep deprived by gentle handling beginning at lights-on. Prior to tamoxifen treatment, flox/cre mice recovered 35+10% of the 6 h of sleep lost. After tamoxifen treatment, the recovery response was reduced to 10+5% ($p=0.03$). Analyses of sleep-wake fragmentation revealed a reduction in the number of NREM bouts after tamoxifen treatment compared to prior ($p=0.001$). To conclude, this study reveals the muscle-specific knockout of the clock gene Bmal1 alters both circadian and sleep homeostatic processes, recapitulating that peripheral tissues can influence sleep and circadian timekeeping.

Disclosures: **A.J. Brager:** None. **E. Oliver:** None. **J. Ehlen:** None. **K. Esser:** None. **K. Paul:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.03

Topic: E.08. Biological Rhythms and Sleep

Title: Is there enough information in the electrocardiogram (ECG) to determine sleep stage?

Authors: *A. M. JONES[1], B. R. SHETH[2];
[2]Electrical & Computer Engin., [1]Univ. of Houston, Houston, TX

Abstract: Polysomnography (PSG) has been the go-to method for determining sleep stage. However, the required equipment, number of probes, and labor-intensive manual scoring are hindrances to taking sleep stage identification out of the lab. Our objective is to develop an automated model for sleep stage determination using only ECG data, with the practical motivation of creating an efficient alternative to PSG. The proposition that “sleep is of the brain, by the brain and for the brain” (Hobson, 2005) has steered sleep science into an almost singular focus on the brain. However, the electroencephalogram is insufficient to determine sleep stage, as even PSG critically utilizes electrical data from the muscles of the eye and chin. Sleep is a corporal state, and the interactions between the brain and bodily organs, such as the heart, are likely to be valuable in determining sleep stage. We hypothesize that the ECG contains sufficient data for reliable determination of sleep stage, since it reflects the changes in activity in the parasympathetic and sympathetic nervous systems seen in distinct stages of sleep. Using an ECG-based technique to determine sleep stage would make data easier to acquire and analyze, enhance its clinical potential and expand its real world applicability. Due to the heart's non-metronomic beat pattern, converting ECG data into intervals between consecutive R waves of the ECG inevitably leads to an irregularly sampled RR time series. Most studies have erroneously used traditional Fourier analysis to overcome this complication when transforming the RR time series. Past studies also have not controlled for the undesirable effects on the RR spectrum due to the prominent, non-sinusoidal, respiratory sinus arrhythmia (RSA). We propose three key improvements to make an ECG-based technique viable. First, we developed a mathematical function, the parameterized flexible cosine (flexcos), to model the RSA and compensate for its undesirable spectral effects. Next, we used least-squares spectral analysis to transform the non-uniformly sampled data without the adverse side effects of interpolation while also suppressing

spurious components in the RR spectrum. Finally, we used state-of-the-art machine learning with the features extracted from the RR spectrum and the parameters of the detected RSA, to identify the sleep stage in each 30 s epoch and compare with existing PSG-based "ground truth" scores. Preliminary results indicate our methods are more robust at dealing with difficult inputs, rendering reliable determination of sleep stage from the ECG likely. Sleep may well also be of, by, and for the body; knowledge of body state may reliably shed light on sleep stage.

Disclosures: **A.M. Jones:** None. **B.R. Sheth:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.04

Topic: E.08. Biological Rhythms and Sleep

Support: SNF Grant P2ZHP3_148608

Title: Sleep Wave Analysis: A toolbox for the detection and analysis of the waves in sleep

Authors: *A. MENSEN[1,2], B. RIEDNER[2], G. TONONI[2];
[1]Ctr. For Sleep and Consciousness, Bern, Switzerland; [2]Dept. of Psychiatry, Ctr. for Sleep and Consciousness, Madison, WI

Abstract: Over the past two decades, the focus of much sleep research has shifted from the temporal dynamics of sleep to the spatio-temporal aspects with the advance of high-density electroencephalography (EEG) and novel experimental paradigms. The most common approach has been to use frequency based analysis to detect 'slow wave power'. However, this is generally just a proxy measure of various properties of the individual slow waves found in deeper stages of sleep, and the accurate detection and exploration of these individual waves would provide much greater insight and specificity into the local mechanisms under investigation. Here we present a user-friendly, open-source, toolbox designed for the analysis of high-density EEG recordings in sleep. The toolbox's main aim is to provide the user with a fast and accurate tool to detect the various waves found in these recordings, such as individual slow waves, sleep spindles and saw-tooth waves. Although default settings for all measurement paradigms are given, the user is able to freely change the parameters and explore the results using a wide range of visualisation options available. We examine the typical workflow from the preparation of raw data recordings, to publication ready measures, including how the toolbox can be used in the scoring sleep stages, as well as the available parameter settings and their expected effects on a sample of 11 control

participant's sleep recordings. In the analysis parameter settings such as choice of EEG reference, amplitude threshold, and channel correlation are examined for their effect on several outcome measures such as basic measures of mean amplitude and wave density to more detailed measures of wave globality, and traveling properties of the individually detected waves. The principle conclusions are that even minor changes in parameter settings can have large subsequential effects on the number and properties of the waves ultimately detected, and as such there is a need to standardise the detection methods, and provide clear justifications for any chosen settings. The toolbox is easy to use, is consistently updated with new features, visualisation options and algorithm optimisations, as well as being designed specifically with potential collaborations in mind. The toolbox can be freely downloaded from https://github.com/Mensen/swa-matlab.

Disclosures: **A. Mensen:** None. **B. Riedner:** None. **G. Tononi:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.05

Topic: E.08. Biological Rhythms and Sleep

Support: NSF Grant DMS-1042134

Title: A beta-theta frontal network during REM sleep in humans

Authors: *S. VIJAYAN[1,2], K. LEPAGE[1], N. KOPELL[1], S. S. CASH[2];
[1]Mathematics and Statistics, Boston Univ., Boston, MA; [2]Neurol., Harvard Med. Sch., Boston, MA

Abstract: The EEG during REM sleep is similar to that during awake activity: irregular and of low voltage. In awake activity, during cognitive tasks, oscillations do emerge in task-relevant areas of the brain. These oscillations are thought to play an important role in aspects of cognition such as working memory and communication between brain areas. Thus knowledge of the prevalent oscillatory activity patterns during REM sleep in brain structures known to be important for memory is likely key for understanding the neural mechanisms underlying memory consolidation during REM sleep. Yet, little is currently known about the oscillatory activity in cortical regions of the brain during REM sleep. To gain a better understanding of cortical oscillatory activity during REM sleep, we analyzed intracranial electrode data from epilepsy patients. We found prominent theta and beta oscillations in the frontal cortices, in particular the cingulate and prefrontal cortices. These beta and theta rhythms were coherent within and

between the cingulate and prefrontal cortices, spatially disparate regions that are both important for memory. We believe the coordination of the beta and theta rhythms across these structures during REM sleep might play an important role in implicit memory consolidation, since REM sleep is known to play an important role in implicit memory consolidation.

Disclosures: **S. Vijayan:** None. **K. Lepage:** None. **N. Kopell:** None. **S.S. Cash:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.06

Topic: E.08. Biological Rhythms and Sleep

Support: NIH Grant R01 MH092638 to DSM and RS

NARSAD Young Investigator Award, Brain and Behavior Research Foundation to CD

Title: Sleep spindle sources in relation to memory consolidation deficits in schizophrenia: Insights from high-density EEG sleep recordings in humans

Authors: *C. DEMANUELE[1,2], M. HAMALAINEN[1,3], B. BARAN[1,2], I. F. KARAHANOGLU[1,2], M. LUESSI[1], T. C. VUPER[1,2], R. A. FOWLER[1,2], D. CORRELL[1,2], B. SEICOL[4], C. CALLAHAN[4], E. PARR[4], S. KHAN[1,3], N. DEHGHANI[5], R. STICKGOLD[4], D. S. MANOACH[1,2];
[1]Psychiatry, Athinoula A. Martinos Ctr. For Biomed. Imagin, Charlestown, MA; [2]Psychiatry, [3]Radiology, Massachusetts Gen. Hosp., Charlestown, MA; [4]Ctr. for Sleep and Cognition, Harvard Med. Sch., Beth Israel Deaconess Med. Ctr., Boston, MA; [5]Wyss Inst. for Biologically-Inspired Engin. at Harvard Univ., Boston, MA

Abstract: Introduction: Sleep spindles, a defining feature of non-rapid eye movement stage 2 (NREM2) sleep, play a critical role in memory consolidation. Schizophrenia (SZ) patients have a dramatic reduction in sleep spindle activity that correlates with impaired sleep-dependent memory consolidation, IQ and executive function. This deficit is also seen in first-degree relatives of SZ patients, suggesting that it indicates genetic risk. Moreover, spindles can be manipulated to improve memory in healthy adults and animal models, suggesting the possibility that treating spindle deficits may improve cognition in SZ. To further characterize the spindle deficit in SZ and its relation to memory we identified the cortical sources of spindles that are associated with procedural motor memory consolidation in healthy adults and examined whether

these differ in SZ. Methods: Twelve SZ patients and 12 demographically-matched healthy controls (HC) spent two overnights in the Clinical Research Center, and were monitored with polysomnography (58 EEG channels, EOG and EMG). They learned a finger-tapping motor sequence task (MST) before bedtime on the second night and were tested on the same sequence the following morning. Sleep spindles during NREM2 sleep were identified using automated wavelet spindle detector. For each participant we used structural MRI to constrain current source estimates of spindles to the cortex. The cortex was segmented into 110 anatomically-defined regions in each hemisphere using FreeSurfer. We computed spindle 9-16 Hz power in each cortical region derived from time-frequency decomposition. Determination of regional significance was based on permutation tests at $p \leq 0.05$ level, corrected for multiple comparisons. Results: Relative to HC, patients showed trends of reduced spindle density and overnight memory consolidation. At baseline (night one), spindles were localized in bilateral centro-parietal and superior parietal regions in HC, and in bilateral frontal regions in SZ. Following learning, we observed increased spindle activity in HC in right M1, contralateral to the hand that performed the MST, and in right dorsolateral prefrontal cortex. In SZ, learning was associated with increased spindle activity in right M1 and superior frontal regions. Conclusions: We demonstrate that SZ patients show qualitatively different cortical sources of spindles. In both groups, learning was associated with more focused spindle activity in motor areas relevant to task performance. We are increasing our sample size and refining these methods to also determine the characteristics of spindles that contribute to memory consolidation and are abnormal in SZ.

Disclosures: **C. Demanuele:** None. **M. Hamalainen:** None. **B. Baran:** None. **I.F. Karahanoglu:** None. **M. Luessi:** None. **T.C. Vuper:** None. **R.A. Fowler:** None. **D. Correll:** None. **B. Seicol:** None. **C. Callahan:** None. **E. Parr:** None. **S. Khan:** None. **N. Dehghani:** None. **R. Stickgold:** None. **D.S. Manoach:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.07

Topic: E.08. Biological Rhythms and Sleep

Support: ANR-10-LABX-0087 IEC

ANR-10-IDEX-0001-02 PSL*

I-CORE Program 51/11

NIMH R01MH099231

NINDS R01

Title: Single neuron activity and eye movements during human REM sleep and awake vision

Authors: *Y. NIR[1], T. ANDRILLON[2], C. CIRELLI[3], G. TONONI[3], I. FRIED[4,5];
[1]Tel Aviv Univ., Tel Aviv, Israel; [2]Lab. de Sci. Cognitives et Psycholinguistique (ENS, EHESS, CNRS), Ecole Normale Superieure, Paris, France; [3]Dept. of Psychiatry, Univ. of Wisconsin-Madison, Madison, WI; [4]Dept. of Neurosurg., David Geffen Sch. of Med. and Semel Inst. For Neurosci. and Human Behavior, UCLA, Los Angeles, CA; [5]Functional Neurosurg. Unit, Tel Aviv Med. Ctr. and Sackler Sch. of Medicine, Tel Aviv Univ., Tel Aviv, Israel

Abstract: In wakefulness, rapid eye movements (REMs, or saccades) allow us to direct our attention to specific parts of the visual scene, shaping visual perception. Intriguingly, REMs are also prevalent during REM-sleep, a state associated with rich mental imagery, while they are absent in non-REM-sleep, during which vivid dreams are less frequent. Are REMs non-specific signatures of arousability or do they represent specific times at which visual processing is updated? The goal of this study was to establish the relation between REMs and the neuronal activity in visual-mnemonic regions, and to compare such modulations with those occurring during awake vision. To this end, we examined intracranial EEG (n=172 depth electrodes) in 13 neurosurgical epilepsy patients as well as single-unit activities in association with REMs during full-night sleep and episodes of wakefulness (n=600 units) and during controlled visual stimulation (n=1457 units). Recordings sites spanned numerous regions across the medial temporal lobe (MTL) and neocortex. REMs were detected semi-automatically and visually inspected to ensure a sensitive and specific detection. Accordingly, REMs were almost exclusively detected in wakefulness and REM-sleep. These REMs were indistinguishable in shape. Neuronal activity was similarly modulated by REMs in wakefulness and sleep, with a decrease in firing rate prior to REMs onset followed by an increase peaking at 250ms after REMs onset. Neurons that modulated their activities around REMs were more readily observed in the MTL (24% and 18% in wakefulness and REM sleep) compared with frontal lobe regions (13% and 12% respectively). REMs in both wake and sleep were associated with a positive peak in the depth EEG immediately before REM onset, akin to PGO potentials observed in animals. The transient reduction in MTL neuronal activity immediately before REM onsets ([-300, 0]ms) could be related to saccadic suppression, while the post-REM increase ([50, 400]ms) is probably related to the update of visual information, since it was absent in REMs performed by awake patients in darkness. Moreover, this increase was associated with a phase-reset within the theta-band and with ERPs in both scalp and depth EEG that were similar to those observed when processing a new image with eyes fixed. Finally, post-REM increases in spiking activity exhibited response latency and selectivity that were conserved across vigilance states at the single-unit level. Overall, the results demonstrate, for the first time, that REMs in sleep represent

privileged time-points at which neuronal activity is updated in a similar fashion as when processing visual information in wakefulness.

Disclosures: **Y. Nir:** None. **T. Andrillon:** None. **C. Cirelli:** None. **G. Tononi:** None. **I. Fried:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.08

Topic: E.08. Biological Rhythms and Sleep

Support: ANR-10-LABX-0087

ANR-10-IDEX-0001-02

ADAM #295603

Title: Neural mechanisms of perceptual learning and suppression of novel information during sleep

Authors: ***T. ANDRILLON**[1], D. PRESSNITZER[2], D. LÉGER[3], S. KOUIDER[1];
[1]Lab. de Sci. Cognitives et Psycholinguistique (ENS, EHESS, CNRS), [2]Lab. des Systèmes Perceptifs, CNRS UMR 8248, Ecole Normale Superieure, Paris, France; [3]Ctr. du Sommeil de l'Hôtel-Dieu, Univ. Paris-Descartes, Paris, France

Abstract: There is growing evidence for a functional link between sleep and memory. Yet, the underlying mechanisms are still debated. It is unclear whether sleep promotes active memory consolidation through synaptic up-scaling of information replayed in sleep or, on the contrary, synaptic normalization during which re-activation would lead to synaptic down-scaling. Here, we addressed this issue by tracking the formation and consolidation of a new memory trace across various vigilance states. We focused on the learning of acoustic noise, a fast and automatic form of perceptual learning. In the noise-memory paradigm, participants have to discriminate between sequences of continuously running white noise (N) and sequences made of repeated fragments of the same, frozen, noise (RN). When one particular repeated fragment recurs across trials (Reference RN: RefRN), repetition-detection dramatically improves, revealing perceptual learning. Importantly, learning can here be tracked with EEG recordings. Twenty human subjects were exposed to acoustic white noise during a full-night protocol. They were first exposed to noise stimuli while being awake (Pre-Test). Consistent with past research,

perceptual learning was evidenced through increased performance for RefRN compared to RN stimuli. Participants were then presented with similar stimuli while they were asleep (Test). Crucially, distinct sets of RefRN stimuli were played selectively during NREM and REM sleep, so as to distinguish their respective influence. In the morning (Re-Test), RefRN from the Pre-Test, NREM and REM-sleep periods, were presented along with new stimuli to quantify memory retention. EEG was recorded during the whole protocol. Behaviorally, prior exposure to RefRN in wakefulness and REM-sleep increased performance at Re-Test. This reveals that perceptual learning for acoustic noise can be established and consolidated not only during wakefulness but also during REM-sleep. Interestingly, however, exposure to RefRN sounds in NREM sleep led to worst performance, suggesting that NREM involves synaptic normalization with a suppression of memory traces. Our EEG marker of learning at Re-Test mirrored this pattern of results. Moreover, memory suppression at Re-Test was correlated with the amount of slow-waves (delta power) during sleep, and RefRN sounds specifically perturbed NREM sleep hallmarks (sleep spindles and slow-waves). These results suggest that synaptic up and down-scaling both occur during sleep, but crucially depend on the sleep stage during which a memory trace is established. The drop of acetylcholine in NREM compared to REM sleep and wakefulness could account for this reversal.

Disclosures: **T. Andrillon:** None. **D. Pressnitzer:** None. **D. Léger:** None. **S. Kouider:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.09

Topic: E.08. Biological Rhythms and Sleep

Support: NIH 1R01AG047671

NIH MH087592

BSF 2011335

Klarman Family Foundation

ELSC postdoctoral fellowship

Title: A causal role of VTA-dopaminergic neurons in sleep-wake regulation

Authors: *A. EBAN-ROTHSCHILD, W. J. GIARDINO, L. DE LECEA;
Psychiatry and Behavioral sciences, Stanford Univ., Palo Alto, CA

Abstract: Dopaminergic (DA) neurons in the ventral tegmental area (VTA) play a central role in many wake-related processes including motivation, reward and learning. While these functions are associated with heightened arousal, the role of these neurons in generating and maintaining arousal is largely unknown. Psychiatric disorders, such as Schizophrenia and substance abuse, are often accompanied by alterations in dopamine neurotransmission, as well as in sleep-wake architecture. However, dopamine was traditionally regarded as the only aminergic group not involved in sleep-wake regulation, since early electrophysiological findings showed that VTA-DA neurons do not change their mean firing rate across sleep-wake states. Nevertheless, it has been recently shown that VTA-DA neurons do change their temporal firing pattern across sleep-wake states. Further support to the premise that dopamine signaling participates in sleep-wake regulation arises from studies using knockout animals and pharmacological manipulations. However, to reveal the causal role of VTA-DA neurons in sleep-wake regulation, it is essential to manipulate their activity with spatial and temporal resolutions relevant to natural sleep-wake events. To this end, we combined pharmaco/optogenetic tools with polysomnographic recordings in freely-behaving mice. To selectively target DA neurons, we stereotactically injected AAV5-EF1α-DIO-ChR2-eYFP (for activation) or AAV5-EF1α-DIO-hM4Di-mCherry (for inhibition) to the VTA of TH:Cre mice. As control, TH:Cre littermate were injected with a virus expressing only the fluorescent protein. We also implanted the mice with a custom-made EEG-EMG device and a fiber optic cannula (in optogenetic experiments). We assessed the effects of optogenetic stimulation/CNO injection on sleep-wake architecture and EEG power spectra. We found that pharmacogenetic inhibition of VTA-DA neurons during the dark phase reduced wakefulness and increased both NREM and REM sleep. In contrast, phasic stimulation of VTA-DA neurons during the light phase induced immediate sleep-to-wake transitions and decreased slow-wave activity, irrespective of sleep pressure. We also found that semi-chronic stimulation of VTA-DA neurons induced long-term wakefulness and suppressed both NREM and REM sleep. Optogenetic stimulation of VTA-DA terminals at the NAc accounted for the majority of the effects of VTA-DA neurons on arousal, whereas mPFC terminals were found to have a minor role. Our results demonstrate a causal role for VTA-DA neurons in the promotion of wakefulness and suppression of sleep, and identify this neuronal population as a key node in the sleep-wake circuitry.

Disclosures: A. Eban-Rothschild: None. **W.J. Giardino:** None. **L. de Lecea:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.10

Topic: E.08. Biological Rhythms and Sleep

Support: NIH MH086415

NIH AG017628

NIH 5K12GM081529

NWO 82507029

Title: The F-actin severing protein cofilin is the critical mediator of memory deficits, LTP impairments, and spine loss associated with sleep deprivation

Authors: *R. HAVEKES[1,2], A. J. PARK[1], S. L. FERRI[1], V. M. BRUINENBERG[2], J. C. TUDOR[1], J. P. DAY[3], S. G. POPLAWSKI[1], S. ATON[4], K. RADWANSKA[5], P. MEERLO[2], M. D. HOUSLAY[6], G. BAILLIE[3], T. ABEL[1];
[1]Biol., Univ. of Pennsylvania, Philadelphia, PA; [2]Univ. of Groningen, Groningen, Netherlands; [3]Univ. of Glasgow, Glasgow, United Kingdom; [4]Univ. of Michigan, Ann Arbor, MI; [5]Head Nincki Inst. of experimental Biol., Warsaw, Poland; [6]Kings Col. London, London, United Kingdom

Abstract: Sleep loss impairs memory storage, but the molecular mechanisms by which sleep deprivation negatively impacts cognitive processes are unknown. We show in mice that 5 hours of sleep deprivation decreases the number of dendritic spines in the hippocampus, which is paralleled by reduced filamentous actin levels, and increased activity of the F-actin severing protein cofilin. A brief period of recovery sleep restores hippocampal spine numbers as well F-actin levels and cofilin activity. Viral suppression of cofilin function selectively in hippocampal excitatory neurons prevents this loss of dendritic spines and filamentous actin levels, and reverses the deficits in hippocampal synaptic plasticity (LTP) and long-term memory caused by sleep deprivation. The elevated cofilin activity observed after sleep loss is caused by the cAMP-degrading phosphodiesterase isoform PDE4A5, which hampers cAMP-PKA-LIMK signaling. Viral suppression of PDE4A5 function selectively in hippocampal neurons prevents changes in LIMK and cofilin signaling as well as the cognitive deficits associated with sleep deprivation. Our work demonstrates that alterations in structural plasticity in hippocampal neurons underlie the deficits in synaptic plasticity and memory caused by sleep deprivation.

Disclosures: R. Havekes: None. **A.J. Park:** None. **S.L. Ferri:** None. **V.M. Bruinenberg:** None. **J.C. Tudor:** None. **J.P. Day:** None. **S.G. Poplawski:** None. **S. Aton:** None. **K. Radwanska:** None. **P. Meerlo:** None. **M.D. Houslay:** None. **G. Baillie:** None. **T. Abel:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.11

Topic: E.08. Biological Rhythms and Sleep

Title: The differential effects of emotional salience on direct associative and relational memory during a nap

Authors: *S. E. ALGER, J. D. PAYNE;
Univ. of Notre Dame, Notre Dame, IN

Abstract: Relational memories are formed by flexibly linking shared components of directly learned memory associations to better inform future judgments. Both direct associative and relational memories have been found to benefit from a period of sleep compared to wake. However, the impact of incorporating emotionally salient information into the learned material and the subsequent interaction of emotional salience and sleep in facilitating both types of memory is unknown. Forty participants initially encoded two sets of picture pairs, with either emotionally negative or neutral objects paired with neutral faces. The same objects were present in both picture sets, paired with two difference faces. Baseline memory for these directly paired associates was tested immediately after encoding, followed by either a 90-min nap opportunity or wake. Five hours after learning, a surprise test was given to assess relational memory, the indirect association between the two faces paired with the same object during encoding, followed by a retest of direct associative memory. Across conditions, negative information was remembered better than neutral, both for face-object pairs and face-face pairs associated indirectly through negative objects. A nap was found to facilitate the preservation of direct associative memories from baseline to retest and formation of relational memories, compared to remaining awake ($F_{1,37}$=6.00, p=.02; $F_{1,36}$=5.18, p=.03, respectively). Interestingly though, this sleep benefit was strictly observed for neutral pairs for both direct associative (t_{37}=3.25, p=.002) and relational memories ($F_{1,36}$=4.71, p=.04). We also found that a full cycle of sleep, including roles for both NREM and REM sleep, was important for neutral relational memory performance.Taken together, the current study provides strong evidence that sleep plays a role in processing both direct and indirect neutral associative memories.

Disclosures: S.E. Alger: None. **J.D. Payne:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.12

Topic: E.08. Biological Rhythms and Sleep

Support: R01MH064109

R01DA034748

Dept of Veterans Affairs

Title: Sleep in preindustrial societies: human sleep under evolutionarily relevant conditions

Authors: *J. M. SIEGEL[1], G. YETISH[2], H. KAPLAN[3], M. GURVEN[4], B. WOOD[5], H. PONTZER[6], P. MANGER[7], C. WILSON[8], R. MCGREGOR[9];
[1]Dept Psychiat, Univ. California Los Angeles, North Hills, CA; [3]Anthrop., [2]Univ. of New Mexico, Albuquerque, NM; [4]Anthrop., Univ. of California, Santa Barbara, Santa Barbara, NM; [5]Anthrop., Yale Univ., New Haven, CT; [6]Anthrop., Hunter Col., New York, NY; [7]Sch. of Anatom. Sci., Univ. of the Witwatersrand, Johannesburg, South Africa; [8]Neurol., [9]Psychiatry, Univ. of California at Los Angeles, Los Angeles, CA

Abstract: How did humans sleep before the modern era? Because the tools to measure sleep under natural conditions were developed long after the invention of the electric light, television, the Internet and related devices that are suspected of delaying and reducing sleep, there is no reliable data on how sleep has changed from levels more characteristic of our species' evolutionary history. To address this question, we have investigated sleep in three traditional human societies, by doing actigraphic recordings from 94 individuals for a total of 1,165 days. Despite their varying genetics, histories, and environments, we find that all three groups show similar sleep organization, suggesting that they express core human sleep patterns, probably characteristic of pre-modern era Homo sapiens. Group sleep time averaged between 5.7 and 7.1 hours across groups with the sleep period between 6.9 and 8.5 h, amounts at the low end of durations reported for healthy subjects in industrial societies, with a difference of nearly one hour between summer and winter sleep durations. Daily variation in sleep duration was strongly linked to the time of sleep onset, rather than the time of sleep offset. Although they lack electric lights, none of these groups began sleep near sunset, with sleep onset occurring, on average, 3.3 h after sunset. Furthermore, awakening was usually before sunrise. The sleep period consistently occurred during the nighttime period of lowest environmental temperature, was not interrupted by extended periods of waking and terminated near the daily nadir of temperature. Light exposure was maximal in the morning and greatly decreased at noon, indicating that all three

groups seek shade at midday, a finding with implications for the timing of light input into the suprachiasmatic nucleus. Napping occurred on less than 7% of days in winter and 22% of days in summer. Mimicking aspects of the natural environment experienced by these groups might be effective in treating certain modern sleep disorders.

Disclosures: **J.M. Siegel:** None. **G. Yetish:** None. **H. Kaplan:** None. **M. Gurven:** None. **B. Wood:** None. **H. Pontzer:** None. **P. Manger:** None. **C. Wilson:** None. **R. McGregor:** None.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.13

Topic: E.08. Biological Rhythms and Sleep

Support: Multi-Institutional Training Program in Genetic/Genomic Approaches to Sleep Disorders (T32 HL110952)

DP22MH104119

NIH grant R01EB018297

Title: Cell-type specific translational profiling during sleep-dependent memory consolidation

Authors: ***T. KARIHARAN**, S. J. ATON;
Mol. Cell. Developmental Biol. MCDB, Univ. of Michigan, Ann Arbor, MI

Abstract: Sleep plays a crucial role in memory consolidation and sleep deprivation causes cognitive impairment. However the molecular mechanism by which sleep mediates structural changes in synapses and neuronal networks is not well understood. Contextual fear memory (CFM) consolidation depends on both post-training sleep and hippocampal protein synthesis. We hypothesized that sleep promotes CFM via cell type-specific protein translational changes. We used translating ribosome affinity purification (TRAP) to assay these changes in pyramidal neurons within the dorsal hippocampus and prefrontal cortex. Cell type specificity was achieved by crossing Ribo-tag transgenic mice (expressing a floxed construct with HA-tagged RPL22 protein) with mice expressing Cre-recombinase in excitatory neurons (Camk2a-CRE). This genetic strategy allowed us to rapidly affinity purify translating ribosomes and associated mRNAs from these specific neuronal populations, after a period of post-CFM-training sleep. TRAP combined with tissue sample pooling significantly increased the ratio between glutamatergic neuronal markers and glial/GABAergic neuronal markers (signal: noise ratio). We

compared three behavioral manipulations: control sleeping mice (sham training+3h sleep), CFM sleeping mice (CFM training+3h sleep), and CFM sleep-deprived mice (CFM training+3h sleep deprivation). Ribosome-associated mRNAs from these groups were quantified and identified using Affymetrix microarray (Mouse gene ST2.1) and confirmed by quantitative real time RT-PCR. Compared to the CFM sleeping group, mRNAs associated with synaptic plasticity, metabolic, epigenetic, cell cycle, circadian, inflammatory, transcription factors and miRNAs showed differential association with ribosomes in CFM sleep-deprived group, in both hippocampus and prefrontal cortex. Surprisingly, however, there were no single mRNAs changed in CFM sleeping group compared to control sleeping group. We hope that by clarifying which mRNAs are translated during sleep-dependent memory consolidation, these studies will open a new window on sleep function in the brain.

Disclosures: T. Kariharan: A. Employment/Salary (full or part-time); Multi-Institutional Training Program in Genetic/Genomic Approaches to Sleep Disorders (T32 HL110952). **S.J. Aton:** A. Employment/Salary (full or part-time); DP2MH104119 and R01EB018297.

Nanosymposium

199. Sleep System and Regulation

Location: S405

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 199.14

Topic: E.08. Biological Rhythms and Sleep

Title: Motor schemas enhance procedural learning speed and sleep-related memory consolidation

Authors: *M. DRESLER[1], N. C. J. MÜLLER[2], L. GENZEL[3], B. KONRAD[2], M. PAWLOWSKI[1], D. NEVILLE[2], G. FERNÁNDEZ[2], A. STEIGER[1];
[1]Max Planck Inst. of Psychiatry, Munich, Germany; [2]Donders Inst., Nijmegen, Netherlands; [3]Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: Memory schemas are acquired knowledge structures into which new, but related information can be integrated easily and rapidly. Schemas have been demonstrated to enhance learning and memory consolidation, however the focus in human memory schema research has been on declarative memory so far. Here we report the effects of a piano motor schema on procedural learning and memory consolidation across the lifespan. 128 participants, systematically varied in terms of piano experience, intelligence, gender, and age, performed a sequential finger tapping task as a simple model for piano playing during two sessions 24 hours apart. We observed significantly enhanced learning speed and offline memory consolidation for

participants with a piano motor schema, however no differences in absolute training gains. In contrast, general intelligence did not affect learning or memory consolidation, indicating that the schema effect was due to differences in piano experience. The consolidation results were, however, largely driven by a strong schema effect in the older participants, whereas younger participants did not benefitted significantly from a piano motor schema, which was reflected by a significant interaction between schema and age. Our results demonstrate that memory schemas enhance learning and consolidation also in the procedural memory domain, and may allow older individuals to compensate for age-related memory decline.

Disclosures: **M. Dresler:** None. **N.C.J. Müller:** None. **L. Genzel:** None. **B. Konrad:** None. **M. Pawlowski:** None. **D. Neville:** None. **G. Fernández:** None. **A. Steiger:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.01

Topic: F.01. Human Cognition and Behavior

Support: 1R01MH095984-01A1

Title: Multivariate assessment of biased competition in human visual attention

Authors: *E. SAAD[1], M. STARRETT[2], J. LAROCQUE[2], N. ROSE[2], B. POSTLE[2];
[1]Dept. of Psychiatry, Univ. of Wisconsin, Madison, WI; [2]Univ. of Wisconsin Madison, Madison, WI

Abstract: One of the most enduring ideas in the past quarter-century of neuroscience is that of biased competition as a mechanism for attentional prioritization. We sought evidence for biased competition among population-level stimulus representations by applying multivariate pattern analysis (MVPA) to fMRI data while subjects performed a visual search and sustained attention task. First, we trained classifiers to discriminate neural activity associated with three stimulus types -- a face; a doughnut; and an abacus - while subjects performed a change-detection task, in which the stimulus flickered with a cycle of 750 msec on/250 msec off, and subjects counted the number of "state changes" that the stimulus undergoes during a block. (The face alternated between two expressions; the doughnut between how large a bite has been taken out of it, and the abacus between two configurations of beads.) The experimental task will begin with the 500 msec presentation of a search target (drawn from the set of three stimulus types) followed by a 7-sec delay, followed by a "search array" comprising the target plus a second stimulus, both

flickering and periodically changing state. Results (n=7), revealed clear evidence of biased competition. During the initial delay period, while the subject retained a representation of the search template, MVPA indicated that there was sustained, elevated active representation of search target. Although the onset of the two stimuli of the search array prompted a transient increase in the neural representation of the nontarget, this representation was quickly suppressed to an level of activity intermediate between that of the target and baseline. Importantly, this suppression was sustained throughout the search array epoch, despite the fact that the target and the nontarget were both on the screen and were comparably salient in terms of bottom-up properties. The ability to assay, with MVPA, the moment-to-moment activation state of neural representations, offers a powerful means for exploring the mechanisms underlying high-level cognition in the human brain.

Disclosures: E. Saad: None. **M. Starrett:** None. **J. LaRocque:** None. **N. Rose:** None. **B. Postle:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.02

Topic: F.01. Human Cognition and Behavior

Title: Neural correlates of dynamic updating in visual working memory in parietal and frontal cortices

Authors: *Q. YU, W. SHIM;
Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Previous research on visual working memory suggests a privileged role of the most recent item in a sequence in working memory. However, the neural correlates of this “recency privilege” remain unclear. Here, using fMRI and a forward encoding model, we directly assessed the dynamic updating process of visual information held in working memory. Participants viewed two sequentially presented gratings and were cued to remember the orientation of one of the gratings over prolonged delays. Our results demonstrated distinct neural tuning patterns for the initial and final memory items in higher-order frontal and parietal regions compared to early visual areas: while the early retinotopic cortex (V1-V3) maintained representation of the task-relevant item only, regardless of its serial position, higher-order cortical regions such as the intraparietal sulcus (IPS) and the frontal eye fields (FEF), carried robust representation of the final item over delay even when it was task-irrelevant. Such selective tuning responses to the

most recent item were maintained in IPS and FEF throughout the entire retention period. This result suggests that the representation of the most recent item in frontal and parietal regions is resistant to updates required by task demand once it is encoded into working memory, thus obtaining a privileged representational state. Our results provide evidence for a potential neural mechanism of dynamic updating in working memory.

Disclosures: Q. Yu: None. **W. Shim:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.03

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant F32EY022874

NIH Grant 1R01EY022355

Title: Decoding reveals superior IPS VSTM representation tracks the behaviorally perceived contents of VSTM

Authors: *Y. XU, K. C. BETTENCOURT;
Psychology, Harvard Univ., Cambridge, MA

Abstract: Where in the human brain are the contents of visual short-term memory (VSTM) stored? Univariate fMRI analyses have suggested that regions in the parietal lobe, in particular superior intraparietal sulcus (IPS), play a central role in VSTM storage. In contrast, fMRI multivariate pattern analysis (MVPA) has implicated primarily sensory cortices, in particular early visual cortex, in the storage of visual information. In a previous study, we found that, while behavioral performance was unaffected by the presence of distracting visual stimuli during the memory delay, in early visual cortex, VSTM decoding performance depended, not only on whether distractors were present during the delay, but also on participants' foreknowledge of their presence. However, in superior IPS, successfully VSTM decoding was obtained regardless of the presence or absence or the predictability of distractors during the delay, mirroring behavioral performance and supporting previous univariate findings. In the present study, we sought to establish a more direct connection between superior IPS VSTM representation and behavior. We asked participants to retain one of six distinctive orientation gratings in a VSTM task and obtained fMRI response patterns for these six orientations during the delay period.

Using support vector machine, we performed pairwise discrimination of these patterns and constructed a neural representation similarity measure for these orientation gratings in early visual areas V1-V4 and superior IPS. We also conducted a behavioral change detection VSTM task using the same six orientated gratings. We used reaction time (RT) in this task as a measure of the similarity between the sample and the test gratings. From the pairwise RTs, we constructed a behavioral representation similarity measure for the six orientations and correlated it with the neural representation similarity measures. We found a significant correlation in superior IPS but not in V1-V4. Thus, representations formed in superior IPS, but not in V1-V4, tracked the behaviorally perceived contents of VSTM. These results provide definitive evidence showing that superior IPS, and not early visual areas, plays a central role in the storage of VSTM contents.

Disclosures: Y. Xu: None. **K.C. Bettencourt:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.04

Topic: F.01. Human Cognition and Behavior

Support: AA017347

AA017168

Title: Blood and brain correlates of cognitive deficits in HIV infection

Authors: *N. M. ZAHR[1,2], R. FAMA[1], T. ROHLFING[2], E. V. SULLIVAN[1], A. PFEFFERBAUM[2];
[1]Dept. of Psychiatry and Behavioral Sci., Stanford Univ. Sch. of Med., Stanford, CA; [2]Neurosci., SRI Intl., Menlo Park, CA

Abstract: Structural MRI, neuropsychological testing (Cambridge Neuropsychological Test Automated Battery (CANTAB)) and blood counts were acquired in individuals positive for HIV infection (HIV, n=36, 49.9yrs, 13 women) and controls (Ctrl, n=31, 44.6yrs, 12 women). Each CANTAB subtest score was standardized on controls' performance and 3 theoretically-driven composite scores were computed: Working Memory (WM), Visual Recognition Memory (VRM), and Decision Making (DM). HIV scored significantly lower (p=.003) than Ctrl on all 3 CANTAB composite scores. MRI data were quantified with an automated parcellation procedure

using the SRI24 atlas. HIV had smaller volumes in two cortical regions: lateral frontal cortex (p=.04) and precentral gyrus (p=.004). Total red blood cell (RBC) count was lower in HIV than Ctrl (p=.004). In the HIV group, poorer WM performance correlated with smaller temporal lobe volumes (r=.56, p=.0003) and lower levels of hemoglobin (r=.40, p=.02) and hemotocrit (r=.37, p=.03). Together, these variables explained 38% of the variance in WM performance; temporal lobe volume uniquely explained a significant proportion of the variance (p=.004). Poorer VRM performance correlated with smaller volumes of temporal (r=.40, p=.01), parietal (r=.36, p=.03), and precuneus (r=.37, p=.03) regions, lower white blood cell (WBC, r=.44, p=.007) and RBC (r=.35, p=.04) counts, and lower hemoglobin (r=.51., p=.001) and hematocrit (r=.50, p=.002) levels. Together, these variables explained 53% of the variance in VRM performance; WBC count independently explained a significant proportion of the variance (p=.009). DM performance did not correlate with any brain volumes but correlated with RBC count (r=.54, p=.0006), hemoglobin (r=.52, p=.0009), and hematocrit (r=.59, p=.0002) levels. Together, these variables explained 40% of the variance in DM performance; RBC count uniquely explained a significant proportion of the variance (p=.03). The combined influence of brain structural integrity and hematological indices of nutrition or physiological status (e.g., effects of medications or of HIV on hematopoiesis) on level of cognitive ability indicates their interactive roles and suggests a need to address cytopenias in HIV patients even in the era of highly active antiretroviral therapy.

Disclosures: **N.M. Zahr:** None. **R. Fama:** None. **T. Rohlfing:** None. **E.V. Sullivan:** None. **A. Pfefferbaum:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.05

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant EY019889

Title: Performance of discrete versus continuous neural coding protocols

Authors: ***J. TEE**[1,2], L. T. MALONEY[1,2,3];
[1]Dept. of Psychology, [2]Inst. for the Interdisciplinary Study of Decision Making, [3]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: INTRODUCTION: Is neural information coded continuously or discretely [1-3]? Neural signaling takes place in channels (i.e. axons) that are continuous, stochastic. Information is typically transmitted not once but many times. Under repeated transmissions using a continuous coding protocol, error accumulates and any signal is eventually reduced to noise. A discrete coding protocol is a method that uses a noisy continuous channel but avoids the accumulation problem by limiting the number of possible transmitted signals (messages) to a finite set [4] and reconstructing the signal at each stage. The cost of a discrete protocol is a positive probability ($e > 0$) that the reconstructed signal is not the transmitted signal. This error probability can be made arbitrarily small [5,6]. We compare the accumulation of errors in discrete and continuous protocols for signals transmitted along a single model axon and through a series of model neurons. METHODS: We modify a model by Rushton [7]. The transmitted signal is bounded within the range [a,b]; a continuous protocol allows any value within [a,b], whereas a discrete protocol only allows a finite subset of values. An axon is modeled as a chain of myelin segments delimited by Nodes of Ranvier (NoR). As the signal propagates along the myelin, it is degraded by conduction loss and thermal noise. The NoR boosts the signal back up with some imperfections before it traverses the next myelinated segment. We first simulate the effect of noise accumulation as a function of the number of myelin-NoR segments. We extend these results to transmission over multiple neurons. RESULTS: With continuous coding, information decays rapidly and irreversibly: after ~100 segments, discrete protocols dominate continuous. DISCUSSION: We conclude that, in the presence of noise, there is no way to communicate reliably between neurons by using a continuous protocol. A discrete protocol is the only feasible option. Maximum information rate is achieved when the signal has only two possible coding values [8]. We extend these results to successive transmissions from one neuron to the next.

REFERENCES

[1] VanRullen R, Koch C. 2003. Is perception discrete or continuous? *Trends Cogn. Sci.* 7:207-213

[2] Luck SJ, Vogel EK. 2013. Visual working memory capacity: from psychophysics and neurobiology to individual differences. *Trends Cogn. Sci.* 17:391-400

[3] Ma WJ, Hussain M, Bays PM. 2014. Changing concepts of working memory. *Nat. Neurosci.* 17:347-56

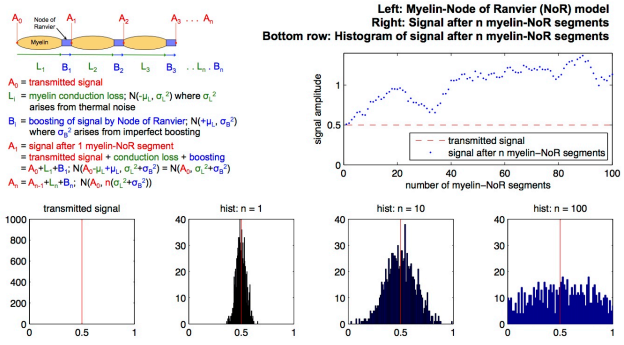
[4] Shannon CE. 1948. A mathematical theory of communication. Bell Syst. Tech. J. 27:379-423,623-656.

[5] VonNeumann J. 1956. Probabilistic logics and the synthesis of reliable organisms from unreliable components. *In CE Shannon and J McCarthy, Eds., Automata Studies. Princeton: Princeton University Press*

[6] Moore EF, Shannon CE. 1956. Reliable circuits using less reliable relays. *J. Franklin Inst.* 262:191-208.

[7] Rushton WAH. 1961. Peripheral coding in the nervous system. *In Rosenblith WA, Ed, Sensory Communication.* Cambridge: MIT Press.

[8] Wiener N. 1961. *Cybernetics: or control and communication in the animal and the machine.* Cambridge: MIT Press.



Disclosures: J. Tee: None. **L.T. Maloney:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.06

Topic: F.01. Human Cognition and Behavior

Support: Barrow Neurological Foundation

Title: Image size has significant and widespread effects on human single neuron firing rates

Authors: *P. N. STEINMETZ[1], J. KINNISON[2], L. PESSOA[2];
[1]Nakamoto Brain Res. Inst., Tempe, AZ; [2]Psychology, Univ. of Maryland, Col. Park, College Park, MD

Abstract: While neurons in the human medial temporal and frontal lobes have been reported to respond to relatively abstract properties of images, such as object identity, very few studies have examined the effect of lower level image properties, such as luminance and contrast. In the present study, we varied the size of images shown to 9 human epilepsy patients as they performed a one-back working memory task while we recorded single neuron activity in the amygdala, hippocampus, anterior cingulate and ventromedial prefrontal cortices. Forty images drawn from 12 categories, including faces, plants, animals, and household objects, were shown in 4 blocks of two sizes: large (subtending ~14 degrees) and small (~9 degrees). The average firing rate from 0-1000 ms after image onset was used as the dependent variable in a linear model of the response including independent factors of image size, luminance (bright or dark), orientation (normal or upside-down for faces), and level of interest to people with autism (for non-faces). An ANOVA showed that image size had a significant effect on the response of neurons in the amygdala (23%), anterior cingulate cortex (29%), hippocampus (24%), and ventromedial prefrontal cortex (20%). These fractions of neurons were significantly above that expected by chance (binomial test, $p<0.05$) and remained significant when each area in each hemisphere was considered separately. Larger image sizes produced reduced responses, suggesting narrower receptive fields, in the right anterior cingulate cortex and left hippocampus. By contrast, larger images sizes produced greater responses in the left ventromedial prefrontal cortex during presentation of images of faces. These results demonstrate a robust effect of relatively low-level image properties, such as image size, on the responses of single neurons in the human medial temporal and frontal lobes. They add to a growing body of evidence that neural coding in these brain areas reflects a variety of image properties represented in a distributed code. These results also highlight the importance of controlling for low-level image properties when studying object selectivity.

Disclosures: **P.N. Steinmetz:** None. **J. Kinnison:** None. **L. Pessoa:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.07

Topic: F.01. Human Cognition and Behavior

Support: DFG Grant BU1837/5-1

Title: Testosterone moderates cognitive performance after a 10 week exercise program in primary school

Authors: ***H. BUDDE**[1,2], F. KOUTSANDRÉOU[3], M. WEGNER[3];
[1]Med. Sch. Hamburg, 20457 Hamburg, Germany; [2]Sport Sci., Reykjavik Univ., Reykjavik, Iceland; [3]Sport Sci., Univ. of Bern, Bern, Switzerland

Abstract: Background: Being physically more active seems to enhance cognitive performance in children. The underlying neurobiological mechanisms in children need further investigations. Being more active influences the hypothalamic-pituitary-gonadal axis (HPG) with its hormone testosterone. The HPG is related to several neurobiological growth processes and therefore might offer an explanatory approach for enhanced cognitive processes. Testosterone changes through acute exercise bouts have shown to influence cognitive performance (Budde et al., 2010) and fine motor skills (Wegner et al., 2014). Methods: 66 children at the age of M = 9.4 years (SD = 0.6) were randomly assigned to an aerobic exercise group (AE), a coordinative exercise group (CE), and a control group (CON). During a 10-week intervention the AE and CE exercised three times a week for 45 minutes, while the CON participated in assisted homework sessions. The AE practiced at a mean intensity of 60-70% of HRmax. The CE completed a coordinative training with a lower intensity of 55-65% of HRmax. The letter-digit span task was performed to measure participants' working memory performance (WMP). Testosterone levels have been conducted as well before and after the intervention. Results/Discussion: A stepwise hierarchical regression analysis showed main effects for change in testosterone level and both exercise groups. An increase in testosterone was associated with improved WMP in all exercising children, $B = .392$, $SE = .174$, $t = 2.26$, $p = .028$. In addition, both participants in the AE, $B = .729$, $SE = .207$, $t = 3.52$, $p = .001$, as well as in the CE, $B = .973$, $SE = .205$, $t = 4.74$, $p = .001$, showed improvements in WMP. Only in the AE increases in WMP were moderated by testosterone changes over the period of intervention, $B = .516$, $SE = .243$, $t = 2.13$, $p = .038$. Therefore, children who experienced higher testosterone increase during the 10 weeks additional aerobic

exercise benefited more in their cognitive performance. References: Budde, H., Voelcker-Rehage, C., Pietrassyk-Kendziorra, S., Machado, S., Ribeiro, P., & Arafat, A. M. (2010). Psychoneuroendocrinology, 35(3), 382-391. Wegner, M., Koedijker, J.M.,& Budde, H. (2014). Plos One 9, e92953.

Disclosures: H. Budde: None. **F. Koutsandréou:** None. **M. Wegner:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.08

Topic: F.01. Human Cognition and Behavior

Support: DFG Grant AX82/2

Title: Gating of feature specific activity during a working memory task

Authors: *M. LESZCZYNSKI[1,2], A. JAHANBEKAM[1], J. FELL[1], O. JENSEN[3], N. AXMACHER[2];
[1]Univ. of Bonn, Bonn, Germany; [2]Dept. of Neuropsychology, Inst. of Cognitive Neurosci., Ruhr Univ. Bochum, Bochum, Germany; [3]Donders Inst. for Brain, Cognition, and Behaviour, Radboud Univ., Nijmegen, Netherlands

Abstract: Successful performance in a working memory (WM) task requires both maintenance of relevant and inhibition of irrelevant information. The alpha rhythm (9-13Hz) has been found to inhibit redundant visuo-spatial information during WM maintenance. Whether such inhibitory role of alpha activity generalizes to maintenance of other features remains elusive. We used a delayed match-to-sample task with two conditions engaging either ventral or dorsal visual stream. In each trial, participants memorized either the identity or the spatial orientation of a trial unique face. Passive viewing with no memory load was used as a control condition. We recorded intracranial EEG (iEEG) in presurgical epilepsy patients simultaneously from the ventral and dorsal visual stream of extrastriate cortex and from prefrontal cortex. We observed a double dissociation between alpha power in dorsal and ventral visual stream. Alpha power was reduced in ventral stream during maintenance of identity, and in the dorsal stream during maintenance of orientation. We further observed a double dissociation of long-range connectivity between task-relevant visual and prefrontal areas. Theta (3-9Hz) phase synchronization between prefrontal cortex and ventral stream was enhanced during maintenance of identity. In contrast it was enhanced between prefrontal cortex and dorsal stream during maintenance of orientation.

Finally, we found an increased inter-regional phase amplitude coupling (PAC) in fronto-dorsal and fronto-ventral networks which suggest that the prefrontal cortex provides phase-based top-down control over feature specific networks in extrastriate cortex. Our results indicate that task-relevant visual areas are activated during WM maintenance via a reduction of alpha power and selectively interact with prefrontal cortex.

Disclosures: M. Leszczynski: None. **A. Jahanbekam:** None. **J. Fell:** None. **O. Jensen:** None. **N. Axmacher:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.09

Topic: F.01. Human Cognition and Behavior

Support: JHU: Science of Learning Institute Postdoctoral Fellowship

NIH Grant K23NS073626

Title: Distinct oscillatory effects of load on working memory for spatial relations vs. locations

Authors: *K. J. BLACKER[1], A. VERGARA[1], J. B. EWEN[1,2,4], S. M. COURTNEY[1,5,3]; [1]Psychological & Brain Sci., Johns Hopkins Univ., Baltimore, MD; [2]Neurol. and Developmental Med., [3]F.M. Kirby Ctr., Kennedy Krieger Inst., Baltimore, MD; [4]Neurol., [5]Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Previous work has demonstrated that maintenance of spatial relationships and spatial locations in working memory (WM) rely on distinct neural mechanisms. It has been shown that maintaining an abstract spatial relation in WM results in suppression of sensory regions, compared to maintaining a concrete spatial location in WM. Previous results suggest a general role of oscillatory activity in suppressing irrelevant sensory information. Suppressing irrelevant information is particularly important when WM load increases. However, studies of the effects of WM load on oscillatory activity suggest a complex relationship since the literature contains many inconsistencies. One possible explanation for these inconsistencies is that the effect of WM load on oscillatory activity might interact with the type of information maintained. The current study used EEG to investigate how oscillations in the alpha (8-13Hz) and theta (4-7Hz) frequency bands change as a function of WM load and the type of memory representation being maintained in WM. Participants were asked to maintain either 1 or 3 spatial locations (i.e.,

absolute spatial coordinates) or 1 or 3 spatial relations (i.e., relative spatial position between objects) in WM. Nonparametric permutation tests were used to test for differences in delay period power between loads and trial types. We replicated our previous work by demonstrating that maintaining 1 spatial relation in WM resulted in increased posterior alpha power compared to maintaining 1 spatial location, which suggests that sensory cortex is suppressed when a spatial relation is maintained. Consistent with some previous studies, increasing WM load for spatial locations resulted in increased posterior alpha power. Increasing WM load for spatial relations, however, resulted in marginally decreased posterior alpha power. Theta power also demonstrated a dissociation between trial types. While higher WM load for locations lead to lower frontal midline theta power, maintaining a higher load of spatial relations resulted in less posterior theta power. These results suggest that the distinct neural mechanisms found previously for WM maintenance of spatial relations vs. locations is not simply a function of load or difficulty. Importantly, these results suggest that within the context of WM, low frequency oscillations reflect more than a generic effect of load, difficulty, or suppression of sensory information. These low frequency bands appear to also be sensitive to the type of representation that is maintained in WM and further support the idea that the neural mechanisms for abstract, relational WM are distinct from those for concrete, sensory WM.

Disclosures: K.J. Blacker: None. **A. Vergara:** None. **J.B. Ewen:** None. **S.M. Courtney:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.10

Topic: F.01. Human Cognition and Behavior

Support: K08NH080339

MH047073

P50MH45156

Title: Contribution of phase amplitude theta-gamma coupling to visual working memory maintenance of non-serially presented items

Authors: *N. POLIZZOTTO[1], N. RAMAKRISHNAN[1], C. WALKER[1], K. FISSEL[2], E. BELCHER[3], R. CHO[1];

[1]Psychiatry, UTHSC-H, Houston, TX; [2]Univ. of Pittsburgh, Pittsburgh, PA; [3]Univ. of Rochester, Rochester, NY

Abstract: BACKGROUND - Short-term memories are represented by patterns of synchronized activity across a large-scale fronto-parietal network. Multiple bands appears to participate both through amplitude modulation and cross-frequency interactions. Gamma-band activity generally underlies the active maintenance of relevant working memory (WM) items, however cross-frequency couplings are believed to be stimulus and task dependent. While theta-gamma phase-amplitude coupling (TGC) role is suggested to be limited to sequential ordering of items during serial presentation in non-visual tasks, such fronto-temporal pattern has been suggested to be replaced by involvement of alpha synchronization in parietal-occipital networks during coding of discrete visual or spatial information. Such a perspective is largely based on robust positive findings of TGC in sequential presentations and negative findings of theta amplitude modulation during maintenance of simultaneously visually presented items. However the biophysical mechanisms underlying coupling and amplitude can be distinguished, and to date no study has specifically probed the role of TGC in the latter context. Here we provide MEG evidence supporting memory load-dependent TGC during maintenance of simultaneously visually presented items. METHODS - Ten subjects performed a visual delayed-match-to sample task during MEG. Source-localized activity (cortically-constrained minimum-norm current estimates) was wavelet transformed to analytically extract frequency specific phase and amplitude measures. The strength of their association during the maintenance was quantified by mutual information and provided coupling estimates for each trial. RESULTS - TGC in the right middle frontal gyrus appeared to be modulated by the working memory load. Moreover individual coupling measures also showed robust correlations with WM capacity (r=0.8). CONCLUSIONS - Such findings suggest TGC to be a general mechanism underlying WM, extending to maintenance of non-serially presented items. The evidence speaks against the sequential ordering functional hypothesis of coupling or suggests that itemization and storing of a simultaneously presented array is effectively accomplished by items ordering on a time microscale. Impairments of the TGC machinery should be investigated in the pathophysiology of conditions accompanied by generalized working memory deficits.

Disclosures: **N. Polizzotto:** None. **N. Ramakrishnan:** None. **C. Walker:** None. **K. Fissel:** None. **E. Belcher:** None. **R. Cho:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.11

Topic: F.01. Human Cognition and Behavior

Support: Swedish Research Council (349-2007-8654, Linnaeus Centre HEAD)

Social Research Council of Great Britain (RES-620–28–6001; RES-620-28-0002)

Title: Working memory and crossmodal plasticity in congenitally deaf individuals

Authors: *V. CARDIN[1], M. RUDNER[2], R. F. DE OLIVEIRA[3], J. ANDIN[2], L. BEESE[1], B. WOLL[1], J. RONNBERG[2];
[1]Univ. Col. London, London, United Kingdom; [2]Linkoping Univ., Linkoping, Sweden; [3]London South Bank Univ., London, United Kingdom

Abstract: Crossmodal reorganization in humans is the result of an interplay between sensory and cognitive factors. Congenital deafness provides a unique model to understand the contribution of each of these factors, given that neural reorganization is not only caused by sensory deprivation, but also by the use of language in a visual modality (i.e. sign language and lipreading). Here we characterized plastic changes driven by auditory deprivation and sign language experience in the neural substrates supporting visual working memory (WM). We conducted a functional magnetic resonance imaging (fMRI) experiment with three groups of participants: deaf native signers, hearing native signers and hearing non-signers. Participants performed a 2-back WM task and a control task on two sets of stimuli: signs from British Sign Language or moving non-sense objects. Stimuli were presented as point-light displays to control for differences in visual features. Our results show characteristic activations in a fronto-parietal network for WM processing in all groups, independently of stimulus type. We also replicated previous findings showing stronger activations in deaf signers for all stimuli and tasks in the right posterior superior temporal cortex (STC) - a crossmodal plasticity effect for visuospatial processing driven by auditory deprivation. The group of deaf signers also showed stronger bilateral STC activation for sign language stimuli, an effect that was not present in the hearing signers group. Stronger activations in bilateral STC and reduced activation in the left inferior parietal cortex for WM were found in deaf signers compared to both groups of hearing individuals. These activations were independent of the linguistic content of the stimuli, being observed in both WM conditions: signs and objects. These results suggest a cognitive role for STC in deaf individuals, beyond sign language processing.

Disclosures: V. Cardin: None. **M. Rudner:** None. **R.F. de Oliveira:** None. **J. Andin:** None. **L. Beese:** None. **B. Woll:** None. **J. Ronnberg:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.12

Topic: F.01. Human Cognition and Behavior

Support: Academy of Finland Grant 259752

Academy of Finland Grant 273147

Academy of Finland Grant 137795

Sigrid Jusélius Foundation Grant

Päivikki and Sakari Sohlberg Foundation Grant

Instrumentarium Foundation Grant

Finnish Cultural Foundation Grant

Title: Navigated transcranial magnetic stimulation of prefrontal cortex modulates tactile working memory

Authors: J. GOGULSKI[1], R. ZETTER[2], *A. PERTOVAARA[1], S. CARLSON[2,1,3];
[1]Fac Med. Univ. Helsinki, Helsinki, Finland; [2]Dept. of Neurosci. and Biomed. Engin., [3]Aalto Neuroimaging, Aalto Univ. Sch. of Sci., Espoo, Finland

Abstract: Brain imaging studies show that visual, auditory and tactile working memory (WM) tasks activate the prefrontal cortex (PFC), and suggest possible functional parcellation between spatial and nonspatial WM. Navigated transcranial magnetic stimulation (nTMS) of a middle frontal gyrus (MFG) site with tractography-informed connectivity with the primary somatosensory cortex (S1) facilitates tactile working memory (WM)[1]. Here we examined with nTMS the role of the MFG-S1 link in tactile temporal and spatial WM and introspective accuracy, and compared the results to nTMS of a tractography-informed SFG-S1 link and a control cortical site (vertex). Healthy, right-handed subjects performed tactile temporal and spatial WM tasks. Tactile stimuli were delivered using a Braille stimulator (Metec AG, Stuttgart, Germany). Trials consisted of tactile mechanical stimulus pairs, whose interstimulus interval and distance were varied. Before the WM experiment, we examined whether the Braille pin distance and interstimulus interval (ISI) affect temporal discrimination of a pin pair. Then, in the temporal WM task, the subjects indicated, by pressing one of two buttons, whether the first or second stimulus pair was longer. In the spatial WM task, the subjects answered whether the first and the second stimulus pair had the same spatial pattern or not. In addition, subjects gave a verbal confidence rating for each response. WM performance was evaluated with Type I Receiver

Operating Characteristic curve (ROC[AUC]) and introspective accuracy with Type II ROC(AUC)^2. A single nTMS pulse was delivered during WM retention period to the MFG-S1 link, SFG-S1 link, or to vertex. ISI (n=10, F=86.1, p=0.05), between the pins of a pair affected temporal discrimination. nTMS of the PFC affected WM performance. So far (n=5), ANOVA showed significance when comparing Type I ROC(AUC)'s of the three different stimulation sites and two tasks (F=4.7, p=0.03), the most pronounced changes being facilitation of temporal and suppression of spatial WM performance by nTMS of the MFG-S1 link. Comparing Type II ROC(AUC)'s produced a near-to-significant result, the most pronounced change being facilitation of introspective accuracy by nTMS of the SFG-S1 link. The results suggest that the PFC, through the MFG-S1 link, may control in a dissociative fashion tactile temporal versus spatial WM ability. Moreover, Type II ROC responses suggest that the PFC, through the SFG-S1 link, may affect metacognitive, introspective accuracy. References 1. Hannula et al., Neuroimage 2010;49:1091-8. 2. Fleming et al., Science 2010;329:1541-3.

Disclosures: J. Gogulski: None. **R. Zetter:** None. **A. Pertovaara:** None. **S. Carlson:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.13

Topic: F.01. Human Cognition and Behavior

Support: ERC-2012-AdG 320708-iCONNECT

Title: Regulation of working memory activity through fMRI neurofeedback

Authors: *M. VAN DEN BOOM, M. JANSMA, N. F. RAMSEY;
Brain Ctr. Rudolf Magnus / Neurol. and Neurosurg., Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: Background. Working memory (WM) is an important brain function for cognition as it is optimized for storage and manipulation of novel information. Due to the very limited capacity of WM, efficient use is likely to be an important factor for cognitive performance. Regulation of brain activity in areas relevant to WM might prove beneficial for WM efficiency. Several neuroimaging studies have shown that the left dorsolateral prefrontal cortex (DLPFC) is an important part of the WM system in the brain [1]. In the current study we examined the ability to regulate the level of activity in the left DLPFC using neurofeedback (NF) with fMRI. Method. 24 healthy volunteers participated in a 7 tesla fMRI experiment (TR/TE: 2.0 s/25 ms; 2.2 mm

isotropic). A ‘count back’ paradigm was used to reliably activate the left DLPFC. Participants performed a NF task, where they were able to control the position of a figure on the screen by the BOLD signal in left DLPFC. By moving the figure, subjects could pick apples from a tree, where the goal was to pick as many apples as they could in 2.5 minutes. Participants were divided in an experimental group (N=13) that was allowed to practice the task for five periods and a control group (N=11) which received sham feedback during these five periods. Both groups also performed the task before and after these five practice periods. Several characteristics of the BOLD signal were analyzed in a number of subjects to examine the effect of practice on the ability to control DLPFC activity. Results. The experimental group showed an improvement in task performance after practice that was significantly higher than that of the control group ($F(1,22) = 3.38$, $p = .040$). Furthermore, the slope of the declining BOLD signal correlated highly with the task performance ($r = 0.62$, $p < .001$). The experimental group was able to decrease their BOLD signal significantly faster after practice ($t(9) = -2.940$, $p = .016$), which was not the case in the control group ($t(5) = .081$, ns). Conclusion. The results provide evidence that it is possible to gain control over DLPFC activity with a short period of practice. The significant improvement of the performance and faster decline of the BOLD signal indicate that the improvement is due to increased control over deactivation of the left DLPFC. Our results suggest the possibility to use NF as a way to improve efficiency in WM usage, and can thereby perhaps improve cognition. Additionally, a more efficient use of WM could be beneficial in patients with schizophrenia, where the WM-system responds differently to WM demands in comparison to healthy people [2]. Refs. [1] Wager, T. D. & Smith, E. E. (2003). Cog Aff Beh NeuroSci, 3(4) [2] Jansma et al. (2004). Schiz res, 68(2)

Disclosures: M. Van Den Boom: None. **M. Jansma:** None. **N.F. Ramsey:** None.

Nanosymposium

200. Assessment and Modulation of Human Working Memory

Location: N227

Time: Sunday, October 18, 2015, 1:00 PM - 4:30 PM

Presentation Number: 200.14

Topic: F.01. Human Cognition and Behavior

Support: JSPS Grant M4081355

NTU 5K Incentive Grant M4081302

SINAPSE R-719-001-102-232

Title: Preparatory oscillatory activity to encode spatial, temporal and item information during a working memory task

Authors: *Y. YICK[1], F. TAYA[2], J. LIM[1], J. DE SOUZA[2], Y. SUN[2], A. BEZERIANOS[2], A. CHEN[1];
[1]Nanyang Technological Univ., Singapore, Singapore; [2]Singapore Inst. for Neurotechnology, Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Spatial, temporal and item information are the constituent of contextual experience in memory, recent evidence has indicated that these information are associated with different frequency bands of neural oscillation during the maintenance stage of working memory tasks. Temporal information has been consistently linked to the theta (4-8 Hz) band; whereas spatial and item information have been observed in the alpha (8-12 Hz) and the beta (14-28 Hz) bands. We examined whether oscillatory neural activity during the presentation of the preparatory encoding cue influences the memory encoding for a working memory task. Specifically, we examined whether this activity varied according to the type of information required for encoding, or whether a similar set of preparatory activity operated independent of the task demand. EEG activity was recorded while participants performed a working memory task in which they were cued on a trial-by-trial basis to encode the "temporal", "spatial", or "item" information for four sequentially-presented encoding images that appeared at four fixed screen locations. After a short delay, participants were required to retrieve the relevant information according to the pre-stimulus cue. For temporal trials, participants indicated "when" the test image appeared in the study sequence. For location trials, participants indicated "where" the test image appeared on the screen location. For item trials, participants indicated "which" image, out of four (1 old and 3 new), was previously seen. Behavioral accuracy and reaction times were similar across conditions. Neural oscillatory activity time-locked to the encoding cues was calculated for the 3 conditions based on trials associated with correct retrieval responses. The preliminary EEG analysis indicated that the preparatory oscillatory activity in the theta, alpha and beta bands varied according to the specific task demands (type of information to encode) indicated by the preparatory encoding cues. This suggests that the idea of a generic preparatory mechanism independent of task demands is too simple, instead the preparatory mechanism can vary according to the type of information required to encode. These different neural oscillatory activities could reflect the allocations of cognitive resources according to the working memory demand.

Disclosures: **Y. Yick:** A. Employment/Salary (full or part-time); Nanyang Technological University. **F. Taya:** A. Employment/Salary (full or part-time); National University of Singapore. **J. Lim:** A. Employment/Salary (full or part-time); Nanyang Technological University. **J. de Souza:** A. Employment/Salary (full or part-time); National University of Singapore. **Y. Sun:** A. Employment/Salary (full or part-time); National University of Singapore. **A. Bezerianos:** A. Employment/Salary (full or part-time); National University of Singapore. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or

consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Singapore Institute for Neurotechnology. **A. Chen:** A. Employment/Salary (full or part-time); Nanyang Technological University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Japan Society for the Promotion of Science, Nanyang Technological University.

Nanosymposium

201. Executive Function: Learning and Memory

Location: N228

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 201.01

Topic: F.02. Animal Cognition and Behavior

Support: NIH NICHD CRCNS R01-HD071686

NIH NINDS R01-NS065065

Burroughs Wellcome Fund

NIH 3T32NS007391-15S2

Title: Network constraints dictate the timescale of learning new brain-computer interfaces

Authors: *E. R. OBY[1], A. DEGENHART[1], E. TYLER-KABARA[1], B. YU[2], A. BATISTA[1]; [1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Learning requires networks of neurons to generate new patterns of activity. Brain-computer interface (BCI) users can learn to modulate neural activity to control a computer cursor, via a relationship specified by the experimenter, making it a valuable paradigm for studying learning. To this end, we used a closed-loop BCI paradigm to study learning in a population of neurons recorded in the primary motor cortex (M1) of a rhesus monkey. The activity of a neural population can be represented in a high-dimensional neural space, wherein each dimension corresponds to the activity of one neuron. Characteristic activity patterns comprise a low dimensional subspace, termed the intrinsic manifold (IM), within the neural space. We can create new BCI mappings for the monkey to learn that require unique neural activity patterns within the IM or outside the IM. In our previous work, we found that the IM shapes learning, such that, on the timescale of hours, the monkeys could readily learn to control the cursor using neural activity patterns within the IM, but could not consistently generate neural

activity patterns outside the IM. Here, we hypothesized that with extended exposure to outside-manifold mappings the monkey could learn to generate these neural activity patterns more consistently. We observed improved learning of outside-manifold mappings when the monkey was given several days to practice compared to learning within one day. In order to achieve this, we guided the monkey through a series of successively more difficult mappings, which traversed the neural space between the IM and the space required to perform well under the outside-manifold mapping. Using this "neural coaching", the animal improved performance with outside-manifold mappings within 5-7 days. In summary, our multi-day coaching strategy facilitated the learning of neural activity patterns that were initially outside the IM. This raises important questions about how extended practice leads to skill: perhaps it overcomes network constraints, or perhaps it rearranges the existing network structure.

Disclosures: E.R. Oby: None. **A. Degenhart:** None. **E. Tyler-Kabara:** None. **B. Yu:** None. **A. Batista:** None.

Nanosymposium

201. Executive Function: Learning and Memory

Location: N228

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 201.02

Topic: F.02. Animal Cognition and Behavior

Support: DFG He1721/10-1

Title: Working memory related neuronal activity in early auditory cortex

Authors: *M. BROSCH, Y. HUANG;
Leibniz Inst. für Neurobiologie, Magdeburg, Germany

Abstract: We report that neuronal activity in the auditory cortex of monkeys is related to auditory working memory (WM). The monkeys performed different tasks that were designed such that contrasting them allowed to separate activity related to WM from activity related to other aspects of WM tasks. Neuronal activity related to auditory WM was specific to the frequency of the to-be-remembered tone and was not present in trials in which subjects did not perform the WM tasks correctly. Our results underline the importance of storing information about sounds for several seconds, which is a prerequisite for the analysis of temporal sound patterns in auditory cortex. They also provide support for the hypothesis that early sensory cortex maintains representations of WM content.

Disclosures: **M. Brosch:** None. **Y. Huang:** None.

Nanosymposium

201. Executive Function: Learning and Memory

Location: N228

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 201.03

Topic: F.02. Animal Cognition and Behavior

Support: PA Department of Health Research Formula SAP#4100057653

NIH Grant P30NS076405

Title: Distinct timescales of cortical reorganization in a long-term learning task

Authors: ***X. ZHOU**[1,2], R. TIEN[3,2], S. M. CHASE[1,2];
[1]Biomed. Engin., Carnegie Mellon Univ., Pittsburgh, PA; [2]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [3]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: What are the neural mechanisms of skill acquisition? Motor skill learning is associated with a functional reorganization of the neural activity in primary motor cortex. However, the link between these changes in neural activity and the behavioral improvement that occurs is not well understood, especially for long-term practice that takes place over several weeks. Here we leveraged a brain-computer interface (BCI) learning paradigm to probe this link in detail. In a BCI, the experimenter provides the subject a definitive mapping between neural activity and the movement of an effector (in our case, a computer cursor). Each new BCI mapping thus provides the subject a new tool that must be mastered through continued practice. We trained two Rhesus macaques to perform a two-dimensional center-out cursor control task using a BCI. Each BCI mapped neural activity recorded from a multi-electrode recording array placed in primary motor cortex to the velocity of the computer cursor using a population vector algorithm decoder. Once subjects were proficient at the brain-control task, we provided new mappings for them to learn by rotating the directions in which randomly selected subsets of neurons pushed the cursor. We then held this decoder fixed for several weeks by tracking the neurons so that subjects would have extensive time to practice under the new mapping. Our prior work has identified two types of adaptive responses to this type of perturbation: a global "re-aiming" response that impacts the activity of all neurons equally, and a local "re-tuning" response selective to the perturbed subset of neurons (Jarosiewicz et al. 2008; Chase et al., 2012). In that work, we determined that the global re-aiming response dominated the adaptive response that occurs within the first several hundred trials, accounting for ~85% of the overall

error reduction, while re-tuning accounted for only 15% of the response. Here we found that the weak local re-tuning response gradually builds up with long-term training, eventually accounting for nearly half of the overall error reduction. Interestingly, this long-term cortical reorganization occurs even after the angular error has reached asymptote (which typically takes only one day of training on perturbed BCI). Our study suggests that skill acquisition is a two-stage process, in which rapid global changes in neural activity acting to reduce movement error are followed by gradual local changes in neural tuning acting to increase efficiency.

Disclosures: X. Zhou: None. **R. Tien:** None. **S.M. Chase:** None.

Nanosymposium

201. Executive Function: Learning and Memory

Location: N228

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 201.04

Topic: F.02. Animal Cognition and Behavior

Support: FAPESP

Title: Early postnatal nociceptive stimulation results in deficits of spatial memory in male rats

Authors: *L. COVOLAN, C. T. AMARAL, B. ANTONIO, M. G. M. OLIVEIRA, R. GUINSBURG;
Univ. Federal Sao Paulo, Sao Paulo 04023-900, Brazil

Abstract: In order to increase the survival rate, prematurely-born infants are exposed to multiple invasive procedures. Newborn rats and humans evoke similar behavioral repertoire in response to noxious stimulation. Previous studies have shown that early noxious stimuli may alter the neurogenesis rate in the dentate gyrus and the behavioral repertoire of adult rats. Having this in mind, here we evaluated the late effects of noxious stimulation, imposed in different phases of development on spatial memory by means object recognition (OR) and Morris water maze (WM) tests, carried on in 60 day-old male and female rats. Noxious stimulation was induced by intra-plantar injection of Complete Freund's adjuvant (CFA) on postnatal (P) day 1 (group P1) or 8 (P8). Control animals were not stimulated in any way. In WM three domains of the task were evaluated: task acquisition, probe trial performance and reversal re-acquisition. The number of Nissl stained cells in the dentate granule cell layer was accessed after P60 by stereological counting. The OR test revealed that P1 male rats had poor long term memory compared to control and P8 groups. In the WM test no differences were detected in terms of short- or long-term memory in early postnatal-stimulated male and female rats, when compared to controls.

However, the ability to find the hidden platform moved to a new position was reduced in P1 male rats. The number of dentate granule cells in P8 males is higher than all other groups. This study confirm the previous findings that neonatal noxious alter hippocampal neurogenesis and demonstrates that noxious stimulation on P1 results in spatial deficit in male animals but does not disrupt the development of the hippocampus-dependent strategies of learning and memory.

Disclosures: L. Covolan: None. **C.T. Amaral:** None. **B. Antonio:** None. **M.G.M. Oliveira:** None. **R. Guinsburg:** None.

Nanosymposium

201. Executive Function: Learning and Memory

Location: N228

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 201.05

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant R01MH085828

Title: A comparison of reward prediction error and value encoding during new associative learning in the primate hippocampus and striatum

Authors: *S.-P. KU[1], E. L. HARGREAVES[2], W. A. SUZUKI[1];
[1]Ctr. For Neurosci., New York Univ., New York, NY; [2]Robert Wood Johnson Med. Sch., New Brunswick, NJ

Abstract: In reinforcement learning, reward outcome evaluation and action selection are thought to take place in prefrontal cortex, parietal lobe and striatum. By contrast, the hippocampus (HPC) is thought to influence reinforcement learning by providing contextual information(1). Although one study in rodents(2) showed that the HPC also encodes value information during reinforcement learning, human imaging results have not shown consistent value encoding in HPC. To directly compare the reinforcement learning signals in the monkey HPC and striatum, we recorded 46 cells in the HPC in 3 monkeys and 59 cells in the striatum in 1 monkey as they performed a conditional motor associative learning task. In this task, monkeys learned to associate particular scenes with particular rewarded target locations by trial-and-error. Every trial started with a fixation period (750ms) followed by the presentation of a natural scene (1000ms). After a delay period (750ms) where fixation was still required, the fixation spot disappeared and two saccade targets were presented. Monkeys were required to make an eye movement to one of the targets. An auditory cue was given if they made a correct choice and animals were rewarded with juice after a random delay (750 ~ 1200 ms). To successfully perform this task, monkeys

need to update both the action value (how good the particular action will be given the particular scene) and the chosen value (how good the chosen action is given the current scene) by evaluating reward prediction error (RPE), defined as the difference between the reward outcome and the predicted action value of the current trial. Consistent with previous studies, we found a large proportion of neurons in the monkey striatum encoding action value (30%), chosen value (49%) and RPE (34%). Consistent with a recent report in rats(2), we also found a substantial proportion of neurons in HPC that signaled action value (30%), chosen value (28%) and RPE (26%). Like the striatal neurons half of the hippocampal neurons signal RPE or action value before the animal's behavioral response. Half of the striatal chosen value cells also signals this information before the animal's behavioral response. By contrast, most of the hippocampal chosen value cells signaled this information after the animal's behavioral choice was made. The results provide new evidence that hippocampal neurons signals robust reward prediction error signals during an associative learning task. The analysis of the time course of the signals across the two areas suggest a more prominent role of the striatum relative to the HPC specifically in chosen value. Reference 1.Lee D. et. al., 2012 Ann. Rev. Neuro. 2.Lee H. et. al., 2012 J. Neuros.

Disclosures: **S. Ku:** None. **E.L. Hargreaves:** None. **W.A. Suzuki:** None.

Nanosymposium

201. Executive Function: Learning and Memory

Location: N228

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 201.06

Topic: F.01. Human Cognition and Behavior

Title: Cognitive emotion regulation affects prediction error-related activity and connectivity in a VST-centered network of motivated behavior

Authors: *S. MULEJ BRATEC[1,3], X. XIE[1,4], Y. WANG[5], G. SCHMID[2], C. ZIMMER[1], A. WOHLSCHLAEGER[1], V. RIEDL[1], C. SORG[1];
[1]TUM-NIC Neuroimaging Ctr. & Dept. of Neuroradiology, [2]Dept. of Psychosomatics and Psychotherapy, Klinikum Rechts Der Isar Der TU Muenchen, Munich, Germany; [3]Grad. Sch. of Systemic Neurosciences, [4]Dept. of Psychology, Ludwig-Maximilian-Universitaet Muenchen, Munich, Germany; [5]Ctr. for Cognitive Neuroscience, Neurosci. and Behavioral Disorders Program, Duke-NUS Grad. Med. Sch. Singapore, Singapore, Singapore

Abstract: The current study investigated how cognitive emotion regulation (CER), a critical human ability to face emotional stimuli in a behaviorally flexible way, relates with aversive prediction error (aPE) activity - a critical brain signal relevant for adaptive behavior - in the

ventral striatum (VST). VST is widely known for its role in Pavlovian conditioning, a form of associative learning driven by PEs. A number of studies have indeed demonstrated the existence of aPEs in the VST. Based on animal models of adaptive motivated behavior, VST is seen as an 'integration area', controlled by a number of afferent regions, including the prefrontal cortex (PFC), amygdala, hippocampus and ventral tegmental area (VTA). In the case of human emotional behavior, which is characterized by both emotion adaption and emotion regulation, these models suggest that VST aPE-related signals might be modulated by signals from the PFC, hippocampus, amygdala, or VTA during CER. Using aversive classical conditioning with and without CER (i.e., self-distancing) during fMRI, we provided evidence that CER modulated both aPE-related activity in the VST, as well as aPE-related functional connectivity between the VST afferents (i.e., PFC, amygdala, hippocampus, VTA) and VST. Data suggest that VST aPE activity is a critical target in human CER.

Disclosures: **S. Mulej Bratec:** None. **X. Xie:** None. **Y. Wang:** None. **G. Schmid:** None. **C. Zimmer:** None. **A. Wohlschlaeger:** None. **V. Riedl:** None. **C. Sorg:** None.

Nanosymposium

201. Executive Function: Learning and Memory

Location: N228

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 201.07

Topic: F.02. Animal Cognition and Behavior

Support: NSERC

CIHR

Title: Correlated variability and the fidelity of prefrontal working memory representations

Authors: ***M. LEAVITT**[1], A. J. SACHS[3], J. C. MARTINEZ-TRUJILLO[4,2];
[1]Physiol., [2]Dept. of Physiol., McGill Univ., Montreal, QC, Canada; [3]Neurosurg., Ottawa Hosp. Res. Institute, Univ. of Ottawa, Ottawa, ON, Canada; [4]Dept. of Physiol. and Pharmacol., Robarts Res. Institute, Univ. of Western Ontario, London, ON, Canada

Abstract: Single neurons in the primate dorsolateral prefrontal cortex (dlPFC) are thought to encode working memory (WM) representations of visual space via sustained firing after the removal of external input. Four decades of studies and resulting models tacitly assume that such spatial representations are homogenous; this assumption has never been quantitatively verified. Furthermore, it is unclear if single neuron representations of WM differ from those of

simultaneously-recorded neuronal populations. For example, correlated variability between neurons is known to have dramatic effects on the fidelity of neural representations in other tasks and brain areas, but experimental evidence addressing its effects on WM representations is scant. In order to investigate these problems, we used microelectrode arrays to record from neural ensembles in macaque dlPFC area 8a while subjects performed an oculomotor delayed response task. Here we report that WM representations of visual space in macaque dlPFC area 8a are biased by both vertical and horizontal meridians of the visual field, resulting in a non-linear, quadrantic division of mnemonic space. This bias is consistent across multiple levels of examination: in the firing rates of single neurons, in their ensemble code, in the structure of correlated variability between pairs of neurons, and in the patterns of eye movements. Removing the correlated variability between neurons increases the fidelity of WM representations. These results reveal the need to re-conceptualize models of WM to accommodate the observed non-linearities and correlated variability underlying mnemonic representations of visual space.

Disclosures: **M. Leavitt:** None. **A.J. Sachs:** None. **J.C. Martinez-Trujillo:** None.

Nanosymposium

201. Executive Function: Learning and Memory

Location: N228

Time: Sunday, October 18, 2015, 1:00 PM - 3:00 PM

Presentation Number: 201.08

Topic: F.03. Motivation and Emotion

Title: Neural mechanisms of Social comparison on cooperative decision-making

Authors: ***X. GONG**, A. G. SANFEY;
Donders Institute, Radboud Univ. Nijmegen, Nijmegen, Netherlands

Abstract: Social comparison, whereby we utilize information to evaluate our standing relative to others, is pervasive in human society, and has been liked to a variety of behavioral outcomes. We are interested here at how social comparison plays a role in subsequent interactive social decision-making. The particular social choice we explore is that of cooperation. Cooperation is one of the most important functions in human society. Successful cooperation often benefits both ourselves and others, however, cooperative choices often put us at risk of being taken advantage of by others. The present study aimed to identify the neural mechanisms by which social comparison impacts cooperative decisions. Participants first played a simple cognitive reaction time task, following which various forms of feedback were given about their performance. Participants were sometimes told they performed the best (top rank), sometimes average (middle rank) and sometimes worst (bottom rank), Two conditions were used, one in which these

rankings were relative to other players, and one in which the rankings were relative to their own previous performance, thereby with no social impact. Participants then played a modified Public Goods Game, a standard experimental measure of cooperation. Behaviorally, we found that individuals were more cooperative when they were previously ranked higher as compared to those who ranked at the bottom. This comparison effect is similar but less strong in the non-social (self comparison) condition than the social condition. In terms of neural activation, comparing feedback from higher ranks to that of lower ranks was associated with activity in the right caudate. Secondly, when examining the other- and self-comparison conditions, comparing high versus low rankings led to increased activity in bilateral putamen in the other-comparison condition, whereas this effect was not observed in the self-comparison condition. Interestingly, contrasts between individuals at the higher ranks in the social as compared to the non-social condition was positively correlated with the activity in the bilateral insula, anterior cingulate cortex (ACC), bilateral caudate, medial prefrontal cortex (mPFC), supplementary motor area (SMA), and bilateral temporal parental junction (TPJ). In summary, the present research shows that social comparison (induced via social rankings) shows a demonstrable effect on cooperative behavior, and that the motivation to cooperate may be associated with both reward processing (the so-called 'warm-glow' effect of altruism) as well as with theory of mind mechanisms.

Disclosures: X. Gong: None. **A.G. Sanfey:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.01

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: NIH NIAAA R21 AA021462 (IP)

NIH NIAAA U01 AA0209260 (RDM)

Title: Defining global histone H3 lysine 4 trimethylation (H3K4Me3) changes in the postmortem brain of alcoholics using ChIP-seq

Authors: *K. MARBALLI[1], S. P. FARRIS[1], R. D. MAYFIELD[1], A. WEBER-HALL[2], A. BATTENHOUSE[2], V. IYER[2], R. A. HARRIS[1], I. PONOMAREV[1];
[1]Waggoner Ctr., [2]Inst. for Cell. and Mol. Biol., Univ. of Texas At Austin, Austin, TX

Abstract: Alcohol abuse is a devastating addiction disorder that causes severe damage to multiple organ systems including the brain. Alcohol can exert these effects via global gene expression changes through epigenetic phenomena such as DNA methylation and histone modifications. One such histone modification that is usually associated with active genes and implicated in several psychiatric disorders is the histone 3 lysine 4 trimethylation (H3K4Me3) mark. Our previous studies showed altered total H3K4Me3 levels in brain samples of alcoholics that correlated with gene expression in a subset of genes (Ponomarev et al., 2012, J. Neurosci). As a follow-up to these studies, we used a modified version of the ChIP-seq (chromatin immunoprecipitation followed by next generation sequencing) protocol [n=8 alcoholic and n=8 control, post-mortem frontal cortex] to determine individual genes differentially modified in alcoholics vs. controls. Our preliminary data suggests a total of 2,260 H3K4Me3 peaks (showing differential abundance between groups (n=874 lower occupancy, n=1386 higher occupancy) in alcoholics vs. controls, $p < 0.05$). Functional enrichment analysis of peak-associated genes identified several candidates involved in synapse formation, assembly (e.g. BDNF), voltage-gated channel (e.g. KCN4) and protein kinase activity (e.g. ERBB4). We are currently expanding on our preliminary studies with extended sample sizes (total n=24 alcoholics, n=24 control samples), in order to identify additional biological networks that are regulated significantly by H3K4Me3. We aim to uncover novel gene targets of H3K4Me3 that are involved in alcohol abuse to aid therapeutic intervention.

Disclosures: **K. Marballi:** None. **S.P. Farris:** None. **R.D. Mayfield:** None. **A. Weber-Hall:** None. **A. Battenhouse:** None. **V. Iyer:** None. **R.A. Harris:** None. **I. Ponomarev:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.02

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: Luxembourg Centre for Systems Biomedicine Program (ISB-LCSB Strategic Partnership)

UNCF-Merck Postdoctoral Science Research Fellowship

NIH Grant GM076547

Title: Identifying subpopulations in iPSC-derived cortical neurons using single-cell analysis of gene expression

Authors: *M. N. SHELTON[1], R. BARGAJE[1], K. TRACHANA[1], C. CHADICK[1], A. FOUQUIER D'HEROUEL[2], S. HUANG[1], L. HOOD[1];
[1]Inst. For Systems Biol., Seattle, WA; [2]Luxembourg Ctr. for Systems Biomedicine, Univ. of Luxembourg, Luxembourg City, Luxembourg

Abstract: Traditional biological studies of bulk cell populations mask the true heterogeneity within a population of seemingly homogeneous cells. A major promise of the emerging field of single-cell analysis (SCA) is the ability to observe and characterize this heterogeneity. Here, we use Fluidigm's microfluidics-based BioMark qPCR platform to examine the heterogeneity of a population of cortical neurons derived from induced pluripotent stem cells (iPSCs) by Cellular Dynamics, Inc. We find that (1) the cortical neurons can be reliably subdivided into ~4 subpopulations, with the two largest seeming to correspond with GABAergic and glutamatergic cell lineages; (2) ~30 genes, from a total of 121 genes measured, act as state-specifiers for these subpopulations; and (3) the population structure is dynamic and changes over time with an additional subpopulation appearing at later timepoints. We are currently in the process of verifying that these subpopulations' distinct gene expression profiles correlate with distinct biological phenotypes.

Disclosures: M.N. Shelton: None. **R. Bargaje:** None. **K. Trachana:** None. **C. Chadick:** None. **A. Fouquier d'Herouel:** None. **S. Huang:** None. **L. Hood:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.03

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: NIH 5R01MH094714

Title: Dysregulation of the coding and noncoding transcriptome in autism

Authors: *V. SWARUP[1], N. N. PARIKSHAK[1], T. G. BELGARD[1], S. HORVATH[2], D. H. GESCHWIND[1];
[1]Neurol., [2]Human Genet., Univ. of California At Los Angeles, Los Angeles, CA

Abstract: Autism spectrum disorder (ASD) is a genetically complex neuropsychiatric disorder with immense locus heterogeneity. A fundamental question is whether autism represents an etiologically heterogeneous disorder in which various genetic and environmental factors perturb

common underlying molecular pathways in brain. We previously addressed this question using microarray analysis of gene expression in post mortem brain, identifying convergent molecular pathology in ASD cerebral cortex (Voineagu et al., 2011). To gain more complete coverage of the genome and to increase sample size, we conducted Nextgen RNA sequencing (RNA-seq) to compare frontal cortex (FC), temporal cortex (TC), and cerebellum (CB) in a cohort of 81 individuals (46 ASD, 35 control (CTL), 205 samples). We use ribosomal RNA depleted library preparation followed by RNA-seq, which reduces sequencing coverage bias across transcripts and allows more accurate evaluation of long noncoding RNA (lncRNA) expression and transcript splicing. Through analysis at multiple levels, including differential gene expression (DGE), splicing, lncRNA, and co-expression network analysis, we identify shared biological pathways affected at the transcriptomic level. Analysis of DGE independently replicates previously observed patterns of shared transcriptomic dysregulation in ASD brain, finding a pattern shared by 2/3 of subjects, including subjects under age 10. We were also able to replicate and extend our analysis of disrupted cortical patterning in ASD brain, by showing that regional patterns of gene expression that typically distinguish frontal and temporal cortex are significantly attenuated in the ASD brain. By analyzing samples from 8 individuals with duplication 15q syndrome (dup15q), a major recurrent form of ASD, we show that all of the major alterations in DGE, splicing and gene networks are shared with idiopathic ASD, providing more evidence that these changes observed in the brain are a consequence of genetic perturbations. Together, these findings implicate transcriptional and splicing dysregulation as underlying mechanisms of neuronal dysfunction in ASD.

Disclosures: V. Swarup: None. **N.N. Parikshak:** None. **T.G. Belgard:** None. **S. Horvath:** None. **D.H. Geschwind:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.04

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: NSF GRFP

CHDI Foundation

University of Luxembourg - Institute for Systems Biology Strategic Partnership

Title: Genome-scale transcriptional regulatory network analysis reveals transcription factors involved in the progression of Huntington's disease

Authors: *J. R. PEARL[1], S. A. AMENT[2], C. L. PLAISIER[2], R. BRAGG[3], P. J. SKENE[4], A. GRINDELAND[5], G. CARLSON[5], N. GOODMAN[2], V. WHEELER[6], M. E. MACDONALD[6], J. CARROLL[3], N. S. BALIGA[2], L. E. HOOD[2], N. D. PRICE[2];
[1]Univ. of Washington, Seattle, WA; [2]Inst. for Systems Biol., Seattle, WA; [3]Western Washington Univ., Bellingham, WA; [4]Fred Hutchinson Cancer Res. Ctr., Seattle, WA; [5]McLaughlin Res. Inst., Great Falls, MT; [6]Ctr. for Human Genet. Res. Massachusetts Gen. Hosp., Boston, MA

Abstract: Massive changes in brain gene expression underlie many neurological and psychiatric diseases, yet the roles of specific transcriptional regulators remain poorly understood. We developed a novel approach for Transcriptional Regulatory Network Analysis (TReNA) that predicts interactions between transcription factors (TFs) and their target genes by integrating cis-regulatory DNA sequences, DNase footprinting, and brain gene expression profiles. We applied TReNA to reconstruct genome-scale models of transcriptional regulation in the mouse and human striatum in order to identify TFs involved in the progression of Huntington's disease (HD), a debilitating neurodegenerative disease. Transcriptional changes in the striatum are among the earliest detectable phenotypes in HD mouse models, so it has been proposed that aberrant transcriptional regulation in this brain region is a proximal disease mechanism. Our transcriptional regulatory network model accurately predicted the expression of >10,000 target genes (r^2 > 50%) in both the human and mouse striatum based on the expression levels of ~650 TFs. Comparison to ChIP-seq data for 78 TFs indicated that our model's predictions reflect physical interactions between TFs and their target genes. Our model suggests that distinct regulatory mechanisms control HD-related changes in gene expression related to neuronal excitability, lipid metabolism, and neuroinflammation. 17 TFs were predicted to be key drivers of HD progression because their target genes were differentially expressed both in mouse models of early-stage HD and in human post-mortem striatum from late-stage HD. We used ChIP-seq to validate genome-wide binding sites for two of these TFs in striatal tissue from the *Hdh.Q111* mouse model. The driver TFs identified by our model include promising targets for novel therapeutics. Our approach can be readily applied to reconstruct genome-wide models of transcriptional regulation in any human or mouse tissue.

Disclosures: J.R. Pearl: None. **S.A. Ament:** None. **C.L. Plaisier:** None. **R. Bragg:** None. **P.J. Skene:** None. **A. Grindeland:** None. **G. Carlson:** None. **N. Goodman:** None. **V. Wheeler:** None. **M.E. MacDonald:** None. **J. Carroll:** None. **N.S. Baliga:** None. **L.E. Hood:** None. **N.D. Price:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.05

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: Kavli Institute for Brain and Mind

NIH Grant R00NS080911

NIH Grant GM046883

Title: Brain-specific DNA methylation signatures of escape from X chromosome inactivation in the mouse frontal cortex

Authors: *C. L. KEOWN[1,3], J. B. BERLETCH[4], C. M. DISTECHE[5], J. R. ECKER[6], E. A. MUKAMEL[2,3];
[1]UCSD, San Diego, CA; [2]Cognitive Sci., UCSD, La Jolla, CA; [3]Computat. Neural Data and Dynamics Lab., La Jolla, CA; [5]Dept. of Pathology and Med., [4]Univ. of Washington, Seattle, WA; [6]Genomic Analysis Lab., The Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: X-inactivation in female mammals equalizes gene expression with males by epigenetically silencing transcription from one X chromosome. X-inactivation is essential for healthy cell function and cognition, yet the epigenetic mechanisms controlling it are not completely established. Because of the stochastic inactivation of maternal and paternal alleles across cells in the same individual, it has been difficult to study the distinct epigenetic and transcriptional regulation of the active (Xa) and inactive (Xi) X chromosomes. Here, we focus on the potential role of brain-specific DNA methylation patterns in regulating a subset of genes that escape X-inactivation and are expressed from Xi. Non-CG methylation accumulates in neurons, and to a lesser extent glia, during post-natal brain development. Notably, non-CG methylation on the X chromosome is reduced in brains of adult females compared to males, yet it is enriched at escape genes. Still, the distribution of these marks on Xi and Xa are unknown. Here, we identify allele-specific patterns of DNA methylation and address their relationship with gene expression in mouse brain. We used an F1 cross between male Spretus wild type and female C57/BL6 Xist mutant mice. The loss of function of one allele of Xist, the long noncoding RNA that initiates X-inactivation in cis, causes deterministic inactivation of the paternal allele in these mice. Whole-genome bisulfite sequencing (MethylC-Seq) was used to measure methylation, and RNA-Seq to profile gene expression in frontal cortex in two independent biological replicates. Genetic variants between Spretus and BL6 were used to assign sequencing reads to the parents of origin. CG methylation at promoters on the active X chromosome (Xa) showed a bimodal distribution as on the male X, but was consistently high at promoters on the Xi. Gene bodies on the Xa accumulate substantial non-CG methylation as in the male X but was virtually absent on the Xi.

Based on RNA-seq we confirmed 14 previously reported escape genes and identified seven novel escape genes in mouse frontal cortex. Of the 21 escape genes identified, we found that eight genes, previously shown to escape X-inactivation in multiple tissues, had gene body non-CG hypermethylation on the Xi. These genes also showed low promoter CG methylation. In summary, allele-specific, base-resolution DNA methylation profiling offers insight into the unique epigenetic regulation of X chromosome expression and dosage compensation in brain cells.

Disclosures: **C.L. Keown:** None. **J.B. Berletch:** None. **C.M. Disteche:** None. **J.R. Ecker:** None. **E.A. Mukamel:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.06

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: NIH R01 MH097268 to P.M.T.

NIH R01 AG040060 to P.M.T.

NIH K24 MH102743 to K.L.N.

Title: The C677T variant in MTHFR modulates associations between cognitive functioning and mood scores in old age: implications for vascular risk factors as treatment targets for both age-related cognitive decline and geriatric depression

Authors: *F. F. ROUSSOTTE[1], K. L. NARR[1], P. M. THOMPSON[2];
[1]Neurol., UCLA, Los Angeles, CA; [2]Neurol., USC, Los Angeles, CA

Abstract: Introduction: We recently reported a link between the C677T variant (MAF=0.245) in the methylene-tetrahydrofolate reductase (*MTHFR*) gene with smaller regional brain volumes in Mild Cognitive Impairment (MCI). We subsequently expanded these findings to healthy and demented elderly individuals, and reported an interaction of C677T with circulating Vitamin B_{12} levels affecting CSF neurodegeneration markers. The T "risk" allele also confers increased susceptibility for cardiovascular diseases (CVDs), which are strongly linked to both cognitive decline and depression in old age; here, we hypothesized that this variant may modulate associations between emotional and cognitive functioning. Methods: We used general linear models (GLMs) to examine associations between scores on the Mini Mental Status Examination

(MMSE) and Geriatric Depression Scale (GSD-15), and their modulation by C677T and circulating Vitamin B_{12} levels, in a large cohort of elderly individuals (N=738, mean age 75.52 years) from the Alzheimer's Disease NeuroImaging Initiative. Participants included 300 women, 206 healthy elderly subjects, 359 individuals with MCI, and 173 patients with Alzheimer's disease. Age and sex were included as covariates in all analyses. Results: The C677T variant showed no significant main effects on GDS scores, but the genotype by MMSE interaction term was a strong predictor of mood scores (p=0.011), and these results became even more significant after including Vitamin B_{12} levels as an additional covariate (p=0.002). Within carriers of the T "risk" allele, lower cognitive functioning strongly predicted higher depression scores (p=0.012 and p=0.003 with and without Vitamin B_{12} as a covariate, respectively). In non-carriers, we detected no significant associations between emotional and cognitive functioning in this cohort. Conclusion: MTHFR is the enzyme that produces the form of folate (vitamin B_9) necessary to re-methylate homocysteine into methionine. Vitamin B_{12} is another co-enzyme required for methionine synthesis. The C677T functional variant, which results in reduced enzymatic activity, is therefore associated with hyperhomocysteinemia, which in turn correlates with higher rates of atherosclerosis. Our results suggest a possible genetic mechanism underlying previously reported associations between MMSE and GDS-15 scores in elderly individuals at elevated risk for CVDs. Given the causal relationship between atherosclerosis and both cognitive decline and depression in the elderly, vascular risk factors and their genetic modulators represent promising research avenues for the prevention and treatment of these devastating conditions.

Disclosures: **F.F. Roussotte:** None. **K.L. Narr:** None. **P.M. Thompson:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.07

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: CHDI Contract to ISB

Institute for Systems Biology--University of Luxembourg Strategic Partnership

NIH Grant P50 GM076547

NSF Graduate Research Fellowship to JRP

Title: Gene network dynamics in the transition from wellness to neurodegenerative disease

Authors: *S. A. AMENT[1], J. R. PEARL[3], S. HUANG[2], N. GOODMAN[2], L. E. HOOD[2], N. D. PRICE[2];
[1]Dept Neurosci, [2]Inst. For Systems Biol., Seattle, WA; [3]Dept. of Mol. and Cell. Biol., Univ. of Washington, Seattle, WA

Abstract: Preventive therapies for neurodegenerative disease will require early detection in order to intervene before irreversible changes occur. Early warning signs, such as increased variance of state variables, increased auto-correlation or critical slowing down (slower returns to equilibrium states) precede critical transitions in some physical, environmental, and ecological systems. To determine if clinical manifestation of neurodegenerative diseases represent critical transitions of a dynamical system, we searched for early warnings in neurodegenerative disease. We analyzed the temporal evolution of brain gene expression profiles from mouse models of Huntington's disease, prion disease, and Alzheimer's disease. Using novel network-based algorithms to extract high-dimensional equivalents of early warning signs, we found age- and model-specific changes in the variance of expression profiles and in the strength of gene-gene correlations prior to the detection of differentially expressed genes or cellular pathology indicating disease onset. These changes occurred specifically in gene networks that later became differentially expressed, suggesting disease-specific processes rather than generic indicators of sickness. Our results suggest that the onset of neurodegenerative disease is preceded by early warning signs in the states of brain gene networks and identify network biomarkers for the transition from wellness to disease.

Disclosures: S.A. Ament: None. **J.R. Pearl:** None. **S. Huang:** None. **N. Goodman:** None. **L.E. Hood:** None. **N.D. Price:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.08

Topic: G.02. Genomics, Proteomics, and Systems Biology

Title: Circuit-specific drug target identification by single-cell transcriptomics in adult rodent brain

Authors: *T. PORTMANN, H. HO, I. GALLAGER, D. ZWILLING, H. LEE, E. ZHAO, V. GONTCHAROVA, K. R. THOMPSON, S. P. BRAITHWAITE;
Circuit Therapeutics, Inc., Menlo Park, CA

Abstract: Single-cell transcriptome analysis holds great promise for understanding neuronal diversity and cell type-specific gene expression in the brain. With the advent of technologies such as optogenetics, allowing the functional assessment of specific circuitry, the significance of precise neuronal circuits to drive behaviors is becoming increasingly apparent. It has become clear that precision molecular understandings at the levels of single circuits and single cells are actually necessary to fully appreciate the molecular drivers of behavioral function. We have used optogenetics to demonstrate defined functions of the dopamine D1 and D2 receptor expressing medium spiny neurons (MSN) in the striatum. Our studies demonstrate that they alone can drive relevant and opposing behaviors indicating that for therapeutic benefit specific modulation is critical. To identify specific transcriptomes of MSN subtypes we developed a pipeline for neuronal circuit-specific drug target identification. Fluorescent reporter transgenes in combination with stereotaxic dye injection for cell type- and region-specific labeling of striatal MSN have been utilized to identify distinct functional MSN subtypes. Single MSN were isolated by fluorescence-activated cell sorting (FACS) and screened for expression of dopamine D1 and/or D2 receptor genes. Selected MSN were then compared for expression of over 1000 genes using multiplexed quantitative real-time RT-PCR (qRT-PCR) analysis on the Biomark platform. Our data confirm major known MSN subtype-specific marker genes including Drd1a, Pdyn, Tac1, Chrm4, Drd2, Penk, Adora2a, and Gpr6. In comparison to other state-of-the-art approaches for cell type-specific gene expression profiling our studies demonstrate the importance of single-cell resolution in generating understandings that are independent of limitations including reporter transgene specificity or contaminating signal from the neuropil. We identified that reportedly differentially expressed genes identified by less focused approaches can be understood as false positives. For the first time we demonstrate that single-cell transcriptomics using qRT-PCR can be multiplexed to over 1000 genes per cell and thus give a coverage to greatly enhance our understanding of cell type-specific therapeutic targets in the brain.

Disclosures: **T. Portmann:** A. Employment/Salary (full or part-time); Circuit Therapeutics Inc., Menlo Park, CA94025. **H. Ho:** A. Employment/Salary (full or part-time); Circuit Therapeutics Inc., Menlo Park, CA94025. **I. Gallager:** A. Employment/Salary (full or part-time); Circuit Therapeutics Inc., Menlo Park, CA94025. **D. Zwilling:** A. Employment/Salary (full or part-time); Circuit Therapeutics Inc., Menlo Park, CA94025. **H. Lee:** A. Employment/Salary (full or part-time); Circuit Therapeutics Inc., Menlo Park, CA94025. **E. Zhao:** A. Employment/Salary (full or part-time); Circuit Therapeutics Inc., Menlo Park, CA94025. **V. Gontcharova:** A. Employment/Salary (full or part-time); Circuit Therapeutics Inc., Menlo Park, CA94025. **K.R. Thompson:** A. Employment/Salary (full or part-time); Circuit Therapeutics Inc., Menlo Park, CA94025. **S.P. Braithwaite:** A. Employment/Salary (full or part-time); Circuit Therapeutics Inc., Menlo Park, CA94025.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.09

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: DARPA-13-34-RTA-FP-007

LCI GC Grant

Title: Proteome-wide effects of down syndrome explored with human induced pluripotent stem cell-derived cerebral organoids

Authors: *T. D. MCCLURE-BEGLEY, M. KLYMKOWSKY, C. E. EBMEIER, K. BALL, W. OLD;
MCD Biol., Univ. of Colorado, Boulder, CO

Abstract: In order to better understand the cellular and molecular processes associated with Down syndrome (DS) in the human central nervous system (CNS), we generated a model of early neuronal development that capitalizes on the use of human induced pluripotent stem cells (IPSc) as a starting template. We obtained IPSc from an individual where lines had been created that both contained (C2; T21), and had lost the extra copy of chromosome 21 (C2-43; D21). With some modifications to the method first described by Lancaster et al (Nature, 2013), we successfully generated human cerebral organoids from both the C2 and C2-43 cell lines and used them for imaging experiments with whole-mount immunostaining and laser scanning confocal microscopy as well as a deep proteome profile with label-free quantitation of over seven thousand proteins in each sample. Our imaging analysis shows that at the time of our sample preparation, neurons had been generated that populated the outer edges of the tissue, with evidence of populations of radial glia restricted to the inner regions of the tissue; a distribution of cell types indicative of radial migration and differentiation, similar to the development of human cortex. Our proteomics analysis shows many proteins changing in significant abundance due to Trisomy 21, with striking alterations in members of the Wnt and Notch signaling pathways, as well as catecholamine metabolism, axon guidance, and cell adhesion. These early data are the first to demonstrate the utility of IPSc-derived cerebral organoids in the study of complex genetic conditions with a spectrum of neurological phenotypes.

Disclosures: T.D. McClure-Begley: None. **M. Klymkowsky:** None. **C.E. Ebmeier:** None. **K. Ball:** None. **W. Old:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.10

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: NIH grant DP1 OD003961

Title: Proteomic maps of the excitatory and inhibitory synaptic clefts via peroxidase-mediated biotinylation in living neurons

Authors: *K. LOH[1], P. A. STAWSKI[1], N. D. UDESHI[2], T. SVINKINA[2], T. J. DEERINCK[3], M. ELLISMAN[3], S. A. CARR[2], A. Y. TING[1];
[1]Chem., MIT, Cambridge, MA; [2]Broad Inst., Cambridge, MA; [3]UC San Diego, San Diego, CA

Abstract: The synaptic cleft is the central subcellular structure that underlies brain function, learning, and memory. Yet our molecular understanding of this region is very incomplete. A major challenge to defining the "parts list", or proteomic composition, of the cleft has been the inability to purify it for subsequent mass spectrometric analysis. Here, we apply an enzymatic proximity tagging strategy to map the cleft proteome in living neurons, bypassing the need for organelle purification. A peroxidase was genetically targeted to the cleft of either excitatory (glutamatergic) or inhibitory (GAGAergic) synapses in cultured rat neurons. The peroxidase catalyzed biotinylation of proximal endogenous proteins in the cleft over 1 minute. Subsequently, biotinylated proteins were enriched and identified by mass spectrometry. The resulting excitatory and inhibitory proteomic lists consist of 214 and 39 surface-exposed proteins, respectively. >83% of each list consists of proteins with prior synapse annotation. The remaining members include novel, previously unrecognized synaptic cleft proteins, confirmed by follow-up fluorescence and electron microscopies. We will further describe our characterization of two novel proteins that play a role in regulating excitatory versus inhibitory synapse specificity.

Disclosures: K. Loh: None. **P.A. Stawski:** None. **N.D. Udeshi:** None. **T. Svinkina:** None. **T.J. Deerinck:** None. **M. Ellisman:** None. **S.A. Carr:** None. **A.Y. Ting:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.11

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: Swiss National Science Foundation (FNRS) grant 31003A_140945/1

SwissTransMed grant "Gene therapy platform for CNS and sensory organ pathologies »

Title: Cell-type specific transcriptome profiling in the adult mouse striatum

Authors: *N. DEGLON[1], C. MEUNIER[2], A.-B. ROCHER[3], L. PELLERIN[2], J.-Y. CHATTON[3], N. MERIENNE[1];
[1]Lausanne Univ. Hosp. (CHUV), Lausanne, Switzerland; [2]Dept. of Physiology, Lab. of Neuroenergetics, Univ. of Lausanne, Lausannne, Switzerland; [3]Dept. of Fundamental Neurosciences, Univ. of Lausanne, Lausanne, Switzerland

Abstract: Neurons have been long considered as the major actors of thoughts and actions in the central nervous system (CNS). However, a critical step to take into account the vast cellular diversity of the brain and contributions of neuronal and non-neuronal cell populations to cerebral functions, is a cell-type specific characterization. Here, we report a new and original protocol for physiological cell-type specific profiling of adult CNS cells. The method combines the advantages of fluorescent transgenic mice from the GENSAT project and sectioning in physiological conditions to avoid fluorescent signal loss together with laser-captured microdissection (LCM) without fixation to guarantee high quality cellular content. We performed a transcription-wide profiling of astrocytes (GLT1-eGFP mice), microglia (Cx3cr1-eGFP mice) and the two medium-sized spiny neurons types implicated in striatonigral (direct pathway, Drd1-Tomato mice) or striatopallidal (indirect pathway, Drd2-eGFP mice) loops. Neurons from these two pathways are morphologically identical but have distinct implications in the basal ganglia networks, highlighting the necessity to deeply characterize their specific features. RNA sequencing (RNAseq) and microarray were used to identify messenger RNA (mRNA) and microRNA (miRNA) profiles of striatal populations. Bioinformatic analysis reveal differentially expressed genes as molecular signatures discriminating astrocytes, microglial and the two neuronal subtypes. In addition, a comparison with published databases highlights cell-type specific responses to a neurodegenerative context.

Disclosures: N. Deglon: None. **C. Meunier:** None. **A. Rocher:** None. **L. Pellerin:** None. **J. Chatton:** None. **N. Merienne:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.12

Topic: G.02. Genomics, Proteomics, and Systems Biology

Support: Children's Discovery Insitute of Washington University (MD-II-2013-269)

NIH (R21 MH099798-01, R21 NS083052-02, R21 DA038458-01)

Title: The coding and noncoding landscape of nuclear transcription in neurons and glia

Authors: ***J. D. DOUGHERTY**, D. O'BRIEN, N. PISAT, J. DALAL, A. REDDY;
Genet. and Psychiatry, Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Recent characterization of the transcriptional landscape of cell lines or bulk tissues has suggested widespread transcription of the genome, and there are a variety of key regulatory non-coding RNAs that do not escape the nucleus. Here, we have defined the nuclear transcriptional landscape of the three major cellular divisions of the nervous system and characterized the unique expression of coding, non-coding and intergenic RNAs in the mature mouse brain. We discovered a remarkable diversity across the cell types *in vivo* in all classes of RNAs, including long non-coding RNAs, several of which were confirmed as highly enriched in the nuclei of specific cells with anatomical methods. Finally, we also discovered several examples of the cell-type specific expression of tandem gene fusions, and cell-type specific expression of circular RNAs, notably a neuron specific and nuclear enriched RNA arising from Hnrnpu.

Disclosures: **J.D. Dougherty:** None. **D. O'Brien:** None. **N. Pisat:** None. **J. Dalal:** None. **A. Reddy:** None.

Nanosymposium

202. Genomic and Systems Level Analyses of Neurologic Disease

Location: N230

Time: Sunday, October 18, 2015, 1:00 PM - 4:15 PM

Presentation Number: 202.13

Topic: G.02. Genomics, Proteomics, and Systems Biology

Title: Identification of proteins enriched in axons of cultured rat cortical neurons by stable isotopic dimethyl labeling

Authors: *C.-F. CHUANG;
Natl. Tsing Hua University/Molecular Med., Hsinchu, Taiwan, Taiwan

Abstract: Neurons consist of three major structural compartments, cell body, dendrite and axon. A typical neuron contains a slender and long axon. In the early phase of development, the growth cone at the tip of axon guides the axon to navigate through the maze of cells to reach its target area. Upon reaching the target area, part of axon differentiates into presynaptic termini, which participate in signal transmission between the neuron and its target cells. Various studies have indicated that the protein composition of axon is distinct from that of somatodendrites. Here, by using a chip which allows us to harvest pure axons, we have collected the axons of cultured rat cortical neurons. Equal amounts of proteins of the lysate of isolated axons and the lysate of whole cells were dimethyl labeled by formaldehyde-^{13}C-D_2 (heavy) and formaldehyde (light) respectively, mixed and then subjected to 2D-LC-MS/MS analysis. A total of 1800 proteins are identified with their heavy-to-light ratios being quantified. There are 300 proteins enriched in axons. These proteins are categorized by their subcellular localizations and functions. Among the axon-enriched proteins are 60S and 40S ribosomal proteins, translation machinery proteins, heterogeneous nuclear ribonucleoproteins, RNA-binding proteins, Golgi and ER proteins and signaling molecules. The abundances of axon proteins have also been compared with their respective mRNAs in the axon. The protein composition of the axon will shed lights to the molecular basis of functions of this unique cellular compartment.

Disclosures: C. Chuang: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Kun-Yi Chien.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.01

Topic: A.04. Axon and Dendrite Development

Support: NIH-NEI F32 EY024184

NIH-NEI R21 EY022725

Title: Fat3 and Ena/VASP coordinate the polarized development of retinal amacrine cells

Authors: *S. J. HENLE[1], A. KROL[2], L. V. GOODRICH[2];
[2]Neurobio., [1]Harvard Med. Sch., Boston, MA

Abstract: In the retina, amacrine cells develop a unipolar morphology, with one dendrite that forms synapses restricted to the inner plexiform layer (IPL). We previously showed that in mice lacking the atypical cadherin Fat3, retinal amacrine cells develop two dendritic arbors: one in the IPL and one that extends outside of the IPL to form an ectopic layer of synaptic connections. To understand how this change in morphology emerges at the cellular level, we developed a time-lapse slice culture imaging method that allowed us monitor the progression of amacrine cell development in mice for the first time. Amacrine cells migrate toward the IPL with a leading and a trailing process. Ultimately the leading process elaborates into a dendritic arbor and the trailing process is removed. Comparison of wildtype and *fat3* mutant amacrine cells revealed an overall increase in the movement of the cell body in *fat3* mutants. However, the mutant cells reversed direction more often and were therefore slower to reach their final position near the IPL. Next we examined trailing process dynamics during amacrine cell development. In wildtype amacrine cells, the trailing process was smoothly retracted, but in *fat3* mutants the trailing process extended towards and away from the IPL more frequently, showed increased branching, and ultimately failed to be fully retracted. Taken together, these observations indicate that *fat3* mutant amacrine cells are less polarized throughout development. Since Fat3 is a transmembrane molecule, we hypothesized that it dictates amacrine cell polarity by inducing asymmetries in the cytoskeleton through its intracellular domain (ICD). We focused on three sites in the Fat3 ICD that were predicted to bind the Ena/VASP family of actin regulatory proteins. We determined that the Fat3 ICD does bind Ena/VASP family members, but only through one of the predicted sites. Since Fat3 protein localizes to amacrine cell processes in the IPL, one possibility is that Fat3 recruits Ena/VASP proteins and thus alters the overall organization of the actin cytoskeleton. To test this idea, we wanted to recruit Ena/VASP uniformly to the membrane without changing protein levels. To do this, we used *in vivo* electroporation to express an Ena/VASP binding domain with a membrane targeting sequence in a subset of amacrine cells. This resulted in amacrine cells that formed ectopic neurites outside of the IPL, thereby recapitulating the *fat3* mutant phenotype. Taken together our results indicate that Fat3 acts in IPL-restricted processes to recruit cytoskeletal regulators, thereby creating an asymmetry in the cytoskeleton that confines dendritic arborization and synapse formation to the IPL.

Disclosures: **S.J. Henle:** None. **A. Krol:** None. **L.V. Goodrich:** None.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.02

Topic: A.04. Axon and Dendrite Development

Support: NIH Grant NS048884

Title: Abnormal mGluR5 activity upregulates NGF/TrkA signaling in cortical glutamatergic neurons leading to aberrant dendritic morphogenesis

Authors: *J.-Y. HUANG, H.-C. LU;
Indiana Univ. Bloomington/ Dept. Psychologica, Bloomington, IN

Abstract: The role of metabotropic glutamate receptor 5 (mGluR5) in dendritic morphogenesis is complex, with both loss and excess of mGluR5 function increasing the intricacy of dendritic networks. We found that either deleting or stimulating mGluR5 receptors resulted in similar increases in nerve growth factor (NGF). Postnatal overexpression of NGF increased the dendritic complexity of layer IV cortical glutamatergic neurons, in a fashion reminiscent of the dendritic complexity of these same neurons in mGluR5 KO mice. Using Tropomyosin receptor kinase AF592A (TrkAF592A) mice, we demonstrated that TrkA (and its kinase activity) mediates NGF signaling to modulate neuronal morphology. Genetic deletion of mGluR5 increased the abundance of calcium-permeable AMPA receptors (CP-AMPARs), and inhibiting these receptors in mGluR5 KO neurons reversed NGF levels to normal. Interestingly, in wildtype neurons, excessive glutamate neurotransmission upregulated NGF transcription in an AMPAR and mGluR5-dependent fashion. In these neurons, mGluR5 activation also increased dendritic complexity in a TrkA-dependent manner. Taken together, our data suggest that either too much, or too little, mGluR5 activity upregulates NGF expression, culminating in excessive dendritic arbors of layer IV cortical glutamatergic neurons leading to miswiring of cortical circuits.

Disclosures: J. Huang: None. **H. Lu:** None.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.03

Topic: A.04. Axon and Dendrite Development

Title: A neurodevelopmental regulator of the mtor pathway

Authors: *D. M. FELICIANO;
Biol. Sci., Clemson Univ., Clemson, SC

Abstract: Pathogenic mutations in the mechanistic target of rapamycin (mTOR) pathway cause abnormal brain development and lead to epilepsy, intellectual delay, and autism spectrum disorders (ASDs). mTOR is a kinase that maintains a homeostatic balance between anabolic protein translation and autophagy. Imbalances in protein translation and autophagy may be a cause of ASDs. Mutations in translational regulatory proteins are common in ASDs and loss of translational machinery is sufficient to cause ASD-like behaviors. For example, Tuberous Sclerosis Complex (TSC) patients have elevated mTOR activity, anabolic protein translation, and a high co-morbidity with autism. In ASDs and TSC, mTOR causes sustained inhibition of autophagy and defects in neuron morphology. The previous studies of my colleagues and I have ascribed cell specific developmental roles for mTOR pathway proteins in the brain including for those that cause TSC. We have found that hyper-activation of mTOR leads to developmental abnormalities including cytomegally and dendritic hypertrophy. However, mTOR activity is tightly regulated during development, restricted to specific cell types and subcellular regions, leading us to propose that mTOR is selectively turned on and off in the brain. Amino acids can activate mTOR in culture and are required for anabolic protein translation. More specifically, mTOR is activated by arginine, glutamine and leucine. These amino acids are transported by solute carrier (SLC) family members of amino acid transporters. We hypothesized that a SLC transporter is required for mTOR-dependent control of protein translation, inhibition of autophagy, and proper control of neuronal morphology in the developing cortex. Our data demonstrate that an SLC is expressed within newborn neurons of the developing cerebral cortex of mice and in neurogenic regions of the adult brain. SLC knockdown in Neuro2a cells and *in vivo* reduces mTOR activity, protein translation, and cell size. In the absence of amino acids or the SLC transporter, mTOR activity is dampened leading to reduced anabolic protein translation and disinhibition of the ULK1 pro-autophagic kinase. Over-expression of the amino acid transporter also reduces mTOR activity. Ultimately, knockdown or over-expression of the amino acid transporter have the same effect, activation of autophagy at the expense of anabolic protein translation and reduced dendrite formation. Based on these results, we suggest that amino acids and their transporters are critical regulators of cortical development and neuron morphology and that changes in their levels may have a lasting effect on the developmental trajectory of the cerebral cortex.

Disclosures: D.M. Feliciano: None.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.04

Topic: A.04. Axon and Dendrite Development

Support: NIH R01MH095741

James S. McDonnell Foundation

California Institute for Regenerative Medicine- Bridges Program

The Leona M. and Harry B. Helmsley Charitable Trust grant #2012-PG-MED002

Title: Imaging the growth and pruning of dendritic trees using *in vivo* 2-photon microscopy

Authors: *J. GONCALVES[1], C. W. BLOYD[2], S. T. JOHNSTON[2], M. SHTRAHMAN[2], S. T. SCHAFER[2], T. TRAN[2], T. CHANG[2], F. H. GAGE[2];
[1]Salk Inst. LOG-G, La Jolla, CA; [2]Lab. of Genet., Salk Inst., La Jolla, CA

Abstract: The dentate gyrus (DG) is one of two regions of the mammalian brain where neurogenesis takes place during adulthood. The integration of newborn neurons into DG circuitry has been extensively studied using histology and *in vitro* slice preparations but thus far it has been impossible to follow the same adult-born cell at several time-points during its maturation process. Here, by placing an imaging 'window' implant into the hippocampus we are able to image retrovirally labeled adult-born granule neurons and follow them for 6+ weeks *in vivo* at different development stages, using 2-photon laser scanning microscopy. This approach allowed us to characterize the dendritic development time-course of individual adult-born dentate granule cells (DGCs). We found that DGC dendrites grow in size and increase their branching up to ~21 days post-mitosis, followed by a period of pruning that is characterized by a net removal of branches. By the end of the fourth week post-mitosis dendritic trees are generally mature and stable. Dendritic growth is influenced by both molecular cues and neuronal activity. Knocking-down CELSR3, a core component of the Wnt/Planar Cell Polarity (PCP) pathway resulted in stunted dendritic growth, confirming our previous findings (Schafer et al. 2015). Interestingly, increased neuronal activity resulted in faster dendritic growth and earlier pruning. In summary we established a novel method for longitudinally following the morphological development of adult-born DGCs and we were able to characterize the effect of specific molecular cues and neuronal activity on dendrite growth and pruning.

Disclosures: **J. Goncalves:** None. **C.W. Bloyd:** None. **S.T. Johnston:** None. **M. Shtrahman:** None. **S.T. Schafer:** None. **T. Tran:** None. **T. Chang:** None. **F.H. Gage:** None.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.05

Topic: A.04. Axon and Dendrite Development

Support: H25-ninchisho-ippan-004.

Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science, 22221004.

Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science, 2546128.

Title: 8-Oxoguanine accumulated in mitochondrial DNA disturbs neuritic regeneration of cultured adult mouse cortical neurons under conditions of oxidative stress

Authors: *J. LEON, K. SAKUMI, S. OKA, E. CASTILLO, Y. NAKABEPPU; Neurofunctional Genomics, Kyushu Univ., Fukuoka-shi, Japan

Abstract: Oxidative stress and mitochondrial dysfunction are considered to be important in the etiology of several neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. 8-Oxoguanine (8-oxoG), a common DNA lesion caused by oxidative stress, is known to be highly accumulated in patient brains with neurodegeneration. MTH1 with an 8-oxo-dGTPase activity hydrolyzes 8-oxo-dGTP to 8-oxodGMP and pyrophosphate in nucleotide pools, while OGG1 with an 8-oxoG DNA glycosylase activity excises 8-oxoG paired with cytosine in DNA, thereby minimizing accumulation of 8-oxoG in DNA. We have shown that *Mth1/Ogg1*-double knockout (*Mth1/Ogg1*-DKO) mice are highly vulnerable to neurodegeneration under oxidative condition with increased accumulation of 8-oxoG in mitochondrial DNA (mtDNA) in neurons. In the present study, we examined how MTH1 and OGG1 contribute to protect neurons from oxidative stress using *in vitro* cultured neurons. We isolated cortical neurons from 15-19 week-old wild-type and *Mth1/Ogg1*-DKO brains and maintained them in medium supplemented with B27 containing or lacking antioxidants for 2 to 5 days, and examined neuritic regeneration. Regenerating neurites were identified by MAP2-immunofluorescence with confocal imaging. After 2 days of culture, neuronal populations were classified and quantified based on the extent of neurite outgrowth as follows: stage 1 neurons lacking neurites, stage 2 with one or more minor neurites, and stage 3 with one neurite at least twice as long as any other. We also quantified neuronal dendritic arborization after 5 days of culture with the Sholl analysis. In the presence of antioxidants, *Mth1/Ogg1*-DKO as well as wild-type neurons exhibited efficient neuritic regeneration: about 10% in stage 1, 15 to 20% in stage 2, and 60% in stage 3. On the other hand, when neurons were maintained in the absence of antioxidants, neurons isolated from *Mth1/Ogg1*-DKO cortices exhibited significantly less population in stage 3 (20%), compared to those from wild-type cortices (60% in stage 3). *Mth1/Ogg1*-DKO neurons also exhibited

significantly decreased complexity of dendritic arborization only in the absence of antioxidants, indicating that the neuritic regeneration is highly vulnerable to oxidative DNA damage. Furthermore, we found that levels of 8-oxoG accumulated in mtDNA were significantly increased in *Mth1/Ogg1*-DKO neurons compared with wild-type neurons. Now, we are examining extents of mitochondrial dysfunction in these neurons in order to delineate the molecular pathology induced by 8-oxoG accumulated in mtDNA.

Disclosures: J. Leon: None. **K. Sakumi:** None. **S. Oka:** None. **E. Castillo:** None. **Y. Nakabeppu:** None.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.06

Topic: A.04. Axon and Dendrite Development

Support: NIH F31 Grant Number 1 F31 NS087837-01A1

RO1GM108970 NIH/NIGMS

Title: Deletion of the E3 ubiquitin ligase TRIM9 disrupts hippocampal neuron morphology, anatomy and spatial learning and memory

Authors: C. C. WINKLE[1], *S. L. GUPTON[2];
[1]Curriculum in Neurobio., [2]Cell Biol. and Physioloyg, UNC, Chapel Hill, NC

Abstract: During development, hippocampal neurons progress through stereotypical shape changes to achieve a polarized morphology integral to the structure and function of hippocampal circuitry. Here we show that the brain-enriched E3 ubiquitin ligase TRIM9 is a novel regulator of hippocampal cell morphology, hippocampal anatomy and hippocampus dependent learning and memory. Using *TRIM9*$^{-/-}$ mice, we show that TRIM9 is expressed in the hippocampus at both developmental and adult timepoints. In dissociated embryonic hippocampal neurons, genetic loss of *TRIM9* leads to accelerated cell shape progression and a significant increase in dendritic arborization. Increased dendritic arborization also occurs in *TRIM9*$^{-/-}$ mice *in vivo*, and is associated with an increased hippocampal size, the presence of long, immature spines, and an increase in hippocampal axons projecting into the septo-fimbrial area compared to *TRIM9*$^{+/+}$ littermates. Using behavioral testing we found that *TRIM9*$^{-/-}$ mice exhibit hyperactivity in the open field test, and a significant decrease in marble burying activity. Furthermore, these mice

exhibited overt deficits in hippocampal-dependent spatial learning and memory as observed in the Morris water maze. Taken together, these behavioral data suggest that *TRIM9*-mediated regulation of hippocampal neuron morphology and circuitry during development is required for proper hippocampal circuit formation and function.

Disclosures: C.C. Winkle: None. **S.L. Gupton:** None.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.07

Topic: A.04. Axon and Dendrite Development

Support: MRC

Title: MST1/ MST2 kinase function in neuronal development

Authors: K. GILL, A. LIN, S. CLAXTON, *S. K. ULTANIR;
Francis Crick Inst., London, United Kingdom

Abstract: Evolutionarily conserved Mammalian Ste20-like 1/2 (MST1/2) (hippo in *Drosophila*) kinase cascade is regulated by cell-cell contact, cell polarity and mechanical cues to control cell proliferation, survival, organ size and tissue growth, which when deficient could lead to cancer, via a main output of Yes-associated protein (YAP) transcription factor. Although hippo/ MST1/2 kinase signalling cascade has received widespread interest in its roles on tissue size control and cell fate determination, little is known about MST1/2's role in neuronal connectivity. Neuron-specific deletion of hippo or its target warts (wts/ LATS1/2 in mammals) in *Drosophila* sensory neurons leads to deficiencies in maintenance of neuronal dendritic arbors[1,2], while deletion of hippo and its target tricornered (trc / NDR1/2 in mammals) causes increased dendrite branching in flies[1] and mammals[3], implicating hippo/MST1/2 signalling in dendritic development. Whether or not MST1/2 functions in mammalian neuronal development is an open question. MST1 and MST2 are expressed in the mouse brain. We have characterized MST1 and MST2 expression in developing brain and in various brain regions and found that both MST1 and MST2 are expressed during development in most brain regions. In addition, *in situ* hybridization revealed MST1's localization to hippocampal pyramidal cell layers and dentate granule cells. MST1 and MST2 can substitute each other's function as single mutants are viable without any major phenotypes while Mst1/2 double mutant is embryonically lethal. In order to test if MST1/2 function is required in neurons, we generated conditional MST1/2 knockout mice where MST1

and MST2 are knocked out in excitatory neurons of hippocampus and cortex. As expected, MST1 and MST2 protein levels were reduced in the knockout hippocampi. Remaining protein could be due to expression in inhibitory neurons and/or non-neuronal cells. We have started conducting electrophysiological and morphological analysis of hippocampal neurons. Changes in synaptic properties in these knockout mice were identified and will be described. 1. Emoto, K., Parrish, J. Z., Jan, L. Y. & Jan, Y. N. The tumour suppressor Hippo acts with the NDR kinases in dendritic tiling and maintenance. *Nature* **443**, 210-213 (2006). 2. Emoto, K. Signaling mechanisms that coordinate the development and maintenance of dendritic fields. *Curr Opin Neurobiol* **22**, 805-811, doi:10.1016/j.conb.2012.04.005 (2012). 3. Ultanir, S. K. *et al.* Chemical genetic identification of NDR1/2 kinase substrates AAK1 and Rabin8 Uncovers their roles in dendrite arborization and spine development. *Neuron* **73**, 1127-1142, doi:10.1016/j.neuron.2012.01.019 (2012).

Disclosures: K. Gill: None. **A. Lin:** None. **S. Claxton:** None. **S.K. Ultanir:** None.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.08

Topic: A.04. Axon and Dendrite Development

Support: NIH Grant P01 HL046925-16

Title: Eltrombopag, a thrombopoietin mimetic, induces iron deficiency and impairs mRNA expression of neurodevelopmental genes in cultured primary hippocampal neurons

Authors: *T. W. BASTIAN[1,2], L. M. LANIER[2], M. C. SOLA-VISNER[3], M. K. GEORGIEFF[1]; [1]Pediatrics, [2]Neurosci., Univ. of Minnesota, Minneapolis, MN; [3]Div. of Newborn Med., Boston Children's Hosp., Boston, MA

Abstract: Background: Thrombocytopenia, low blood platelets, is a common hematological condition in pre-term and sick neonates. Neonatal platelet transfusions are accompanied by numerous side effects, making thrombopoietin mimetic treatment (e.g. eltrombopag) a potential alternative therapy for neonates with severe and prolonged thrombocytopenia. However, eltrombopag also chelates intracellular iron, which may result in unwanted side effects during development. Iron deficiency (ID) affects an estimated 2 billion people and is particularly deleterious during fetal/neonatal brain development, impairing neurotrophic factor signaling, dendritic arborization, neurotransmission, and synaptic plasticity in the developing hippocampus.

This ultimately leads to long-term neurological impairments (e.g. hippocampal-dependent learning and memory). Objective: The objective of this study was to determine whether eltrombopag causes neuronal ID and impairs hippocampal neuron development. Methods: Embryonic hippocampal neuronal cultures were treated with 5-Fluoro-2'-deoxyuridine (an anti-mitotic drug that inhibits glia proliferation) beginning at 3 days *in vitro* (DIV) and either 6 μM eltrombopag or 10 μM deferoxamine (an iron chelator) beginning at 7DIV. At 14DIV, quantitative PCR was used to quantify changes in mRNA levels for genes indexing neuronal iron status and neurodevelopment. At 18DIV the dendritic arbors of deferoxamine-treated neurons were manually traced and total dendritic branching was determined. Results: *Transferrin receptor 1* and *Divalent metal transporter 1* mRNA levels were 133% and 44% higher in eltrombopag-treated neurons, respectively, indicating neuronal ID of the degree seen in animal models of ID and human ID infants. Eltrombopag treatment decreased *Brain derived neurotrophic factor VI*, *Calcium/calmodulin-dependent protein kinase II alpha*, and *Vesicle-associated membrane protein 1* mRNA levels by ~20% suggesting impaired dendritic and axonal development and synaptic function. These mRNA changes were similar to deferoxamine-treated neurons, which also showed a 25% reduction in total dendritic branching at 18DIV. Conclusions: Our findings suggest that treatment of neonates or young infants with eltrombopag may impair neurodevelopment due to secondary neuronal iron deficiency, although it is unknown if eltrombopag crosses the developing blood-brain barrier. More pre-clinical studies are warranted to assess the safety and efficacy of thrombopoietin mimetics in developing children.

Disclosures: **T.W. Bastian:** None. **L.M. Lanier:** None. **M.C. Sola-Visner:** None. **M.K. Georgieff:** None.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.09

Topic: A.04. Axon and Dendrite Development

Support: NSFC 31371101

NSFC 31070955

NSFC 81171152

Title: Conditional knockout of Frizzled3 in the retina disrupts visual function and retinal development

Authors: *N. SHEN, Y. XU, L. ZHOU;
Guangdong-Hong Kong-Macau Inst. of CNS Regeneration, Jinan Univ., Guangzhou, China

Abstract: Frizzled3 (Fzd3), one of core planar cell polarity (PCP) members, plays critical roles in brain development, particularly in axonal wiring in different regions. Studies have shown that Fzd3 inactivation in retinal ganglion cells (RGCs) results in subtle abnormalities in RGC projections. Here we conditionally removed Fzd3 in bipolar cells and some RGCs by crossing Fzd3 "floxed" mice with Isl1-Cre mice to generate Fzd3f/-;Isl1-Cre mice (Fzd3|Isl1 for short). Using anti-LacZ staining, we found Fzd3 is highly expressed in bipolar cells, horizontal cells, amacrine cells and ganglion cells at postnatal day (P) 0, 5, 7, 14 and 18. By double staining, Fzd3 and Isl1 were co-expressed in rod bipolar cells and some RGCs. In Fzd3|Isl1 mice, the numbers of rod bipolar cells and RGCs were significantly reduced compared to the control, although the retinal lamination was undisrupted in line with the reports. In Fzd3|Isl1 mice, the dendrites of rod bipolar cells were abnormally fasciculated, which formed a disordered pattern in the outer plexiform layer (OPL). The dendrites of bipolar cells failed to invaginate into the rod spherules and to form the ribbons. Optomotor tests showed Fzd3|Isl1 mice had a reduction in visual acuity. Using electroretinogram (ERG), we found that Fzd3|Isl1 mice harbored an obvious reduction of b-wave and the ratio b-wave/a-wave compared to control animals, suggesting the function of bipolar cells to convey information from photoreceptor to ganglion cells is defective in our mutants. In conclusion, conditional knockout Fzd3 in bipolar cells and some RGCs affects mouse visual function and local connections, particularly between photoreceptors and bipolar cells.

Disclosures: **N. Shen:** None. **Y. Xu:** None. **L. Zhou:** None.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.10

Topic: A.04. Axon and Dendrite Development

Support: NSF grant IOS-1353724

NJCBIR fellowship CBIRFEL002

NJCBIR grant CBIR14IRG019

Title: Cypin overexpression distinctly alters dendrite arborization at different developmental time points as shown by novel Sholl analyses

Authors: *K. O'NEILL[1,2], B. F. AKUM[2], S. T. DHAWAN[2], M. KWON[2], C. G. LANGHAMMER[2], B. L. FIRESTEIN[2];
[1]Biomed. Engin., [2]Cell Biol. & Neurosci., Rutgers Univ., Piscataway, NJ

Abstract: The dendritic architecture of a neuron determines how it receives input, and thus, changes in dendrite morphology affect connectivity among neurons. Aberrant changes in the development of the arbor or after the arbor has formed can disrupt the functioning of neural circuits, causing severe brain dysfunction and leading to pathologies seen in cognitive disorders, neurological diseases, and trauma. Much work has been done by our laboratory and others to characterize the intrinsic and extrinsic factors that regulate dendrite number. Usually, this analysis consists of Sholl analysis and/or simple dendrite counting. However, neither of these methods offers a complete picture of the changes that can occur to the arbor. Previously, our laboratory developed a program called "Bonfire" to perform centripetal (outside in) Sholl analysis and Sholl analysis that assesses changes to root, intermediate, and terminal neurites in addition to conventional centrifugal (inside out) Sholl analysis and simple dendrite counting. We reported that these new Sholl analyses revealed previously unknown changes to hippocampal dendrites when cultures were treated with brain-derived neurotrophic factor (BDNF). In specific, exposure to BDNF increases primary branching with no effect on higher order branches, consistent with previous studies. We also found that BDNF significantly increased root and terminal branches with no effect on intermediate branches, pointing to a reorganization of the arbor. Here we show how cytosolic PSD-95 interactor (cypin), an intracellular protein through which BDNF signals to increase dendrites, alters the dendritic arbor when it is overexpressed in hippocampal neurons from DIV 6-10 and from DIV 10-12. We perform our novel Sholl analyses to reveal previously unknown changes to the arbor. Our results suggest that conventional Sholl analysis and dendrite counting are not sufficient methods for revealing the changes that occur in the arbor at different times in neuronal development.

Disclosures: K. O'Neill: None. **B.F. Akum:** None. **S.T. Dhawan:** None. **M. Kwon:** None. **C.G. Langhammer:** None. **B.L. Firestein:** None.

Nanosymposium

278. Dendritic Growth and Branching

Location: N426A

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 278.11

Topic: A.04. Axon and Dendrite Development

Support: NS-041963

Title: Actin filaments within the proximal axon comprise a vesicle filter

Authors: *V. BALASANYAN, K. WATANABE, D. B. ARNOLD;
USC, Los Angeles, CA

Abstract: The bipolar structure of neurons is established and maintained through the differential trafficking of vesicles carrying axonal and dendritic proteins. In particular, vesicles carrying dendritic proteins enter the proximal axon but then halt and reverse course. Previously, we provided evidence using electron microscopy as well as observation of vesicle trafficking and myosin movement in living cells that this halting and reversing took place as a result of interaction with actin filaments within the proximal axon. Here we directly observe actin patches and bundles within the proximal axon of living neurons, characterize their structure and demonstrate how they function as a vesicle filter. We conclude that, as previously observed, the vesicle filter is comprised of actin filaments that are oriented in parallel with their plus ends facing the cell body. Specialized actin structures comprised of high density patches and/or bundles of filaments are present in 100% of cortical neurons in culture. This actin filter is present immediately following specification of the axon. Vesicles carrying dendritic proteins halt and reverse following contact with the elements of the filter and disruption of the filter causes those vesicles to proceed to the distal axon. Thus, the vesicle filter restricts dendritic proteins specifically to the somatodendritic compartment and plays a key role in the specification and maintenance of neuronal polarity.

Disclosures: V. Balasanyan: None. **K. Watanabe:** None. **D.B. Arnold:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.01

Topic: B.08. Synaptic Plasticity

Support: Lord Foundation fellowship

NIH Grant R01HG004037-7

NIH grant RC1HG005334

Glenn Foundation Grant

Neurodegeneration Consortium Grant

Title: Activity-induced DNA breaks govern the expression of early response genes in neurons

Authors: *R. MADABHUSHI[1], F. GAO[1], A. PFENNING[2], L. PAN[1], S. YAMAKAWA[1], J. SEO[1], R. RUEDA[1], T. PHAN[1], H. YAMAKAWA[1], P.-C. PAO[1], R. STOTT[1], E. GJONESKA[1], A. NOTT[1], S. CHO[1], M. KELLIS[2], L.-H. TSAI[1];
[1]Brain and Cognitive Sci., [2]MIT, Cambridge, MA

Abstract: Neuronal activity triggers the rapid expression of immediate early genes (IEGs) that play important roles in experience-driven synaptic changes, learning, and memory. IEGs are primed for rapid induction in many ways. Even in the absence of a stimulus, the chromatin landscape at IEG promoters is highly permissive for transcription, and the promoters are already decorated with activating transcriptional factors, and even paused RNA polymerase II (RNAPII) in some cases. Despite these details, however, the precise molecular switch that governs the rapid induction of IEGs in response to neuronal activity remains poorly understood. Here we report that the expression of an important subset of IEGs, including *Fos, Npas4,* and *Egr1,* is normally constrained through the imposition of a topological barrier by the architectural protein, CTCF. Even more surprisingly, activity-dependent stimulation of neurons triggers the formation of DNA double strand breaks (DSBs) in the promoters of these IEGs. We show that activity-induced DSBs are generated by the topoisomerase, Topo IIβ, and that Topo IIβ-mediated DSBs are sufficient to drive the expression of these IEGs even in the absence of an external stimulus. Together, our observations suggest that activity-induced DSB formation is a physiological event that rapidly overcomes topological barriers to gene expression in response to neuronal activity. The existence of such "hotspots" for DSB formation in neurons also has important pathophysiological implications. Defects in DNA repair have been linked to various congenital and age-related neurological disorders, yet the specific contribution of DNA damage to the development of these disorders remains unclear. We describe how changes in the formation and repair of activity-induced DNA breaks could underlie the etiology of neurological disorders that manifest from defective DNA repair.

Disclosures: **R. Madabhushi:** None. **F. Gao:** None. **A. Pfenning:** None. **L. Pan:** None. **S. Yamakawa:** None. **J. Seo:** None. **R. Rueda:** None. **T. Phan:** None. **H. Yamakawa:** None. **P. Pao:** None. **R. Stott:** None. **E. Gjoneska:** None. **A. Nott:** None. **S. Cho:** None. **M. Kellis:** None. **L. Tsai:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.02

Topic: B.08. Synaptic Plasticity

Title: An enhancer code underlying the epigenomic regulation of learning and memory

Authors: *F. TELESE[1], Q. MA[2], P. MONTILLA PEREZ[2], D. NOTANI[2], W. LI[2], S. OH[2], D. COMOLETTI[3], M. G. ROSENFELD[2];
[1]Med., [2]UCSD, La Jolla, CA; [3]Rutgers Univ., New Brunswick, CA

Abstract: Reelin controls a signaling pathway required for proper lamination of the neocortex as well as for the plasticity of mature glutamatergic synapses. Alteration of Reelin signaling has been linked to the etiology of various neuropsychiatric disorders, including schizophrenia. Here, we provide genetic and global genomic evidence that the Reelin-LRP8 pathway is required for hippocampal-dependent associative learning measured by fear conditioning paradigms. By using a wide array of deep sequencing technologies, we establish a link between higher cognitive behaviors and epigenetic control of gene transcriptional programs initiated by the delivery of Reelin to neurons. The molecular cascade triggered by the Reelin signaling involves a novel crosstalk between N-methyl-D-aspartate receptor (NMDA-R) activity and γamma-secretase-dependent release of the intracellular domain of the Reelin receptor LRP8, and converges on the activation of specific cohorts of enhancer elements in the genome that we refer to as LRP8-Reelin Regulated Neuronal (LRN) Enhancers. LRN enhancer regulation involves the dismissal of NCoR corepressor complex that functions as a gatekeeper for the fine-tuned activation of enhancer-dependent transcriptional events. Here, we provide data showing the *in vivo* function of NCoR in mechanisms of learning and memory. Together our results uncover a novel epigenetic mechanism modulated by Reelin-LRP8 signaling that contributes to the molecular basis of normal cognition and offers a candidate mechanism underlying the pathophysiology of cognitive deficits observed in psychiatric disorders.

Disclosures: F. Telese: None. **Q. Ma:** None. **P. Montilla Perez:** None. **D. notani:** None. **W. li:** None. **S. Oh:** None. **D. Comoletti:** None. **M.G. Rosenfeld:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.03

Topic: B.08. Synaptic Plasticity

Title: Unique experience-induced gene programs in interneuron subtypes shape cortical circuits

Authors: ***A. R. MARDINLY**[1], I. SPIEGEL[2], J. E. BAZINET[2], E. CENTOFANTE[3], D. A. HARMIN[2], C. MANDEL-BREHM[2], C. TZENG[2], M. FAGIOLINI[3], H. ADESNIK[1], M. E. GREENBERG[2];
[1]MCB, Univ. of California, Berkeley, Berkeley, CA; [2]Neurobio., Harvard Univ., Boston, MA; [3]Boston Children's Hosp. FM Kirby Neurobio. Ctr., Boston, MA

Abstract: Neural circuits in the cortex adapt to sensory-evoked activity during development and in adult life. This plasticity is mediated in part by the experience-dependent induction of genes that function at synaptic sites to regulate circuit activity and to maintain the balance between excitation and inhibition (E-I balance). Nevertheless,cortical circuits exhibit significant cellular diversity, particularly at the level of inhibitory cell types, where multiple functionally distinct types of GABAergic neurons play key roles in the processing of sensory input. Despite an emerging understanding of the connectivity and function of inhibitory circuits in the cortex, the molecular mechanisms underlying the adaptation of specific inhibitory neuron subtypes to sensory experience are still not well understood. Here, we report the gene expression profiles of inhibitory neuron subtypes in the visual cortex upon manipulation of visual experience. We find that visual experience induces unique programs of gene expression in each inhibitory neuron subtype, and that notably, these transcriptional programs include genes that encode subtype-specific neuropeptides and growth factors. In particular, we identify IGF-1 as a cell-type-specific experience-induced secreted factor in disinhibitory VIP neurons, and demonstrate that IGF-1 specifically controls inhibitory input to VIP neurons. Taken together, this analysis reveals that experience-induced gene programs in inhibitory neurons are far more subtype-specific than previously appreciated, and these gene programs are adapted to the function of each neuronal subtype within a circuit. Thus, by inducing the expression of distinct subsets of secreted factors in each neuronal subtype within a cortical circuit, experience-dependent gene programs mediate neural circuit homeostasis and plasticity within the cortex.

Disclosures: **A.R. Mardinly:** None. **I. Spiegel:** None. **J.E. Bazinet:** None. **E. Centofante:** None. **D.A. Harmin:** None. **C. Mandel-Brehm:** None. **C. Tzeng:** None. **M. Fagiolini:** None. **H. Adesnik:** None. **M.E. Greenberg:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.04

Topic: B.08. Synaptic Plasticity

Support: BBSRC Doctoral Training Partnership SWBio

Title: The involvement of MEF2A in mGluR-dependent AMPAR endocytosis

Authors: *R. E. CARMICHAEL[1], K. A. WILKINSON[1], M. C. ASHBY[2], J. M. HENLEY[1]; [1]Sch. of Biochemistry, Fac. of Med. and Vet. Sci., [2]Sch. of Physiol. and Pharmacology, Fac. of Med. and Vet. Sci., Univ. of Bristol, Bristol, United Kingdom

Abstract: The myocyte enhancer factor 2 (MEF2) family of transcription factors activate numerous transcriptional programmes to regulate both universal and neuronal-specific functions, including those involved in memory formation. MEF2 activity is well established to regulate structural plasticity, and has also recently been shown to modulate synaptic plasticity via AMPA receptor (AMPAR) endocytosis, though the molecular mechanisms behind this are unclear. Here, we show MEF2A is required for metabotropic glutamate receptor (mGluR)-dependent AMPAR internalisation in cortical neuronal culture. Chronic knock-down of MEF2A prior to Group I mGluR activation by dihydroxyphenylglycine (DHPG) prevents the endocytosis of GluA2-containing AMPARs that is associated with mGluR long term depression (LTD). Since MEF2A is a transcriptional activator and therefore mediates cellular processes on a time scale of hours to days, it is possible that MEF2A is required to prime neurons for mGluR LTD by increasing expression of the mRNAs and/or proteins required for AMPAR endocytosis in response to Group I mGluR activation. We are currently investigating the molecular mechanisms and transcriptional targets underlying the requirement of MEF2A in mGluR-dependent AMPAR endocytosis and investigating possible activity-dependent signalling that may regulate MEF2A to mediate mGluR LTD priming. Additionally, Small Ubiquitin-like Modifier 1 (SUMO1) modification has been reported to repress MEF2A-dependent transcription, so we are investigating possible roles of MEF2A SUMOylation in mGluR-dependent AMPAR endocytosis, via knock-down/rescue experiments with MEF2A mutants exhibiting altered SUMOylation.

Disclosures: R.E. Carmichael: None. **K.A. Wilkinson:** None. **M.C. Ashby:** None. **J.M. Henley:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.05

Topic: B.08. Synaptic Plasticity

Support: NIMH T-32 Training Grant

Title: A transcriptional program underlying homeostatic scaling

Authors: ***K. SCHAUKOWITCH**, A. L. REESE, G. KILARU, J.-Y. JOO, E. T. KAVALALI, T.-K. KIM;
Neurosci., UT Southwestern Med. Ctr., Dallas, TX

Abstract: Homeostatic scaling is a phenomenon seen in neuronal cultures, in which neurons globally change their synaptic strength in response to changing activity levels. This process allows cells to maintain a proper firing rate, and deficits in scaling have been seen in models of autism spectrum disorder and schizophrenia. One mechanism by which this occurs is through up- or down-regulating surface AMPA receptors. Decreasing activity by blocking action potentials with the sodium channel blocker, TTX, leads to an upregulation in synaptic strength, as seen by increases in mEPSC amplitudes. In the opposite way, increasing activity with the $GABA_A$ receptor antagonist, bicuculline, decreases mEPSC amplitudes. It was previously shown that the increase in mEPSC amplitude in response to TTX could be blocked by the transcription inhibitor Actinomycin D, suggesting that transcription is necessary for the scaling response (Ibata, 2008). However, very little is known about the genes whose transcription is directly regulated by activity suppression or the signaling mechanisms underlying the transcriptional control. To determine whether there were genes that were specifically upregulated, we performed RNA-Seq in cortical neurons that were treated with TTX. We identified nearly 100 genes that were upregulated in response to TTX, suggesting that neurons do possess a transcriptional program to control the increase in synaptic strength. These genes were largely non-overlapping with genes that are upregulated in response to bicuculline, indicating that this program is distinct from that induced by an increase in activity. Future experiments will aim to understand how these genes contribute to the scaling process as well as the signaling mechanism that activates the upregulation of these genes during this quiescent state.

Disclosures: K. Schaukowitch: None. **A.L. Reese:** None. **G. Kilaru:** None. **J. Joo:** None. **E.T. Kavalali:** None. **T. Kim:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.06

Topic: B.08. Synaptic Plasticity

Title: Rewarding and aversive experiences are encoded by unique transcriptional signatures

Authors: *B. M. IGNATOWSKA-JANKOWSKA[1], D. MUKHERJEE[2], D. HARITAN[2], B. J. GONZALES[2], H. TURM[1], A. CITRI[1];
[1]Edmond and Lily Safra Ctr. for Brain Sci., [2]Alexander Silberman Inst. of Life Sci., Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: How an individual responds to a situation is a function of cumulative past experience. We are interested in identifying plastic changes induced in the brain by experience, and understanding how they modify the behavior in future. We focus on experience-dependent plasticity at the molecular level, aiming to identify signatures of transcriptional dynamics that are unique to the encoding of aversive or rewarding experiences in the mesolimbic and limbic brain areas. Our entry point to this study is the comparative investigation of rewarding (cocaine, sucrose) and aversive (LiCl, foot shock) experiences. For each experience, we assessed the induction of immediate-early genes (0,1,2,4 hrs following the experience) in multiple brain regions: Nucleus Accumbens, Dorsal Striatum, Prefrontal Cortex, Amygdala, Lateral Hypothalamus, Hippocampus and Ventral Tegmental Area. We investigated the transcriptional response to different experiences, by assessing gene expression patterns in naïve mice and mice exposed to acute or repeated experiences. Unique and robust transcriptional programs were identified in response to distinct experiences, and dramatic differences were revealed in the encoding of aversive vs rewarding experiences. We observed a strong linkage between different features of an experience and the activation of specific brain regions. Aversive experiences (LiCl administration or foot shock) induced a robust transcriptional response in the Amygdala. On the other hand - the Nucleus Accumbens responded both to positive and negative experiences. Also, development of a transcriptional response differed between experiences. Transcriptional response to sucrose developed after repeated exposure while acute exposure had no effect. On the other hand, robust acute response to LiCl was diminished following repeated exposure. In contrast, cocaine administration showed immediate response that persisted following repeated administration. Our results suggest that the acquisition of a natural rewarding habit, as opposed to direct, pharmacological stimulation of the mesolimbic circuit, requires repeated exposure to pass a salience and encoding threshold, while aversive experiences are immediately registered as salient and encoded. Our results reveal that different experiences are encoded by unique transcriptional patterns. Gene expression in distinct brain structures, dependent on the context and quality of the experience, represents encoding that may lead to different behavioral outcomes in the future.

Disclosures: B.M. Ignatowska-Jankowska: None. **D. Mukherjee:** None. **D. Haritan:** None. **B.J. Gonzales:** None. **H. Turm:** None. **A. Citri:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.07

Topic: B.08. Synaptic Plasticity

Title: Activity-dependent changes in miRNAs and alternative 3'UTR usage during hippocampal plasticity

Authors: *M. M. FONTES[1], V. HO[1], A. HUANG[2], D. ZHENG[4], B. TIAN[4], G. COPPOLA[2], T. O'DELL[3], K. C. MARTIN[1];
[1]Biol. Chemistry/ Biol. Sci. Res. Building 354, UCLA/ Kelsey Martin Lab., Los Angeles, CA; [2]Jane & Terry Semel Inst. for Neurosci. & Human Behavior, [3]Dept. of Physiol., UCLA, Los Angeles, CA; [4]Rutgers Med. Sch., Newark, NJ

Abstract: Long-lasting forms of synaptic plasticity that underlie learning and memory require a tight control of gene expression and de novo transcription and protein synthesis. Neurons are highly polarized cells that elaborate extensive processes, form thousands of synapses and are thus comprised of a multitude of subcellular compartments. This remarkable polarity raises questions about the mechanisms underlying the spatial and temporal regulation of gene expression within neurons. This project is aimed at elucidating the mechanisms underlying activity-dependent post-transcriptional gene regulation during long-term potentiation (LTP) of hippocampal CA3-CA1 synapses in mouse. Towards this end, we are focusing on mechanisms of post-transcriptional regulation involving 3'UTR of mRNAs, using deep sequencing to identify changes in alternative 3'UTR usage and in the population of miRNAs following induction of LTP in acute mouse hippocampal slices during post-induction time course. Analysis of 3'READS and RNA-seq from LTP-induced and time-matched control slices allows us to uncover novel activity-dependent 3'UTR switches and wide changes in the transcriptome. Additionally, by small RNAs sequencing we identified the populations of miRNAs that are regulated in an activity-dependent manner and how their expression changes over time. The results of these studies are starting to elucidate networks of alternative 3'UTR isoforms and miRNA-regulatory mechanisms implicated in long-term memory formation and thereby contribute to a deeper understanding of the function of post-transcriptional regulation in the CNS.

Disclosures: **M.M. Fontes:** None. **V. Ho:** None. **A. Huang:** None. **D. Zheng:** None. **B. Tian:** None. **G. Coppola:** None. **T. O'Dell:** None. **K.C. Martin:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.08

Topic: B.08. Synaptic Plasticity

Title: Synaptic vesicles contain small ribonucleic acids (sRNAs)

Authors: *H. LI[1], C. WU[2], R. ARAMAYO[1], M. SACHS[1], M. HARLOW[1];
[1]Biol., Texas A&M Univ., College Station, TX; [2]Biol., Texas A& M Univ., College Station, TX

Abstract: Synaptic vesicles (SVs) are neuronal presynaptic organelles that load and release neurotransmitter at chemical synapses eliciting local changes in membrane excitability that form the basis for locomotion, behavior, learning and memory. In addition to classic neurotransmitters, we have found that synaptic vesicles isolated from the electric organ of the marine ray Torpedo californica also contain small ribonucleic acids (sRNAs), the most abundant of which are around 30 nucleotides (nt) in length. We tested whether the vesicular content of sRNAs is a general phenomenon in the nervous system by isolating SVs from the central nervous system (CNS) of Mus musculus. We found abundant levels of sRNAs within CNS SVs, including sRNAs known to be involved with transcription and translation regulation. The discovery of sRNAs inside of synaptic vesicles indicates that in addition to neurotransmitter-induced changes in local excitability, SVs may, through the release of specific RNAs, directly regulate local dendritic transcription and translation in an activity dependent manner.

Disclosures: H. Li: None. **C. Wu:** None. **R. Aramayo:** None. **M. Sachs:** None. **M. Harlow:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.09

Topic: B.08. Synaptic Plasticity

Support: NIH Grant NS062811

Ellison Young Scholar Award AG-NS-0415-07

Title: Insulin signaling negatively regulates the presynaptic release of neurotransmitter via the Foxo-dependent regulation of the eif-4e binding protein

Authors: *B. A. EATON[1], R. MAHONEY[2], J. AZPURUA[2];
[2]Physiol., [1]UTHSCSA, San Antonio, TX

Abstract: Altered insulin signaling within the brain has been linked to cognitive dysfunction and neurodegenerative disease. Appropriate signaling downstream of the insulin/IGF-1 receptor has been linked to a number of cell processes that could contribute to the effects of insulin signaling on brain function including maintenance of neuronal health, reduced cell stress, neuron development, and synapse function. However, a role for insulin signaling during the regulation of neurotransmission has not been demonstrated. Using a novel synaptic preparation in adult *Drosophila*, we have found that cell autonomous insulin signaling negatively regulates the presynaptic release of neurotransmitter via the activity of the eif-4e binding protein (4eBP), a negative regulator of protein translation. In this context, the activity of 4eBP is regulated transcriptionally by the forkhead transcription factor Foxo and not the mammalian target of rapamycin (mTOR). Furthermore, the regulation of neurotransmission by insulin signaling requires the mRNA binding protein Staufen, which is known to localize mRNAs to distinct compartments within neurons, and is blocked by the protein synthesis inhibitor cycloheximide. Our data supports the model that cell autonomous insulin signaling regulates the presynaptic release of neurotransmitter via the local translation of negative regulators of synaptic vesicle exocytosis. Analysis of candidate molecules required for the effect of insulin signaling on synaptic vesicle exocytosis will be presented.

Disclosures: B.A. Eaton: None. **R. Mahoney:** None. **J. Azpurua:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.10

Topic: B.08. Synaptic Plasticity

Support: NIH grant GM84364/NS083085-19

Title: Glutamate induces post-synaptic β-actin mRNA localization and translation

Authors: *Y. J. YOON, B. WU, R. H. SINGER;
Anat. and Structural Biol., Albert Einstein Col. of Med., Bronx, NY

Abstract: Localization of mRNA allows protein synthesis within discrete compartments. In dendrites, β-actin mRNAs move as observed by single molecule imaging and traffic to synaptic spines stimulated by diffraction-limited glutamate uncaging. Localization occurred within 10 minutes after stimulation and required the activity of NMDA receptors and dynamic actin cytoskeleton. Strikingly, β-actin mRNA failed to localize in ZBP1 knock-out neurons upon uncaging. To assess local uncaging-dependent translation, we expressed a β-actin reporter fused to MS2 stem-loops and HaloTag to visualize the reporter RNA and the translated fusion-protein in dendrites. Newly synthesized actin was enriched in dendritic spines near the site of stimulation. Thus, our results demonstrate that post-synaptic activity leads to capture and subsequent translation of β-actin mRNA.

Disclosures: Y.J. Yoon: None. **B. Wu:** None. **R.H. Singer:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.11

Topic: B.08. Synaptic Plasticity

Support: CIHR Grant MOP-125985 (JCL)

FRQS; GRSNC (JCL)

Canada research chair in cellular and molecular neurophysiology (JCL)

FRQS and CIHR postdoctoral fellowship (AAL)

FRQS postdoctoral fellowship (JA)

Stériade-Savoy postdoctoral scholarship (IR)

CIHR studentship (PX)

Title: Cell type specific knock-out of TSC1 in excitatory or inhibitory cells differentially affects hippocampal synaptic transmission, plasticity and contextual fear memory

Authors: *I. M. RIEBE, N. HAJI, A. AGUILAR VALLES, C. PICARD-DELAND, P. XING, J. ARTINIAN, I. LAPLANTE, J.-C. LACAILLE;
GRSNC, Dept. of Neurosciences, Univ. de Montréal, Montreal, QC, Canada

Abstract: Tuberous sclerosis is one of the most common monogenic causes of autism and epilepsy in humans. Tuberous sclerosis complex 1 (TSC1) is one of the two TSC genes associated with this disease and mice lacking the TSC1 gene express a hyperactive mechanistic target of rapamycin (mTOR) pathway. The mTOR pathway is central in the regulation of cell growth and protein translation, and its hyperactivation has been shown to result in alterations in synapse structure, function and plasticity as well as in aberrant behavioral phenotypes. Whether the different cell types in forebrain circuits are differentially affected by TSC1 knock-out, thus resulting in cell type specific synaptic and behavioral phenotypes is still largely unknown. Here, we study cell-type specific heterozygous conditional knockout of TSC1 in either forebrain excitatory principal cells or inhibitory interneurons by crossing, respectively, $Emx1^{Cre/Cre}$ or $Nkx2.1^{Cre/wt}$ mice with $TSC1^{flox/flox}$ mice. In mice with heterozygous TSC1 knock-out, mTOR pathway is hyperactive, as determined by phosphorylation of ribosomal protein S6, and cell survival is normal. Basic membrane properties of excitatory and inhibitory neurons were unaffected in whole cell current-clamp recordings in acute hippocampal slices from either knock-out mouse. Synaptic transmission was, however, altered. The amplitude and frequency of miniature excitatory postsynaptic currents (mEPSCs) were reduced in pyramidal cells of $Emx1^{Cre/wt}$;$TSC1^{flox/wt}$ mice. Inhibitory synaptic responses evoked by optogenetic stimulation of Nkx2.1 expressing interneurons, and recorded in CA1 pyramidal cells, were reduced in $Nkx2.1^{Cre/wt}$;$TSC1^{flox/flox}$ mice. Late form of long-term potentiation (L-LTP), assessed with field potential recordings in CA1 hippocampal slices, was enhanced in $Emx1^{Cre/wt}$;$TSC1^{flox/wt}$ mice and reduced in $Nkx2.1^{Cre/wt}$;$TSC1^{flox/wt}$ mice. At the behavioral level, contextual fear memory was enhanced in $Emx1^{Cre/wt}$;$TSC1^{flox/wt}$ mice, whereas context discrimination in fear memory was impaired in $Nkx2.1^{Cre/wt}$;$TSC1^{flox/wt}$ mice. In conclusion, our data suggest that conditional heterozygous knock-out of TSC1 in principal cells or in interneurons differentially affects hippocampal synaptic network function and hippocampus dependent memory processes.

Disclosures: I.M. Riebe: None. **N. Haji:** None. **A. Aguilar Valles:** None. **C. Picard-Deland:** None. **P. Xing:** None. **J. Artinian:** None. **I. Laplante:** None. **J. Lacaille:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.12

Topic: B.08. Synaptic Plasticity

Support: NIH Grant F32MH103921

The Robertson Foundation

Title: BET-family protein Brd4 regulates activity-dependent transcription in neurons and BET inhibitor Jq1 prevents memory consolidation in mice

Authors: *E. KORB, M. HERRE, I. ZUCKER-SCHARFF2, R. DARNELL, C. ALLIS; Rockefeller Univ., New York, NY

Abstract: The nervous system requires tight control of transcription in response to external signals. Rapid activation of immediate early gene (IEG) transcription in response to stimulation is critical for synaptic plasticity and is observed *in vivo* during learning and memory. Transcription is regulated in part by modifications of the histone proteins that fold and regulate DNA. However, the link between stimulation and proteins that directly interact with histone modifications to mediate inducible transcriptional activation in neurons remains unclear. In other cell types, the bromodomain protein Brd4 is critical in regulating the recruitment of protein complexes that allow for transcription of target genes in response to a signal. Brd4 is a member of the bromodomain and extraterminal (BET) protein family and functions as a chromatin 'reader' that binds acetylated lysines in histones. Recent work indicates that small molecule inhibitors of BET proteins are a promising therapeutic strategy for several types of cancer yet little is known about how these inhibitors affect the brain. Here we show that Brd4 is critical to neuronal function and mediates the transcriptional regulation underlying learning and memory. We find that Brd4 regulates IEG transcription in neurons in response to activity and is regulated by casein kinase II. Loss of Brd4 function affects critical synaptic proteins and the BET inhibitor Jq1 results in memory deficits but also decreases seizure susceptibility in mice. These results provide the first demonstration of Brd4 function in the brain and provide a critical link between neuronal activity and transcriptional activation that underlies memory formation. In addition, our data call attention to the potential for small molecule inhibitors of BET proteins such as Jq1 to cause neuronal deficits. While BET protein inhibitors are a promising therapeutic strategy for several types of cancer, modifications preventing blood brain barrier penetrability may be necessary to prevent neurological side effects for patients receiving these drugs.

Disclosures: E. Korb: None. **M. Herre:** None. **I. Zucker-Scharff2:** None. **R. Darnell:** None. **C. Allis:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.13

Topic: B.08. Synaptic Plasticity

Support: Stanley Center for Psychiatric Research and the Broad Institute

JPB Foundation

Title: Experience-dependent translation of neurogranin in hippocampus gates contextual memory formation

Authors: ***K. J. JONES**[1], H. HWANG[1], S. B. TEMPLET[1], F. X. PENA[1], C. SAENZ[1], S. NGUYEN[2], M. C. LEWIS[2], W. XU[1];
[1]Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [2]Stanley Ctr. for Psychiatric Res., Broad Inst., Cambridge, MA

Abstract: Contextual memory formation requires new protein synthesis in the hippocampus. However, the identities of the proteins critical for memory formation have remained elusive. We found that novel context exposure induced a rapid significant increase in the expression of neurogranin in mouse hippocampus. This experience-dependent increase of neurogranin wasmediated by elevated translation most likely triggered by NMDAR and adrenergic-dependent signaling. The temporal profile of this experience-dependent upregulation of neurogranin fell into the domain when new protein synthesis is absolutely required for contextual memory formation. Neurogranin is a small calmodulin binding protein primarily expressed in the postsynaptic compartment of projection neurons in selected brain regions including hippocampus, cerebral cortex, and striatum. It has been associated with schizophrenia, mental retardation and neurodegenerative diseases, and is potentially regulated at the translational level. Biochemical and modeling studies have implicated that the levels of neurogranin regulate calcium-dependent signaling events that lead to synaptic plasticity critical for learning and memory. Using viruses expressing the 3'-UTR of neurogranin but not the 3'-UTR of a control gene, we prevented activity-dependent translation of neurogranin. Virus-mediated expression of 3'-UTR of neurogranin in hippocampus blocked contextualmemory formation and protein-synthesis-dependent phase of long-term potentiation. The impairment of contextual memory formation could be rescued through overexpression of the neurogranin along with the expression of the 3'-UTR of neurogranin. Furthermore, overexpressing neurogranin in hippocampus sufficiently facilitated contextual memory formation. Taken together, our results show that activity-dependent translation of neurogranin in hippocampus in response to novel experience is obligatory to gate contextual memory formation.

Disclosures: **K.J. Jones:** None. **H. Hwang:** None. **S.B. Templet:** None. **F.X. Pena:** None. **C. Saenz:** None. **S. Nguyen:** None. **M.C. Lewis:** None. **W. Xu:** None.

Nanosymposium

279. Transcription and Translation in Plasticity I

Location: N230

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 279.14

Topic: B.08. Synaptic Plasticity

Support: NIH Grant K01MH101639

Title: The activity-regulated GTPase Rem2 and its role in neuronal plasticity

Authors: *A. R. MOORE, S. E. RICHARDS, K. KENNY, U. CHAN, S. D. VAN HOOSER, S. PARADIS;
Biol., Brandeis Univ., Waltham, MA

Abstract: The construction and adaptation of neuronal circuits is a carefully orchestrated series of events, which includes the formation of synapses and the morphogenesis of the dendritic arbor of individual neurons. These events are largely dependent on the relationship between spontaneous and experience-dependent activity and underlying intracellular signaling pathways. However, the identity of the molecules that link these changes in sensory experience to corresponding changes in intracellular signaling and, ultimately, neuronal structure and function remain largely unknown. We have identified a previously obscure Ras-like GTPase called Rem2 that has several hallmarks of being a major activity-dependent plasticity gene. For example, dialing Rem2 expression up or down in the context of increased sensory experience in the Xenopus optic tectum decreases or increases dendritic complexity accordingly. Further, Rem2 is a novel target of CaMKII: phosphorylation of Rem2 by CaMKII regulates Rem2 subcellular localization and function. Our preliminary data strongly suggests that Rem2 functions to mediate structural plasticity via translocation to the nucleus where it regulates gene expression; this represents a novel paradigm for GTPase function. Our molecular studies promise to yield significant insight into the transcriptional program by which a neuron instructs its dendritic morphology. In addition, we are investigating the relationship between activity-dependent changes in neuronal morphology and neural circuit function in the visual cortex of transgenic mice harboring either a null (Rem2null) or conditional (Rem2flx, i.e. flanked by loxP sites) allele of the Rem2 gene. Thus, we are combining our *in vitro*, molecular studies of Rem2 signaling mechanisms with *in vivo* assays of Rem2 function, to determine the molecular underpinnings of experience-dependent changes in circuit connectivity.

Disclosures: A.R. Moore: None. **S.E. Richards:** None. **K. Kenny:** None. **U. Chan:** None. **S.D. Van Hooser:** None. **S. Paradis:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association NIRP-12-259289

Title: Clusterin prevents the formation of cerebral amyloid angiopathy

Authors: *J. D. FRYER[1], A. M. WOJTAS[2], S. S. KANG[2], A. AWAN[2], G. BU[2]; [1]Neurosci., Mayo Clin. FL, Jacksonville, FL; [2]Neurosci., Mayo Clin. Jacksonville, Jacksonville, FL

Abstract: Alzheimer's disease (AD) is the most common cause of dementia and is characterized by extracellular plaques formed by the deposition of amyloid-β (Aβ) peptide and intracellular tangles comprised of hyperphosphorylated forms of the tau protein. The majority of AD patients also have abundant Aβ deposition along the walls of cerebral vessels termed cerebral amyloid angiopathy (CAA). CAA leads to vascular dysfunction due to the gradual death of smooth muscle cells as well as micro- and macro-hemorrhages that can be fatal. Although the impact of allelic variants of APOE on CAA has been well studied, another major brain apolipoprotein, clusterin (CLU, aka ApoJ), binds to the Aβ peptide both *in vitro* and *in vivo* but has not been previously implicated in CAA. Multiple large-scale genome wide association studies (GWAS) have demonstrated a highly significant association of CLU with human AD cases. To further explore the role of CLU in AD pathogenesis, we crossed Clu-/- knockout mice to the APP/PS1 mouse model of amyloidosis. We found a dramatic reduction in the amount of parenchymal amyloid plaque in APP/PS1;Clu-/- mice compared to control APP/PS1;Clu+/+ littermates. However, to our surprise, we found that APP/PS1;Clu-/- mice had a dramatic increase in the amount of cerebral amyloid angiopathy. Other pathological endpoints and mechanisms are currently being explored. These data suggest that CLU can have differential effects not just on the amount of fibrillar amyloid, but more importantly where amyloid deposits.

Disclosures: J.D. Fryer: None. **A.M. Wojtas:** None. **S.S. Kang:** None. **A. Awan:** None. **G. Bu:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer Association grant IIRG-13-284849

NIH grant NS083385

Title: Ablation of Mfn2 causes an oxidative stress response and neuronal death in the hippocampus and cortex

Authors: *X. ZHU[1,2], X. WANG[2], P. NANDY[2], C. WANG[2], H.-G. LEE[2], G. PERRY[3]; [2]Pathology, [1]Case Western Reserve Univ., Cleveland, OH; [3]Univ. of Texas at San Antonio, San Antonio, TX

Abstract: Mitochondria are the organelles responsible for energy metabolism and have a direct impact on neuronal function and survival. Mitochondrial abnormalities have been well characterized in Alzheimer disease, and significant advances have been made in the understanding of the changes in morphology and distribution of neuronal mitochondria in this devastating diseases. It is believed that mitochondrial fragmentation, due to impaired fission and fusion balance, likely causes mitochondrial dysfunction that underlies many aspects of neurodegenerative changes. To examine how impaired mitochondrial fission/fusion balance causes neurodegeneration, we developed a transgenic mouse model using the CAMKII promoter to knockout mitofusin 2 (mfn2) in the hippocampus and cortex. Electron micrographs of neurons from these mice show swollen mitochondria with cristae damage and mitochondria membrane abnormalities. Over time the mfn2 KO model demonstrates a progression of neurodegeneration via mitochondrial morphological changes, oxidative stress response, inflammatory changes, cell cycle induction, and loss of MAP2 in dendrites, leading to severe and selective neuronal death. In this model, hippocampal CA1 neurons were affected earlier and resulted in nearly total loss, while cortical neuronal death was associated with fewer neurons and decreased cortical size, but no changes in neuronal density. Hemizygous mfn2 KO mice showed no neurodegeneration, but did display heightened levels of oxidative stress at old age. Finally, knockout of mitofusin 1 (mfn1) did not show any neuronal degeneration, with only subtle changes in mitochondria structure seen by electron microscopic analysis. Overall, our findings indicate that impaired mitochondrial fission and fusion balance can cause many neurodegenerative changes and eventual neurodegeneration that characterize AD in the hippocampus and cortex which makes it a potential target for treatment strategies for AD.

Disclosures: **X. Zhu:** None. **X. Wang:** None. **P. Nandy:** None. **C. Wang:** None. **H. Lee:** None. **G. Perry:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NINDS R01 NS073899

Title: An extracellular chaperone provokes neurovascular damage

Authors: *L. J. BLAIR[1], R. HAINES[2], B. MONTANE[2], B. NORHUES[2], C. DICKEY[2];
[1]Mol. Med., USF Byrd Inst., Tampa, FL; [2]Univ. of South Florida, Tampa, FL

Abstract: Understanding the vascular contributions to cognitive impairment and dementia (VCID) is of great importance given the high coincidence of neurovascular damage in post-mortem tissues derived from dementia and Alzheimer's disease cases. Interestingly, vascular injury has been linked to an increase in the release and circulation of extracellular chaperones. One such chaperone in particular, the small heat shock protein 27 kDa (Hsp27), increases in the blood and extracellular space in peripheral vascular diseases and stroke, but any role for Hsp27 in VCID is completely unknown. While intracellular Hsp27 has been shown to have anti-inflammatory effects, this extracellular Hsp27 up-regulates many pro-inflammatory factors by interacting with the toll-like receptors. We hypothesized that in this capacity, extracellular Hsp27 could damage blood-brain barrier (BBB) integrity in Alzheimer's disease and dementia, serving as a major player in VCID. We have found that Hsp27 is highly expressed in activated astrocytes, and following neurovascular stress, is released from these cells in the brain. Hsp27 levels increase in the brains of rTg4510 tau transgenic mice, which model dementia, neuronal loss and even late stage BBB impairment, and this Hsp27 is found along the vasculature, appearing to be extra-astrocytic. Application of intact, but not heat-denatured, extracellular Hsp27, to an endothelial cell model impaired their resistance capacity as measured by electric cell substrate impedance sensing (ECIS). Biochemical analyses revealed that these changes in resistance were concomitant with reductions in the levels of several junction proteins. These findings suggest that the pro-inflammatory Hsp27 extracellular chaperone could be contributing directly to BBB damage. Therefore, strategies to remove this protein from the blood could mitigate VCID.

Disclosures: L.J. Blair: None. **R. Haines:** None. **B. Montane:** None. **B. Norhues:** None. **C. Dickey:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: P01 HD29587

R01 NS086890

P30 NS076411

ADD Grant -- Brain & Behavior Res. Foundation

Title: S-Nitrosylation of insulin degrading enzyme as a molecular mechanism linking type 2 diabetes mellitus/metabolic syndrome to Alzheimer's disease

Authors: M. W. AKHTAR[1], S. SANZ-BLASCO[1], N. DOLATABADI[1], J. PARKER[1], K. CHON[1], M. LEE[1], W. SOUSSOU[1], S. MCKERCHER[1], R. AMBASUDHAN[1], T. NAKAMURA[1], *S. A. LIPTON[1,2];
[1]Sanford-Burnham Med. Res. Inst., La Jolla, CA; [2]Sch. of Med., UC San Diego, La Jolla, CA

Abstract: Epidemiological studies show that metabolic disorders such as type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) increase the risk of developing Alzheimer's disease (AD), yet the molecular mechanisms linking the diseases remain largely unknown. Here, we report that high glucose concentrations, as found in T2DM/MetS, increase neuronal Ca^{2+} and nitric oxide (NO) levels. Previously, we had observed a similar effect of oligomeric Aβ, as observed in AD. Furthermore, we found that the increased level of NO leads to S-nitrosylation of insulin degrading enzyme (IDE). IDE is a zinc-metalloprotease that degrades insulin and Aβ. IDE hypofunction has been reported in both T2DM and AD, potentially contributing to hyperinsulinemia and increased Aβ. Here, we show that NO inhibits IDE enzymatic activity via S-nitrosylation of specific cysteine residues, and this inhibition can be rescued by a non-nitrosylatable IDE mutant. Taken together, our results suggest that S-nitrosylation of IDE may represent an important molecular mechanism linking T2DM/MetS to AD, and apparently occurs because of an altered redox state that is shared by these diseases.

Disclosures: M.W. Akhtar: None. **S. Sanz-Blasco:** None. **N. Dolatabadi:** None. **J. Parker:** None. **K. Chon:** None. **M. Lee:** None. **W. Soussou:** None. **S. McKercher:** None. **R. Ambasudhan:** None. **T. Nakamura:** None. **S.A. Lipton:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R00AG037716

Title: Mitochondrial F1FO ATP synthase oligomycin sensitivity conferring protein and neuronal mitochondrial dysfunction in Alzheimer's disease

Authors: L. GUO[1], S. J. BECK[1], J. TIAN[1], L. WANG[1], E. GUABA[1], N. TENDON[1], L. LU[1], J. PASCUAL[2], *H. DU[1];
[1]Biol. Sci., The Univ. of Texas, Dallas, Richardson, TX; [2]the university of texas southwestern medical center, dallas, TX

Abstract: A prominent challenge to treat mitochondrial dysfunction, the featured brain pathology in Alzheimer’s disease (AD) is the yet obscured mechanisms of mitochondrial defects in this disorder. Recent studies revealed the multifaceted roles of mitochondrial F1FO ATP synthase in mitochondrial oxidative phosphorylation (OXPHOS) and mitochondrial permeability transition pore (mPTP) which seems to lend credibility to the hypothesis that F1FO ATP synthase dysfunction may stand at the nexus of OXPHOS deregulation and mPTP activation, the known hallmark mitochondrial defects in AD. However, comprehensive study on this issue is still lacking. Here we show the alterations of oligomycin sensitivity conferring protein (OSCP) including its expression loss and interplay with Amyloid beta (Aβ) in AD individuals and 5xFAD mice. Such OSCP changes are associated with F1FO ATP synthase dysfunction, suppressed mitochondrial OXPHOS and sensitized mPTP formation in 5xFAD mouse neuronal mitochondria. Either Aβ exposure or OSCP knockdown leads to severe neuronal mitochondrial dysfunction which is substantially attenuated by OSCP overexpression in mouse or human neurons, highlighting the value of OSCP as a potential AD therapeutic target. Taken together, the simplest interpretation is that neuronal mitochondrial F1FO ATP synthase failure via OSCP may constitute a primary AD event that can be prevented by OSCP protection.

Disclosures: **L. Guo:** None. **S.J. beck:** None. **J. Tian:** None. **L. Wang:** None. **E. Guaba:** None. **N. Tendon:** None. **L. Lu:** None. **J. Pascual:** None. **H. Du:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant AG025493

NIH grant NS074256

Alzheimer's Association NPSPAD-10-174543

Title: Dysfunctional tubular endoplasmic reticulum in Alzheimer's pathogenesis

Authors: *R. YAN[1], M. SHAROAR[2], Q. SHI[2], Y. GE[2], J. ZHOU[2], W. HE[2], X. HU[2], G. PERRY[3], X. ZHU[4];
[1]Dept Neurosci, Lerner Resch Inst., Cleveland, OH; [2]Cleveland Clin. Lerner Res. Inst., Cleveland, OH; [3]Univ. of Texas, San Antoniio, TX; [4]Case Western Reserve Univ. Sch. of Med., Cleveland, OH

Abstract: Aging is the most common predisposing factor for the onset of Alzheimer's disease(AD) and cognitive dysfunction. One distinguishing pathological feature in AD is the occurrence of dystrophic neurites in areas surrounding amyloid deposition. The presence of dystrophic neurites is shown to closely associated with synaptic failure in AD patients, but their formation and molecular origins remain poorly understood. By taking the advantage of the mouse model that overexpresses reticulon 3 (RTN3; Tg-RTN3) and spontaneously develops age-dependent dystrophic neurites in their hippocampus, here we demonstrate that RTN3-immunoreactive dystrophic neurites (RIDNs) contain both RTN3 and REEPs, which are topologically similar proteins and localized in the tubular endoplasmic reticulum (ER). Our ultrastructural examinations of RIDNs, prior to and after their formation in Tg-RTN3 mouse hippocampi, reveal the gradual accumulation of tubular ER in the axonal termini, and such abnormal tubular ER inclusion is also found in surrounding amyloid plaques from biopsy samples of AD patient brains. We also will show that abnormally clustered tubular ER induces enhanced mitochondrial fission in the early stage of RIDNs formation, and eventually causes mitochondrial degeneration at the late stage. Finally, we demonstrate that dysfunctional tubular ER-associated RIDNs are abrogated when RTN3 is knocked out in aging and AD mouse models. Hence, we conclude that clustering tubular ER is functionally impaired as manifested by disruption of mitochondrial dynamics. RTN3, an age-dependently regulated protein, appears to play a critical role in this process via altering tubular ER organization. Our data are the first to

link dysfunctional tubular ER to the occurrence of dystrophic neurites in aging and AD brains, and suggests a novel mechanism for preserving mitochondrial integrity and synaptic function.

Disclosures: **R. Yan:** None. **M. Sharoar:** None. **Q. Shi:** None. **Y. Ge:** None. **J. Zhou:** None. **W. He:** None. **X. Hu:** None. **G. Perry:** None. **X. Zhu:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: RESEARCH TO PREVENT BLINDNESS

NEI EY006311

NIA AG038834

Title: Defective UBE2A-mediated protein ubiquitination and degradation are driven by deficits in circular RNA (circRNA) in Alzheimer's disease (AD) and age-related macular degeneration (AMD)

Authors: ***W. J. LUKIW**[1], Y. ZHAO[2], P. DUA[3], S. BHATTACHARJEE[1]; [1]Neurosci. Ctr., LSU NEUROSCIENCE CENTER, New Orleans, LA; [2]LSU NEUROSCIENCE CENTER, NEW ORLEANS, LA; [3]LA TECHNICAL UNIVERSITY, RUSTON, LA

Abstract: Our understanding of the highly specialized functions for small non-coding single-stranded RNA (ssRNA) in the human central nervous system (CNS) continues to evolve. Circular RNAs (circRNAs) are a naturally occurring, recently discovered class of ssRNA highly represented in the eukaryotic transcriptome. Traditional methods of RNA analysis and quantitation requiring a free 3′ or 5′ ribonucleotide terminus may have significantly underestimated circRNA abundance and significance in CNS function in health and disease. Highly stable and intrinsically resistant to exonucleolytic attack, circRNAs are significantly enriched in human brain and retinal tissues. Interestingly, specific ssRNAs such as the evolutionary ancient homo sapien microRNA-7 (hsa-miRNA-7; chr 9q21.32; ~23 nt; http://www.mirbase.org/cgi-bin/mirna entry.pl?acc=MI000020263; an important post-transcriptional regulator of phagocytosis), are not only very abundant in the human CNS, but are also associated with a circRNA for miRNA-7 (ciRS-7) in the same tissues. ciRS-7 contains about ~70 tandem anti-miRNA-7 sequences; ciRS-7 (~1400 nt) thereby acts as a kind of endogenous,

competing, anti-complementary miRNA “sponge” to adsorb, and hence quench, normal miRNA-7 function(s). Using DNA and miRNA arrays, RNA-sequencing, enhanced Northern and Western blot hybridization and the circularity-sensitive probe RNaseR we here provide initial evidence of a misregulated miRNA-7-circRNA system in sporadic Alzheimer's disease (AD) brain and retina. Deficits in ciRS-7, and ciRS-7 “sponging activities” might be expected to increase ambient miRNA-7 levels in AD-affected cells, as is observed, to ultimately contribute to the down-regulation of selective miRNA-7-sensitive messenger RNA (mRNA) targets. Up-regulated miRNA-7, due to a deficiency in ciRS-7 and ciRS-7-mediated “sponging” effects, was shown to down-regulate AD-relevant targets, including the ubiquitin conjugase protein (UBE2A; miRNA-7-UBE2A mRNA energy of association, $E_A = -22.86$ kcal/mol). UBE2A, a central effector in the ubiquitination cycle that helps to orchestrate the clearance of amyloid peptides via autophagy, is depleted in sporadic AD brain and retina and contributes to amyloidogenesis. Such circRNA-miRNA-mRNA regulatory systems represent another important layer of epigenetic control over normally homeostatic gene expression programs in the human CNS targeted by the AD process.

Disclosures: **W.J. Lukiw:** None. **Y. Zhao:** None. **P. Dua:** None. **S. Bhattacharjee:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: P30 EY003039

UAB Faculty Development Grant (CES)

R01NS075487 (ER)

Title: Gender related differences in the retinal cholinergic system in the J20 Alzheimer’s disease mouse model

Authors: F. G. OLIVEIRA SOUZA[1], M. BOLDING[2], M. L. SMITH[1], E. ROBERSON[3], *C. E. STRANG[4];
[1]Vision Sci., [2]Radiology, [3]Neurol., [4]Psychology, Univ. Alabama Birmingham, Birmingham, AL

Abstract: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by severe cognitive deficits and visual deficits in motion perception, contrast sensitivity, acuity and color.

It is of paramount importance to establish the causes for visual deficits in AD, as they may precede cognitive decline. To evaluate the possible role of the retinal cholinergic system (RCS) in these visual deficits we measured sex differences in acetylcholine receptor (AChR) expression in the J20 mouse model of AD. J20 mice overexpress human amyloid precursor protein (hAPP) with the Swedish KM670/671NL and the Indiana V717F mutations. We conducted quantitative real-time polymerase chain reaction (qPCR) with validated and optimized primers using whole-retina cDNA. After correcting for multiple comparisons, we observed statistically significant ($p<0.045$) differences in nicotinic AChR (nAChR) and muscarinic AChR (mAChR) transcripts in the retinas of J20 mice (6-8.9 months old) as compared to age-matched wild type (WT), namely upregulation (fold-change) in α2 (7.9), α4 (5.9), α7 (6.1) and α9 (9.1) nAChR subunit transcripts; and downregulation in α6 (2.5) nAChR subunit transcripts. We also identified substantial gender-specific differences. As compared to female WT mice, J20 females exhibited upregulation in α2 (79.5), α4 (55.6), α7 (89.0), α9 (107.7) and α10 (14.2) nAChR subunit transcripts, as well as downregulation in α6 (3.3) nAChR subunit transcripts. Furthermore, J20 males as compared to J20 females showed upregulation in α5 (4.3), β2 (2.3) and β3 (2.9) nAChR subunit transcripts and mAChR m2 (5.6) and m3 (7.6) subtype transcripts, as well as downregulation in α2 (9.1), α4 (9.5) and α7 (27.2) nAChR subunit transcripts. There were no statistically significant differences between J20 males and WT males. WT males as compared to WT females showed upregulation in α2 (8.7) and α4 (9.2) nAChR subunit transcripts and mAChR m2 (3.9) subtype transcripts, as well as downregulation in mAChR m4 (2.7) subtype transcripts. The data showed that there are normal gender-related differences (WT males vs WT females), but they are more prominent in transgenic females (J20 females vs WT females) and are exacerbated by AD (J20 males vs J20 females). This suggests that females may be more affected by AD and/or may start displaying changes earlier than males. These data indicate potential involvement of the RCS in AD-related visual dysfunctions and that AD may affect females differently. These results may lead to different paths for gender-tailored treatment, earlier diagnosis, monitoring of disease prophylaxis and progression.

Disclosures: F.G. Oliveira Souza: None. **M. Bolding:** None. **M.L. Smith:** None. **E. Roberson:** None. **C.E. Strang:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Leon Levy Foundation

BrightFocus Foundation

NIH Grant NS37853

Title: Aberrant hypothalamic activation and adipocyte dysfunction in transgenic mice overexpressing amyloid precursor protein

Authors: *M. ISHII, M. J. MCGUIRE, G. RACCHUMI, C. IADECOLA;
Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Weight loss is an early manifestation of Alzheimer's disease (AD) occurring before the mental decline, but its underlying mechanisms are unknown (Arch Neuro 63: 1312, 2006). We recently reported that young (3 month old) Tg2576 mice overexpressing a mutated form of the amyloid precursor protein (APP) exhibit lower body weight and reduced adiposity associated with hypothalamic dysfunction (J Neurosci 34: 9096, 2014). Since the low adiposity was driven by increased energy expenditure, we tested the hypothesis that dysfunction in key hypothalamic areas promotes catabolism by increasing thermogenesis in brown fat (BAT) and inducing BAT specific genes (browning) in WAT through sympathetic activation. To identify hypothalamic areas with aberrant activity, we used phosphorylated ribosomal S6 protein (pS6) immunohistochemistry as an activity marker. Compared to WT mice, young Tg2576 mice had increased pS6+ cells in ventromedial (VMH: 189±28.8%) and dorsomedial hypothalamus (DMH: 211±36.7%, n=5/group, $p<0.05$), two critical areas that modulate BAT and WAT by sympathetic activation (Ann NY Acad Sci 1302: 30, 2013). Next, we investigated if the increased hypothalamic activity was reflected into changes in WAT and BAT. While BAT cell size and morphology were unremarkable, the number of small adipocytes was higher in subcutaneous (SQ) and visceral (VISC) WAT of Tg2576 mice compared to WT mice (VISC WAT: 271±26.8%, SQ WAT: 982±200%, n=5/group, $p<0.05$). As the small adipocytes could represent browning of WAT, mRNA levels of uncoupling protein 1 (UCP1), a marker of browning, were measured. Surprisingly, UCP1 mRNA levels were lower in BAT and WAT of Tg2576 mice (VISC WAT: WT 1.00±0.21, Tg2576 0.27±0.02; SQ WAT: WT 0.04±0.01, Tg2576 0.014±0.006; BAT: WT 34.8±3.62, Tg2576 23.1±5.76, n=5-7/group, $p<0.05$ for VISC WAT and BAT). Additional expression profiling in WAT and BAT did not reveal substantial differences in genes involved in thermogenesis or lipolysis between Tg2576 and WT mice. However, beta-3 adrenergic receptor mRNA levels were elevated in SQ WAT of Tg2576 mice (219.5±38%, n=5/group, $p<0.05$), suggesting increased sympathetic activity. Collectively, the data are consistent with the hypothesis that aberrant activation of DMH and VMH in Tg2576 mice stimulates sympathetic activity in SQ WAT resulting in a catabolic state. Although the mechanisms of these changes need to be defined and verified in AD patients, the findings may provide key insights into the factors underlying the reduced adiposity associated with APP

overexpression and AD. Supported by Leon Levy Foundation (M.I.), BrightFocus Foundation (M.I.), and NS37853 (C.I.).

Disclosures: **M. Ishii:** None. **M.J. McGuire:** None. **G. Racchumi:** None. **C. Iadecola:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Juselius Foundation

UEF-Brain

Title: SEPT5 and its potential role in the molecular pathogenesis of Alzheimer's disease

Authors: ***M. MARTTINEN**[1,2,3], K. M. A. KURKINEN[1,2,3], H. SOININEN[2,3], A. HAAPASALO[2,3], M. HILTUNEN[1,2,3];
[1]Inst. of Biomedicine, [2]Neurol., Univ. of Eastern Finland, Kuopio, Finland; [3]Neurol., Kuopio Univ. Hosp., Kuopio, Finland

Abstract: Objectives: Septins are a highly conserved family of guanosine triphosphate-binding proteins, which play a central role in the axonal transport and vesicle trafficking in the synapses. Particularly SEPT5 has been shown to interact with syntaxin-1 of the SNARE complex and regulate synaptic vesicle (SV) localization at the presynaptic terminal. Furthermore, SEPT5 interacts with SEPT8, which in turn has been suggested to impact SV recycling. Thus, SEPT5 is a potential target for further studies in the molecular pathogenesis of Alzheimer's disease (AD). Methods: Here, we have investigated the possible alterations in SEPT5 mRNA expression and splicing in relation to the AD-related neurofibrillary pathology in the temporal cortex of human brain. Furthermore, we investigated whether the siRNA-mediated down-regulation of SEPT5 in human SH-SY5Y neuroblastoma cells impacts amyloid precursor protein (APP) processing and amyloid-β (Aβ) production. Results: Our data suggest that the expression of SEPT5 is moderately decreased in relation to AD-related neurofibrillary pathology in the brain and that the down-regulation of SEPT5 reduces β-secretase (BACE1), soluble APPβ and Aβ levels *in vitro*. Conclusions: Considering the known mechanistic functions and interactions of SEPT5, our results suggest that SEPT5 plays a role in the regulation of post-translational levels and activity

of BACE1. Further characterizations of the potential role of SEPT5 in the early molecular pathogenesis of AD are currently undergoing.

Disclosures: **M. Marttinen:** None. **K.M.A. Kurkinen:** None. **H. Soininen:** None. **A. Haapasalo:** None. **M. Hiltunen:** None.

Nanosymposium

280. Alzheimer's Disease: Beyond Abeta and Tau

Location: N226

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 280.11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association

Title: A novel mechanism for lowering Abeta

Authors: P. C. MULLEN[1], C.-D. CHEN[1], E. ZELDICH[1], L. E. BROWN[2], J. A. PORCO[2], *C. R. ABRAHAM[1];
[1]Boston Univ. Sch. of Med., Boston, MA; [2]Boston Univ., Boston, MA

Abstract: Alzheimer’s disease (AD) is characterized by accumulation of the neurotoxic amyloid beta peptide (Aβ), a proteolytically-derived fragment of the amyloid precursor protein (APP). Therefore, identifying treatments that inhibit Aβ production may reduce neurodegeneration and cognitive dysfunction associated with AD. Multiple reports suggest that dimerization of APP may play a role in Aβ production. In most cases APP dimers increase Aβ, however, the mechanism is not fully understood. Using APP-Firefly luciferase enzyme complementation, we conducted a high throughput screen of a compound library of 77,440 compounds for inhibitors of APP dimerization, and identified several promising compounds that both inhibited APP dimerization and reduced Aβ levels. These compounds have in common a motif found in several known kinase inhibitors. To elucidate the precise mechanism involved, APP phosphorylation was examined by IP-western blotting using anti Aβ/APP antibodies for IP, and anti-phosphotyrosine antibodies for western blot. Of the dimerization inhibitors we tested, one compound significantly increased APP phosphorylation. These findings indicate that the mechanism of action of our compounds likely involve inhibition of a critical kinase implicated in phosphorylation of APP at one of the protein’s several phosphorylatable residues. Interestingly, this inhibitor and its analogs increased APP phosphorylation, suggesting an indirect effect either via activation of a second kinase or inhibition of a phosphatase. Substantial evidence suggests that phosphorylation of APP is important for regulating its intracellular localization, which

influences Aβ production. We hypothesize that phosphorylation of a specific tyrosine residue within the APP intracellular domain is critical for inhibiting APP dimerization, and reducing Aβ levels. To this end we have mutated several potential phosphorylatable amino acid residues at the C-terminus of APP and identified an amino acid responsible for the effects on Aβ reduction. Thus, regulation of APP phosphorylation by small molecule compounds should be considered as a novel therapeutic intervention for AD.

Disclosures: P.C. Mullen: None. **C. Chen:** None. **E. Zeldich:** None. **L.E. Brown:** None. **J.A. Porco:** None. **C.R. Abraham:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.01

Topic: C.07. Epilepsy

Support: NIH NS065020

NIH NS062806

CAPES - PSE, Brazil

Title: Morphological and physiological alterations of postnatally-generated hippocampal granule neurons following PTEN deletion

Authors: *V. R. SANTOS[1,2], R. Y. K. PUN[2], C. L. LASARGE[2], N. GARCIA-CAIRASCO[3], S. C. DANZER[2];
[1]Dept. of Physiol., Univ. of Sao Paulo, Ribeirao Preto, Brazil; [2]Pediatrics, Univ. of Cincinnati, Cincinnati, OH; [3]Physiol., Univ. de São Paulo, Ribeirao Preto, Brazil

Abstract: The dentate gyrus is hypothesized to function as a "gate," limiting the flow of excitation through the hippocampus. Adult hippocampal neurogenesis is a unique form of neural circuit plasticity that results in the generation of new neurons in the dentate gyrus throughout life. During epileptogenesis, adult-generated granule cells (DGCs) can form aberrant neuronal connections with neighboring DGCs, disrupting the dentate gate. The PI3K/Phosphatase and tensin homolog (PTEN)/mammalian target of rapamycin (mTOR) pathway regulates a variety of neuronal functions, including cell proliferation, survival, growth and plasticity. Deletion of PTEN from a subset of adult-generated granule cells (DGCs) leads to the development of epilepsy in mice. The ability to selectively remove the PTEN gene using cre/lox technology

provides a unique opportunity to examine how this gene alters neuronal behavior. We used electrophysiological techniques, immunohistochemistry, and 3D neuronal reconstruction to investigate the impact of PTEN deletion on DGC physiology and morphology. Consistent with prior studies, PTEN KO cells exhibited dramatically increased soma area (111.93 μm2 in controls; 246.58 μm2 in KO DGCs) and reduced input resistance (control, 547 ± 36 mΩ; KO, 262 ±48 mΩ). Many KO cells (~56%) exhibited a doublet (2 spikes in succession) with an interval of 13.8 ± 4.8 ms; n=18; whereas control cells lacked doublets and had a mean spike interval of 34.1 ± 11.1 ms; n=46. The second spike of the doublet could be abolished by 25μM Ni2+, indicating that it may be meditated by T-type Ca2+ channels. In addition to the increase in soma area, KO cells also exhibited hilar basal dendrites and had a range of abnormal apical dendrite morphologies. KO cells exhibited an increase in total apical dendrite number and length, with more nodes and branches throughout the sub regions of molecular layer. Our results suggest that hyperactivation of mTOR by PTEN deletion can lead to remarkable changes in DGC physiology and morphology. These changes indicate the PTEN deletion increases granule cell excitability, likely contributing to spontaneous seizures in the animals.

Disclosures: **V.R. Santos:** None. **R.Y.K. Pun:** None. **C.L. LaSarge:** None. **N. Garcia-Cairasco:** None. **S.C. Danzer:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.02

Topic: C.07. Epilepsy

Support: NIH NS065020

NIH NS062806

NIH F32NS083239

Title: Evidence of recurrent network activation in a PTEN knockout model of Temporal Lobe Epilepsy

Authors: ***C. L. LASARGE**[1], V. R. SANTOS[1,2], R. Y. K. PUN[1], N. GARCIA-CAIRASCO[2], S. C. DANZER[1,3];
[1]Dept. of Anesthesia, Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [2]Dept. of Physiol.,

Ribeirão Preto Med. Sch., Ribeirão Preto-SP, Brazil; [3]Departments of Anesthesia and Pediatrics, Univ. of Cincinnati, Cincinnati, OH

Abstract: Integration of abnormal hippocampal granule cells is hypothesized to contribute to the development of temporal lobe epilepsy. Isolating the specific effects of abnormal granule cells on hippocampal function, however, has been difficult to assess in traditional epilepsy models as changes occur throughout the brain, and are not restricted to granule cells. The recent development of a novel mouse epilepsy model, in which the mTOR pathway inhibitor PTEN is deleted from postnatally-generated neurons, provides an opportunity to isolate the effects of abnormal granule cells. PTEN deletion from >10% of the granule cell population produces a profound epilepsy syndrome. Here, we conducted acute slice physiology experiments to assess the impact of these cells on hippocampal function. Perforant path stimulation evoked larger amplitude population spikes in slices from knockout animals relative to control slices, and strikingly, multiple spikes were evoked in knockouts, while stimulation of controls elicited only single spikes. Excitatory post-synaptic potentials (EPSPs) were also larger in knockout slices vs. controls. Interestingly, this effect was restricted to lateral perforant path, and was not evident for the medial perforant path. Morphological analysis of knockout cells revealed a 50% increase in dendrite length in the lateral perforant path terminal field, while the medial perforant path field was unchanged; the difference likely accounting for the increased EPSP slopes in the former but not the latter. Results demonstrate that selective disruption of a subset of granule cells can induce hyperexcitability at the network level and implicates abnormal granule cell development in driving hippocampal pathophysiology.

Disclosures: **C.L. LaSarge:** None. **V.R. Santos:** None. **R.Y.K. Pun:** None. **N. Garcia-Cairasco:** None. **S.C. Danzer:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.03

Topic: C.07. Epilepsy

Support: Australian Postgraduate Award

Victorian Life Sciences and Computation Initiative Top-up Scholarship

Title: Phenotypic modelling of sodium channel drug action using the dynamic clamp

Authors: *D. I. KAPLAN[1], E. A. THOMAS[1], C. A. REID[1], S. PETROU[1,2];
[1]The Florey Dept. of Neurosci. and Mental Hlth., The Florey Inst. of Neurosci. and Mental He, Parkville, Australia; [2]Ctr. for Neural Engin., Parkville, Australia

Abstract: Study objective: To develop a dynamic clamp model that incorporates synaptic noise and inputs for the evaluation of drugs and mutant ion channels. Methods: A voltage clamp based dynamic clamp model was developed using xPC target and Simulink (Mathworks) that can incorporate virtual or real sodium and potassium channels. A single compartment model was developed that incorporated channel densities similar to those found in the distal AIS of layer 5 pyramidal neurons. In addition to this and in an effort to simulate *in vivo* conditions, a stochastic model of synaptic noise was incorporated. Finally, an excitatory post-synaptic AMPA receptor conductance was used to probe the excitability of the hybrid model. We first explored the effects of the anti-epileptic drug, carbamazepine (CBZ) as a prelude to using this model to explore precision therapies in ion channel based neurological disorders. NaV1.6 channels were stably expressed in Chinese hamster ovary (CHO) cells. After establishing whole cell mode the dynamic clamp was initiated. Currents were fed, in real time to the model and synaptically triggered action potentials (APs) were readily elicited and excitatory:inhibitory (gExc:gInh) synaptic background noise varied as needed. This model could be tuned to incorporate disease state physiology that could be used to select for interactions of drugs with the expressed sodium channels in voltage and time regimes appropriate to the pathology. Experiments were conducted with and without application of 30uM CBZ to test performance of the model. Results: CBZ had a more significant effect on excitability as the ratio of excitatory to inhibitory conductances increased. This was indicated by a significant reduction in the number of APs generated during a 12s sweep with the higher gExc:gInh but not with the lower. A significant reduction in AP height and a 40% reduction in AP firing probability was observed in the presence of CBZ suggesting a reduction in sodium channel availability. As expected a small yet significant increase in threshold was seen that would impact AP timing and network function. Conclusion: This study uses the dynamic clamp to understand the effect of CBZ on sodium channels in a context relevant to the epileptic phenotype; CBZ is most potent when the ratio of network excitation:inhibition grows, however it still compromises the efficacy of synaptic transmission under non-pathological conditions. In order to adequately characterize changes in ion-channel function - whether induced by mutation or pharmacology - it is ideal to expose the channels to the dynamic voltage trajectories they would experience *in vivo*. Using the dynamic clamp it is possible to do this.

Disclosures: D.I. Kaplan: None. **E.A. Thomas:** None. **C.A. Reid:** None. **S. Petrou:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.04

Topic: C.07. Epilepsy

Support: AHA postdoctoral fellowship

Title: Autoimmune targeting of astrocytes results in progressive seizures: Th1 signaling and brain infiltration of professional antigen presenting cells

Authors: *Y. Y. GRINBERG[1], B. LÓPEZ-BAYGHEN[2], Z. M. RIVAS[1], L. A. NAVARRO[1], D. K. BINDER[1], D. D. LO[1], C. C. PLOIX[3], M. J. CARSON[1];
[1]Univ. of California, Riverside, Riverside, CA; [2]CINVESTAV, Mexico City, Mexico; [3]The Scripps Res. Inst., La Jolla, CA

Abstract: Epilepsy affects 0.5 - 1% of the population and 30% of patients are resistant to antiepileptic drugs (AED), which target neurotransmission. Innate immune signaling, including proinflammatory cytokine modulation of astrocytic function, has been implicated in epileptogenesis. Far less is known about the role of adaptive immunity, although T cells have been found in brain tissue of both epilepsy patients and experimental animals after seizure. Furthermore, autoantibodies against brain antigens are found in a fraction of patients with AED-resistant epilepsy. To determine whether an antigen-driven response against a non-neuronal target is sufficient to initiate epilepsy, we generated a transgenic mouse line (GFAP-HA) in which astrocytes expressed a non-functional antigen (HA). GFAP-HA mice were bred to clone 6.5 (SFE) mice in which >95% of CD4+ T cells recognize HA antigen. Unmanipulated double transgenic GFAP-HA/SFE mice appeared normal, but developed visually overt seizures after pertussis toxin adjuvant stimulation. Immunohistochemical analysis of whole brain sections showed that no one brain structure was specifically targeted, and instead CD4+ T cells were observed throughout the sagittal sections. CD4+ T cells were present in perivascular, periventricular, as well as parenchymal spaces. We looked at the progression of events leading up to seizures to find: 1) altered neuronal activity in hippocampus, as recorded by implanted EEG electrodes, prior to presentation with visually overt seizures; 2) infiltration of macrophages and B cells; 3) Th1-polarized T cells; 4) progressive activation of microglia; and 5) astrogliosis. Unlike brain-infiltrating antigen presenting cells (APCs), microglia expressed low levels of molecules regulating T cell activation, phagocytosis, and inflammatory responses, but upregulated many of these molecules (including CD40 and CD36) over the course of disease progression. This suggests that microglia may be more plastic and are able to progressively become highly activated, providing a greater contribution to inflammatory signaling and regulation of T cell responses later into disease progression. However, APCs appear to have a greater capacity to phagocytose and produce inflammatory responses, and thus may be the determinants of disease initiation. Here we show that autoimmune targeting of astrocytes, and not neurons, can result in progressive seizures. Using this model, we can manipulate the

contribution of distinct immune cell types to progression of epileptogenesis, perhaps working toward development of novel epilepsy therapeutics.

Disclosures: **Y.Y. Grinberg:** None. **B. López-Bayghen:** None. **Z.M. Rivas:** None. **L.A. Navarro:** None. **D.K. Binder:** None. **D.D. Lo:** None. **C.C. Ploix:** None. **M.J. Carson:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.05

Topic: C.07. Epilepsy

Support: EPSRC Industrial CASE Studentship Award EP/K50449X/1

Title: Developing a novel *in vitro* model of mitochondrial epilepsy: 'a dual neuronal - astrocytic hit hypothesis'

Authors: ***F. CHAN**[1], N. LAX[2], C. DAVIES[3], D. TURNBULL[2], M. CUNNINGHAM[1]; [2]Wellcome Trust Ctr. for Mitochondrial Res., [1]Inst. of Neuroscience, Newcastle Univ., Newcastle upon Tyne, United Kingdom; [3]GlaxoSmithKline Res. and Development, Singapore R&D Site, Singapore, Singapore

Abstract: Up to a third of patients with mitochondrial disease develop epilepsy. Patients with mitochondrial epilepsy have extremely poor prognosis and a difficult to control epilepsy. Drug development in this field has been lagging due to a lack of good functional models. Post-mortem neuropathology of temporal neocortex from patients with mitochondrial epilepsy has shown deficiency in mitochondrial respiratory chain complexes I and IV in both GABAergic interneurons and astrocytes, with a pattern of astrogliosis.Building on these observations, we aim to develop a novel *in vitro* brain slice model of mitochondrial epilepsy using various mitochondrial inhibitors; rotenone (complex-I inhibitor), potassium cyanide-KCN (complex-IV inhibitor), and fluorocitrate (astrocytic specific aconitase inhibitor). Epileptic activity was readily generated in both the hippocampus (CA3) and temporal neocortex by adding fluorocitrate (0.1 mM) followed by co-application of rotenone (500nM) and KCN (10μM). Applying either fluorocitrate or rotenone-KCN alone did not generate any epileptic activity. We have also replicated these experiments in surgically resected human temporal neocortical slices from patients undergoing amygdalohippocampectomy or tumour removal (n=6). Six commonly used conventional antiepileptic drugs - carbamazepine, lamotrigine, levetiracetam, sodium valproate, midazolam, and sodium pentobarbital - were tested and all the drugs but sodium pentobarbital

failed to suppress the epileptic activity. Post-hoc immunohistochemistry of these epileptic brain slices showed a pattern of astrogliosis. There was also a significant reduction in the population of GABA-ergic interneurons (n=5), especially parvalbumin-expressing interneurons (n=6) and calbindin-expressing interneurons (n=5), in the hippocampus CA3 while relatively sparing the excitatory pyramidal neurons (n=3).The epileptic activity is responsive to administration of GABA, L-glutamine, and L-ketoglutarate, suggesting deficiency in the glutamate-glutamine cycle downstream of aconitase inhibition in the astrocyte. In conclusion, we have successfully developed a novel *in vitro* brain slice model for mitochondrial epilepsy. It replicates most of the features seen in the human neuropathology and also shows pharmacoresistant properties. Together, the data suggest a susceptibility of inhibitory interneurons towards mitochondrial dysfunction, that when coupled with astrocytic impairment, could lead to epileptogenesis.

Disclosures: F. Chan: None. **N. Lax:** None. **C. Davies:** None. **D. Turnbull:** None. **M. Cunningham:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.06

Topic: C.07. Epilepsy

Support: NIHRO1NS039587

R21NS072099

F31NS086405

UO1NS083422

Title: Targeting gamma-ketoaldehydes attenuates perirhinal- associated memory deficits in experimental temporal lobe epilepsy

Authors: *J. PEARSON[1], L. J. ROBERTS, II[2], M. PATEL[1];
[1]Univ. of Colorado, Aurora, CO; [2]Vanderbilt, Nashville, TN

Abstract: Cognitive dysfunction is an important comorbidity of temporal lobe epilepsy (TLE). However, the mechanisms underlying cognitive impairment, specifically deficits in learning and memory associated with TLE remain unclear. We hypothesize that oxidative damage and consequent neuronal loss contributes to cognitive decline associated with injury-induced

epileptogenesis. Isoketals (IsoKs) and Neuroketals (NeuroKs) are highly reactive gamma-ketoaldehydes (γ-Ks) formed via the free-radical catalyzed isoprostane and neuroprostane pathways, respectively. They are attractive candidates for oxidative protein damage and resultant cognitive dysfunction due to their ability to rapidly and irreversibly adduct lysine residues and crosslink proteins. We asked if γ-Ks were increased in the perirhinal cortex (PRh) following epileptogenic injury and whether scavenging them with salicylamine (SA), an orally available, brain permeable γ-K scavenger would attenuate neuronal loss in the PRh and recognition memory deficits. PRh tissue was obtained from adult male, Sprague-Dawley rats, 24 hours after kainic acid (KA)- induced status epilepticus (SE) and subjected to mass spectrometry for analysis of γ-K lysine adducts. Compared to saline treated controls, rats that experienced SE showed significantly higher levels of IsoK and NeuroK adducts in PRh ($p= 0.03$, $p= 0.04$ respectively). A separate cohort of animals was treated with KA, followed by a single injection of SA 30 minutes later and allowed free access to water supplemented with SA for 7 days. SA treatment starting 30 minutes after KA had no effect on overall intensity of electrographic activity or activity in any frequency band (i.e. alpha, theta, etc.) as measured by EEG observation of a separate cohort. After a 7 day treatment period, animals were tested for indices of learning and memory in a novel object recognition task (NOR). KA treated animals that received SA performed significantly better than control (saline treated) animals (KA vs KA+SA $p= 0.01$), at a level equivalent to control animals (KA+SA vs Control $p= 0.15$). Upon completion of the behavioral task, brain tissue was collected for FluoroJade B (FJB) staining of degenerating neurons. Rats treated with SA had significantly fewer FJB positive neurons compared to KA alone (55% decrease, $p= 0.03$) suggesting that SA is neuroprotective and providing a potential mechanism by which scavenging of γ-s protects cognition. These data suggest that γ-Ks are potential mediators of cognitive dysfunction associated with experimental TLE and establish SA as a novel therapeutic to attenuate these deficits.

Disclosures: **J. Pearson:** None. **L.J. Roberts:** None. **M. Patel:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.07

Topic: C.07. Epilepsy

Support: Department of Defense W81XWH-13-1-0180

NINDS NS078333

CURE (Infantile Spasms Initiative)

Heffer Family Foundation

Segal Family Foundation

Abbe Goldstein/Joshua Lurie and Laurie Marsh/ Dan Levitz families

Title: Role of anti-inflammatory and antioxidant drugs in the treatment of spasms in the multiple-hit rat model of infantile spasms

Authors: O. SHANDRA[1], Y. WANG[1], W. MOWREY[2], *A. S. GALANOPOULOU[4,3];
[1]Saul R. Korey Dept. of Neurol., [2]Epidemiology and Population Health; Saul R. Korey Dept. of Neurol., [3]Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY;
[4]Dept Neurol, Albert Einstein Col. Med., Bronx, NY

Abstract: BACKGROUND: Infantile Spasms (IS) are epileptic seizures that typically occur in infants, have poor neurodevelopmental and epilepsy outcomes, and may increase early mortality. Early cessation of spasms may improve outcomes. To identify new therapies for IS which achieve rapid cessation of spasms, we used the multiple-hit rat model of medically refractory IS due to structural lesions. OBJECTIVE: To determine whether a single injection of anti-inflammatory and/or anti-oxidant drugs, given after the onset of spasms, can stop spasms. We tested the effects of the tripterene celastrol (inhibits lipid peroxidation, NF-kB activation and cytokine release) and edaravone (free radical scavenger and antioxidant, inhibits NF-kB activation). METHODS: Male Sprague-Dawley rats received right intracerebral injections of doxorubicin and lipopolysaccharide on postnatal day (PN) 3 and intraperitoneal (i.p.) injection of p-chlorophenylalanine on PN5. Neurodevelopmental milestones were scored daily. Video monitoring was done intermittently on PN4 (1 hour pre-drug injection and 5 hours post-drug injection) and on PN5 (2 two-hour sessions). A blinded, randomized, dose-response study design was used, with single i.p. injection of drugs or vehicles given after spasms onset on PN4. Celastrol (1, 2, or 4mg/kg) or edaravone (1, 10, or 30 mg/kg) or their respective vehicles were tested. Histology was done on PN5 for injury. Immunofluorescence assays for inflammatory markers were done on perfused PN4 rat brains. Linear mixed model analysis of raw or normalized log-transformed spasm rates, considering the repeated observations was used. 10-17 rats per group were studied. RESULTS: Activation of NF-kB was seen on the cerebral cortex of PN4 rats treated with the multiple-hit protocol. A single i.p. injection of Celastrol suppressed spasms acutely dose-dependently within 3 hours and was well tolerated. Edaravone has no effect on spasms. DISCUSSION: Targeting anti-inflammatory and/or anti-oxidant pathways may be useful for the acute treatment of IS. The superiority of celastrol over edaravone may indicate distinct effects on specific targets (currently under investigation). Video-EEG studies to confirm the efficacy of celastrol on electroclinical spasms and EEG background are in progress.

Disclosures: **O. Shandra:** None. **Y. Wang:** None. **W. Mowrey:** None. **A.S. Galanopoulou:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.08

Topic: C.07. Epilepsy

Support: NIH NS058585

Title: Notch regulation of subgranular zone neurogenesis in a model of mesial temporal lobe epilepsy

Authors: ***M. J. KORN**[1], I. P. MAILLARD[2], J. M. PARENT[1];
[1]Dept. of Neurol., [2]Life Sci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Mesial temporal lobe epilepsy (mTLE) is a common and often intractable epilepsy associated with extensive hippocampal pathology. In the hippocampal dentate gyrus in human and experimental mTLE, dentate granule cells (DGCs) are located ectopically, and show mossy fiber sprouting and hilar basal dendrites (HBDs). Evidence suggests that newly generated DGCs produced following epileptogenic insults contribute to these abnormalities, and that integration of altered DGCs produces hyperexcitability. Persistent deficits in neural stem cell (NSC) self-renewal and maturation in chronic mTLE are also implicated in comorbidities such as depression and memory loss. However, the relative contributions and the mechanisms leading to disturbed adult neurogenesis during epileptogenesis are largely unknown. Here we focus on potential molecular mechanisms underlying perturbed DGC neurogenesis in experimental mTLE. We first evaluated the spatiotemporal distribution of type-1 and type-2 neural progenitors within the dentate subgranular zone (SGZ) in the adult mouse pilocarpine status epilepticus (SE) model of mTLE. We evaluated brains at 24 h, 3, 7, 21, 28, 42 and 56 d after pilocarpine induced SE. Immunolabeling for Sox2, the cleaved Notch intracellular domain (NICD), glial fibrillary acidic protein and doublecortin indicate that there is a dynamic shift in pro-neuronal gene expression that could underlie aberrations observed in mTLE. A transient alteration of NICD abundance was observed in the SGZ, returning to baseline 7 d post-SE. This change was associated with increased Sox2-expressing progenitors 24 h after SE, followed by a decrease 21 d later. These findings implicate altered Notch signaling in seizure-induced changes in neurogenesis. Notch-dependent expression of Hes5 is downstream of Reelin, known to be decreased in human and experimental mTLE. Thus, to examine whether suppression of Notch signaling generates

changes similar to those seen in mTLE, we used a mouse line with conditional expression of a dominant negative (DN) form of mastermind-like protein 1 (MAML1). DNMAML suppresses Notch signaling by preventing coactivators from binding to the Notch-CSL/RPB-J complex. We find that inhibition of canonical Notch signaling increases SGZ cell proliferation and neurogenesis. Additionally, the dysregulation of Notch produces ectopically located neurons and HBDs. These results suggest that NICD plays an integral role at each phase of adult DGC progenitor differentiation. Moreover, a transient imbalance of Notch signaling may give rise to aberrantly integrating cells that contribute to the spontaneous seizures and comorbidities of mTLE.

Disclosures: **M.J. Korn:** None. **I.P. Maillard:** None. **J.M. Parent:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.09

Topic: C.07. Epilepsy

Support: NIH/NINDS 2R01NS060757

Title: Regulation of sonic hedgehog signaling pathway by dentate gyrus gaba neurons

Authors: ***L. E. GONZALEZ**[1,2], C. C. CHIANG[2], A. H. KOTTMANN[3], D. M. DURAND[2]; [2]Biomed. Engin., [1]Case Western Reserve Univ., Cleveland, OH; [3]Sophie Davis Sch. of Biomed. Med., City Univ. of New York, New York, NY

Abstract: Optical stimulation of GABA neurons may be used to suppress seizures and has been recently shown to increase hippocampal neurogenesis. However, the role of GABA transmission in adult neurogenesis is controversial since activation of GABA receptors decreases neurogenesis, while direct stimulation of GABA interneurons promotes neuronal progeny survival and enhance neurogenesis. One possible reason for this discrepancy is that hilar GABA interneurons co-release the trophic factor Sonic Hedgehog (Shh). While there is extensive literature describing how Shh targets hippocampal neurogenesis, the source and secretion mechanisms of Shh remain ill-defined. The fact that Shh is “secreted” glycoprotein acting at multiple levels through long range diffusion makes difficult the identification of cellular sources. By using a gene reporter system that restricts expression to cells producing the protein, we found that GABAergic neurons are the main cellular source of Shh in the hilar dentate gyrus (DG). Next, to investigate whether the activation of the Shh signaling pathway is linked to local activity

of GABAergic neurons, we stimulated DG GABA neurons using a transgenic mouse that expresses Channelrhodopsin 2 (CHR2) under the control of the vesicular GABA transporter (VGAT) promoter. We found that stimulation of GABA neurons (8 Hz/30s blue light pulse every 5 min for 2 h) induced electrophysiological responses in GABAergic cells that was associated with a robust transcriptional upregulation of several Shh downstream pathway genes (Shh, Ptc and Gli). These experiments support the hypothesis that Shh is produced and release by DG GABA neurons though activity dependent/non- cell autonomous mechanisms. The therapeutic implications of these findings for epilepsy and neurodegenerative diseases are discussed.

Disclosures: L.E. Gonzalez: None. **C.C. Chiang:** None. **A.H. Kottmann:** None. **D.M. Durand:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.10

Topic: C.07. Epilepsy

Support: CHOP Foerderer

PENN PMNC

NIH R01NS082046

Title: Intracellular chloride accumulation in dentate granule cells in pilocarpine treated organotypic cultures studied using fluorescence lifetime imaging microscopy (FLIM)

Authors: *H. TAKANO, F.-C. HSU, D. A. COULTER;
Neurol., Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: In the brain, maintaining low levels of intracellular chloride concentration ([Cl-]i) is critical in sustaining GABAA receptor-mediated inhibition. Chloride ions (Cl-) play a crucial role in inhibitory function by mediating neuronal hyperpolarization during activation of Cl-permeable GABA receptors. In the current study, mouse organotypic hippocampal slice cultures were prepared from P3-8 mice, maintained for 3 weeks, and then treated with 5 mM of the convulsant, pilocarpine, for 24 hours. Using extracellular recording and calcium imaging, we verified that there was no ictal-like activity in control slices, while sustained seizure-like activity was observed ~30 min after pilocarpine treatment. One and two days after pilocarpine treatment, [Cl-]i of dentate granule cells was determined using FLIM in cultures bulk loaded with N-

(Ethoxycarbonylmethyl)-6-Methoxyquinolinium Bromide (MQAE), a chloride sensitive dye. We employed a two-photon microscopy system equipped with a femtosecond laser (SpectraPhysics MaiTai DeepSee) tuned at 780 nm and the emission between 440 nm and 500 nm was collected with a GaAsP PMT. The signal was then processed with Becker-Hickle time correlated photon counting system for FLIM analysis. FLIM allowed us to evaluate 30-50 individual granule cells in each field of view. The data from chloride FLIM indicated that [Cl-]i was significantly increased ($n > 1000$, $p < 0.001$) in pilocarpine treated granule cells. The effect was not homogeneous in all cells, as multiple Gaussian distributions of [Cl-]i were observed. This [Cl-]i accumulation would change synaptic responses, and presumably increase granule cell excitability. This pathophysiological process may be one of the mechanisms contributing to injury-mediated epileptogenesis *in vivo*.

Disclosures: **H. Takano:** None. **F. Hsu:** None. **D.A. Coulter:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.11

Topic: C.07. Epilepsy

Support: FCT PhD grant SFRH/BD/80421/2011, Portugal

MRC grant G0301067, UK

National Institute for Health Research UCL Hospitals Biomedical Research Centre, UK

Title: Morphology of Interictal Epileptiform Discharges (IEDs) and the BOLD signal: A study of haemodynamic coupling using simultaneously acquired intracranial EEG - fMRI data

Authors: *T. MURTA[1,2], U. J. CHAUDHARY[1], D. W. CARMICHAEL[3], P. FIGUEIREDO[2], L. LEMIEUX[1];
[1]Dept. of Clin. and Exptl. Epilepsy, UCL Inst. of Neurol., London, United Kingdom; [2]Inst. Superior Técnico, Univ. de Lisboa, Lisbon, Portugal; [3]UCL Inst. of Child Heath, London, United Kingdom

Abstract: The use of BOLD fMRI to locate sources of neuronal activity conventionally captured by electrophysiological techniques (e.g. EEG) is particularly relevant in epilepsy, where the non-invasive 3D mapping capability of fMRI complements the temporal richness of EEG. However, the mechanisms underlying the BOLD and EEG signals differ, which raises the need to improve

our understanding of the relationship between them. Most EEG-fMRI studies in epilepsy use delta functions at each Interictal Epileptiform Discharge (IED) onset as the predictor of BOLD changes. Only a few reports have investigated the relationship between IED amplitude and related BOLD signal, in humans and animals [1-3]. We used simultaneous and co-localised icEEG and fMRI data to investigate whether a number of IED features (amplitude, width, sharpness, and field (spatial) extent) explain additional variance of the BOLD signal, when compared to IED onsets alone. We focused on the individual icEEG data from the 10 contacts showing the largest IED (contact of interest: COI) in 6 different patients; and on the BOLD signal within a 10mm radius sphere centred at each COI (region of interest: ROI). The amplitude and width of individual IED were estimated using STEP1 [4]. IED sharpness was defined as the ratio of amplitude over width. IED field extent was computed as the sum of the correlation coefficients between 600ms data epochs centred at each IED marked at the COI, and the concurrent epochs at all other contacts. For each IED feature, the residual variance (unexplained BOLD signal) for the model comprising the IED feature, IED onsets, and motion-related confounds was compared with the residual variance for the model comprising IEDs onsets and motion-related confounds. BOLD signal models were estimated using SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12/). The residuals of each model were computed using the R2adj metric, which accounts for the different degrees of freedom. The amount of variance explained by the additional regressor (VE) was obtained as the difference between the R2adj value of each new model and the R2adj value of the base model. VE values were averaged over the ROI voxels. At the group level, we found a trend for significantly positive VE for IED amplitude only (p=0.07). Future EEG-fMRI studies in epilepsy should include IED amplitude as a modulatory effect, as it seems to explain additional variance of the co-localised BOLD signal. [1] Benar CG et al. (2002) Neuroimage [2] Levan P et al. (2010) Neuroimage [3] Geneslaw AS et al. (2011) J Cereb Blood Flow Metab [4] Hu L et al. (2011) Journal of Neurophysiology

Disclosures: **T. Murta:** None. **U.J. Chaudhary:** None. **D.W. Carmichael:** None. **P. Figueiredo:** None. **L. Lemieux:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.12

Topic: C.07. Epilepsy

Title: Emulating endogenous synchrony dynamics with deep brain stimulation rapidly terminates temporal lobe seizures

Authors: *T. SOBAYO, D. J. MOGUL;
Biomed. Engin., Illinois Inst. of Technol., Chicago, IL

Abstract: Deep brain electrical stimulation (DBS) is a treatment modality being explored for many neurological diseases and is a potentially potent means for disrupting the aberrant rhythms that arise during the epileptic seizures that afflict over 1% of the population. However, current DBS protocols typically employed are formulated a priori and do not reflect the electrophysiological dynamics within the brain as seizures arise which may underlie their limited efficacy. In this study, multi-site brain dynamics were calculated in a chronic rat limbic epilepsy model. Male Sprague-Dawley rats were induced via lithium chloride/pilocaprine intraperitoneal injections. Stimulation/recording electrodes were placed in the CA3 region of left and right hippocampi and the anteromedial nucleus of left thalamus. Local field potentials (LFPs) containing evoked and spontaneous seizures were recorded from the animals. Deconvolution of the LFPs using empirical mode decomposition (EMD) and phase synchrony analysis revealed multi-site coherence as seizures approached natural termination. Synchrony analysis using standard Fourier techniques were unable to identify these same dynamics. The location and frequency of the natural termination synchrony varied between subjects but was stable in time within each animal. DBS protocols were significantly more effective at rapidly stopping seizures when the frequency and location of multi-site stimulation reflected the endogenous synchrony dynamics observed in each subject at natural termination. These results strongly suggest that tailoring DBS protocols to individual endogenous rhythms that may represent how brains naturally resolve epileptic seizures could play a critical role in vastly improving the overall efficacy of this important therapy.

Disclosures: **T. Sobayo:** None. **D.J. Mogul:** None.

Nanosymposium

281. Mechanisms of Epilepsy

Location: S403

Time: Monday, October 19, 2015, 8:00 AM - 11:15 AM

Presentation Number: 281.13

Topic: C.07. Epilepsy

Support: NIH Grant 1R01 NS084142

Dr. Ralph and Marian Falk Medical Research Trust

Title: Long-range effects of local spike trains during human seizure activity

Authors: *T. EISSA[1], C. SCHEVON[2], R. EMERSON[2], G. MCKHANN[2], R. GOODMAN[3], W. VAN DRONGELEN[1];
[1]Univ. of Chicago, Chicago, IL; [2]Columbia Univ., New York, NY; [3]Mt. Sinai, New York, NY

Abstract: The electrocorticogram (ECoG) observed during seizures strongly depends on the local field potential (LFP) associated with postsynaptic potentials evoked around these macroscopic electrodes. Here, we tested the hypothesis that the postsynaptic ECoG activity can predominantly be attributed to neuronal output (i.e. spike trains from multiunit firing activity) of a relatively small (core) area in the epileptic zone. In this context, we focused on two principal questions. (1) How much of the ECoG can be explained by local multiunit activity? (2) How far does this postsynaptic effect of local neuronal activity reach? In order to address these questions, we extended the methods from Nauhaus et.al. (2008) and estimated the post-synaptic effects of ictal LFPs by creating spike-triggered averages (STAs) from concurrent microelectrode array (MEA) and ECoG recordings of human seizures. We investigated effects across grid distances between spiking neurons and ECoG records up to 4cm. For each distance we estimated the signal-to-noise ratio (SNR) and amplitude range of the STA, and found clear effects of spiking activity on the ECoG, plateauing at 3cm away from the spiking neurons (SNR reduction from ~45 dB to ~28 dB and amplitude reduction from ~313 μV to ~220 μV. To investigate the linear effect of local multiunit activity on the produced signal, we then convolved the estimated post-synaptic effects (STAs) and the individual spike trains to produce a reconstructed ECoG. These reconstructions were compared to the measured ECoG recordings from distances up to 4cm away from the MEA as measure on the ECoG grid. Correlations between the measured and reconstructed signals decreased from > 0.75 to < 0.3 over a distance of 3cm. Similarly, coherence analysis between these signals showed a strong peak, > 0.65, in the theta band frequencies (3-7Hz) that decreased to ~ 0.5 beyond 3cm. Our data indicates that ictal spike activity from groups of neurons in an mm-sized network can be used to reconstruct signals recorded on ECoG electrodes multiple centimeters away, supporting the notion of an epileptic core in which pathological neuronal outputs affect a wide area of surrounding cortex, previously defined as penumbra.

Disclosures: **T. Eissa:** None. **C. Schevon:** None. **R. Emerson:** None. **G. McKhann:** None. **R. Goodman:** None. **W. van Drongelen:** None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.01

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NARSAD /BBR Independent Investigator Award (#20350)

EU-FP7 MC-ITN IN-SENS (#607616)

Title: Insoluble NKCC1 (SLC12A2) as a marker in chronic mental illness

Authors: *C. KORTH[1], R. MARREIROS[2], P. OTTIS[2], I. PRIKULIS[2], K. LI[3], T. HYDE[4], J. KLEINMAN[4], S. MOSS[5], L. SILAYEVY[6], N. BRANDON[7], A. B. SMIT[3], W. HENNAH[8]; [1]Heinrich Heine Univ. Dusseldorf, Dusseldorf, Germany; [2]Univ. of Düsseldorf, Düsseldorf, Germany; [3]VU Amsterdam, Amsterdam, Netherlands; [4]Lieber Inst., Baltimore, MD; [5]Tufts Univ., Boston, MA; [6]TUfts Univ., Boston, MA; [7]AstraZeneca, Boston, MA; [8]Univ. of Helsinki, Helsinki, Finland

Abstract: Background: Protein pathology is a major hallmark in chronic conditions of brain disease, such as typically found in neurodegenerative diseases resulting from disturbed proteostasis. It is likely that intermediate forms of disturbed proteostasis underlie the wide spectrum of chronic brain conditions observed. Schizophrenia is a chronic brain condition, though currently with no detectable degeneration. Identification of insoluble proteins specific for schizophrenia or of patient subsets will help to biologically improve disease classification. Methods: Insoluble proteome was prepared similar to a previously described approach (Leliveld et al., 2008 J Neurosci 28:3839) from brain samples provided by the Stanley Research Medical Institute (SMRI). Pools of insoluble proteins from four conditions schizophrenia, depression, bipolar disorder and normal controls, each composed of 15 individual samples were each analyzed by mass spectrometry. Genetic analysis was applied to support significance of data. Results: Proteomic analylsis of the insoluble proteome, identified NKCC1, but not KCC2, specifically in the insoluble proteome of the diseased brain, which was confirmed by Western blotting of individual samples. Genetic analysis of a Northern Finnish birth cohort confirmed genetic association of NKCC1 with an endophenotype of schizophrenia both independently and in a DISC1-dependent way. Conclusion: NKCC1 has been attributed a role in schizophrenia (Mortia et al. 2014, J Neurosci 34:4929) and has been demonstrated to interact with DISC1 (Kim et al, 2012, Cell 148:1051). Here we further our understanding of NKCC1 by demonstrating it to be associated with protein pathology in a disease-specific way.

Disclosures: C. Korth: None. **R. Marreiros:** None. **P. Ottis:** None. **I. Prikulis:** None. **K. Li:** None. **T. Hyde:** None. **J. Kleinman:** None. **S. Moss:** None. **L. Silayevy:** None. **N. Brandon:** A. Employment/Salary (full or part-time); AstraZeneca. **A.B. Smit:** None. **W. Hennah:** None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.02

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH F32 Fellowship MH106265

NIH award DP1EY024503

NIH grant R01EY011787

NIH grant R41MH100895

DARPA grant W91NF-14-1-0269

MURI grant ARO W911NF-12-1-0594

NARSAD

Title: Fragmented cortical microcircuit motifs in an NMDAR-hypofunction mouse model support an attractor hypothesis of psychotic states

Authors: *J. P. HAMM, D. PETERKA, R. YUSTE;
Columbia Univ., New York, NY

Abstract: At the microcircuit level, layer 2/3 neocortical neurons cooperate in distributed synchrony, forming recurrent patterns of activity which are the likely building blocks of perceptions or thought. Psychotic brain states, such as those experienced in schizophrenia (SZ) or some neurological syndromes (e.g. anti-NMDA-receptor encephalitis), may involve a critical disruption in the stability and reliability of these network activity patterns (i.e., motifs). Such a disruption could theoretically explain abnormalities in perception and thought characteristic to psychosis. Past work has only supported this hypothesis computationally, or has probed patterned network dynamics indirectly with electrophysiology (EEG, LFPs). Here we used two-photon calcium imaging to measure the simultaneous activity of 60-110+ cortical neurons in awake mice. We virally expressed calcium indicators (GCaMP6s/f) in primary visual cortex, a region with known functional and anatomical abnormalities in SZ as well as direct functional relevance for understanding psychosis phenomenology (e.g. visual hallucinations). We imaged populations at rest (no visual stimuli) and during the presentation of full-field moving square wave gratings (6 orientations, 12 directions) of 100 % contrast and .08 cycles per degree. We quantified single cell responses and network-level activity before and one week after continuous delivery of ketamine (KET), an NMDA-receptor antagonist previously demonstrated to recreate perceptual and cognitive symptomology of SZ in healthy humans as well as electrophysiological

and anatomical biomarkers of SZ in rodents. Chronic KET increased ongoing activity and decreased orientation selectivity at the single neuron level, consistent with known abnormalities in cortical inhibitory interneurons identified in SZ brains post-mortem as well as after chronic KET in rodents. When network activity was considered en masse, population-level activity patterns became largely disorganized after KET, exhibiting diminished regularity across both periodic "upstates" during rest and in visually evoked brain states. Pairwise correlations between cells showed a shift toward intermediate values across the network (i.e. away from uncorrelated and highly correlated values). These changes were not accompanied with an increase in functional dimensionality (or number of activity states), suggesting an overall disorganization of cortical activity. These results suggest a shallowing of the basins of dynamical attractors in cortical microcircuits which could explain or contribute to disordered perception and cognition fundamental to psychotic pathology.

Disclosures: **J.P. Hamm:** None. **D. Peterka:** None. **R. Yuste:** None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.03

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH Grant NS059957

NIH Grant MH103374

NIH Grant NS077986

NIH Grant AA021074

NIH Grant NS039444

NIH Grant MH082441

OTKA grant K83830

Title: Spine pruning in frontal cortex drives antipsychotic-sensitive locomotion via circuit control of striatal dopamine

Authors: ***I. KIM**[1], M. A. ROSSI[2], D. K. ARYAL[3], B. RACZ[5], N. KIM[2], A. UEZU[1], F. WANG[4], W. C. WETSEL[3], R. J. WEINBERG[6], H. YIN[2], S. H. SODERLING[1];

[1]Cell Biol., [2]Psychiatry and Behavioral Sci., [3]Mouse Behavioral and Neuroendocrine Analysis Core Facility, [4]Neurobio., Duke Med. Ctr., Durham, NC; [5]Anat. and Histology, Szent István Univ., Budapest, Hungary; [6]Cell Biol. and Physiol., Univ. of North Carolina, Chapel Hill, NC

Abstract: Psychiatric and neurodevelopmental disorders may arise from anomalies in long-range neuronal connectivity downstream of pathologies in dendritic spines. However, the mechanisms that may link spine pathology to circuit abnormalities relevant to atypical behavior remain unknown. Using a mouse model to conditionally disrupt a critical regulator of the dendritic spine cytoskeleton, the actin-related protein 2/3 complex (Arp2/3), we report here a molecular mechanism that unexpectedly reveals the inter-relationship of progressive spine pruning, elevated frontal cortical excitation of pyramidal neurons and striatal hyperdopaminergia in a cortical-to-midbrain circuit abnormality. The main symptomatic manifestations of this circuit abnormality are psychomotor agitation and stereotypical behaviors, which are relieved by antipsychotics. Moreover, this antipsychotic-responsive locomotion can be mimicked in wild-type mice by optogenetic activation of this circuit. Collectively these results reveal molecular and neural-circuit mechanisms, illustrating how diverse pathologies may converge to drive behaviors relevant to psychiatric disorders.

Disclosures: I. Kim: None. **M.A. Rossi:** None. **D.K. Aryal:** None. **B. Racz:** None. **N. Kim:** None. **A. Uezu:** None. **F. Wang:** None. **W.C. Wetsel:** None. **R.J. Weinberg:** None. **H. Yin:** None. **S.H. Soderling:** None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.04

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: MH084018

Title: PCM1 is necessary for the maintenance of focal ciliary integrity and dopamine signaling in the postnatal brain

Authors: *E. OH;
Duke Univ., Durham, NC

Abstract: The neuronal primary cilium and the pericentriolar matrix (PCM) have established roles in neurogenesis. However, the role of this subcellular region in the postnatal brain is not

clear. Here we show that perturbation of the PCM alters brain anatomical and behavioral patterns in a spatial and temporal manner. Ablation of the pericentriolar material 1 gene (Pcm1) in the mouse leads to enlarged lateral ventricles and sensorimotor gating deficits in adult, but not juvenile animals. Cytoanatomical analyses revealed progressive shortening of the primary cilium in discrete brain regions, most prominently the CA1 region of the hippocampus, the amygdala, and the prelimbic cortex. These were associated with an aggregation of dopamine D2 receptors (D2R) at the PCM and failure to fully ameliorate adult sensorimotor gating defects by treatment with antipsychotic drugs. Given the previous association of PCM1 with schizophrenia (SZ) and our present observations, we sequenced the locus in a cohort of SZ patients unresponsive to antipsychotics. In doing so, we identified a significant enrichment for rare alleles in cases, the effects of which were established by systematic modeling in a zebrafish pcm1 model. Together, our data highlight a role for the PCM in the postnatal brain; they suggest that a progressive degenerative ciliary/PCM phenotype can induce behavioral defects in adults, and intimate a role for PCM1 in severe psychosis.

Disclosures: E. Oh: None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.05

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Evaluation of chronic nicotine treatment on hippocampal oscillatory activity and sleep pattern analysis of a G72 transgenic mouse model for schizophrenia

Authors: *A. PAPAZOGLOU[1], A. LUND[1], J. SOÓS[1], C. HENSELER[1], M. BAKKI[1], D. OTTE[2], B. HAMBSCH[2], A. ZIMMER[2], K. BROICH[1], M. WEIERGRAEBER[1];
[1]Federal Inst. for Drugs and Med. Devices, Bonn, Germany; [2]Inst. of Mol. Psychiatry, Univ. of Bonn, Bonn, Germany

Abstract: The primate specific gene locus G72/G30 encoding the G72 protein is highly associated with the cognitive and behavioral symptoms of schizophrenia. Transgenic mice expressing the human G72/G30 gene locus show similar cognitive deficits as seen in schizophrenia patients which are often related to hippocampus dysrhythmia. In addition, disturbed sleep could be found in 30-80% of schizophrenic patients, depending on the degree of psychotic symptomatology. It is quite common schizophrenia patients to present difficulties initiating or maintaining sleep. Several studies suggest that treatment with nicotine reduces the

cognitive impairments in schizophrenia patients. G72 mice showed increased α7-nAChR density in the dentate gyrus and the motor cortex. To investigate the impact of chronic nicotine treatment on hippocampal oscillation activity and the hippocampus/motor cortex interaction, we performed radiotelemetric intrahippocampal (dentate gyrus) recordings in nicotine treated G72 mice. Chronic nicotine treatment was delivered by subcutaneous implanted osmotic mini-pumps. The effect of nicotine on EEG recordings was evaluated by time-frequency analysis. We also studied sleep patterns of spontaneous and artificial urethane-induced sleep on G72 mice using implantable video-EEG radiotelemetry. Data would be analysed for alterations in sleep architecture using sleep staging software and time-frequency analysis.

Disclosures: **A. Papazoglou:** None. **A. Lund:** None. **J. Soós:** None. **C. Henseler:** None. **M. Bakki:** None. **D. Otte:** None. **B. Hambsch:** None. **A. Zimmer:** None. **K. Broich:** None. **M. Weiergraeber:** None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.06

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Leenaards and Jeantet Foundations

the National Center of Competence in Research (NCCR)

“SYNAPSY - Swiss National Science Foundation (n° 51AU40_125759)

SNSF n° 320000-122419

Alamaya and Avina Foundations

Title: GCLC gene predicts prefrontal glutathione levels: association with peripheral glutathione peroxidase/glutathione reductase

Authors: L. XIN[1], R. MEKLE[2], C. FERRARI[3,4], P. S. BAUMANN[3,4], L. ALAMEDA[3,4], H. MOSER[3], M. FOURNIER[3], P. CONUS[4], R. GRUETTER[1,5,6], *K. Q. DO[3];
[1]Lab. of Functional and Metabolic Imaging, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; [2]Physikalisch-Technische Bundesanstalt, Berlin, Germany; [3]Ctr. for Psychiatric Neurosci., Prilly-Lausanne, Switzerland; [4]Dept. of Psychiatry, Lausanne Univ. Hosp.

(CHUV), Lausanne, Switzerland; [5]Dept. of Radiology, Univ. of Lausanne, Lausanne, Switzerland; [6]Dept. of Radiology, Univ. of Geneva, Lausanne, Switzerland

Abstract: ***Introduction***: Oxidative stress and redox dysregulation may be involved in the pathogenesis of schizophrenia. As a major redox regulator, glutathione (GSH), is metabolized by glutathione peroxidase (GPx) to detoxify ROS and generate oxidized GSH (GSSG), which is reduced back to GSH by glutathione reductase (GR).The ratio of GPx/GR enzymatic activities could be a peripheral biomarker for the (dys)regulation of redox status. GAG-trinucleotide repeat polymorphisms (GAG-TNR) in glutamate-cysteine ligase catalytic gene (GCLC), the rate-limiting enzyme for GSH synthesis, are associated with schizophrenia [Gysin&al.2007]. The aim of this study is to investigate brain GSH levels, its association with GCLC genotypes and blood GPx/GR activity in early psychosis patients (EP). ***Methods***: Subjects: Caucasian 29 EP patients and 33 controls. MRS measurement: 3T Trio MR scanner; Spectra obtained in medial prefrontal cortex (mPFC) using SPECIAL sequence [Mekle&al.2008]; Metabolite concentrations were quantified by LCModel [Provencher&al.1993]. GAG-TNR polymorphism was genotyped [Gysin&al.2007] and the activities of GPx and GR in blood cell were determined [Günzler&al.1974 and Long&al.1961]. Statistics: The potential effect of medication was assessed by correlating antipsychotic doses with GSH levels, GPx and GR activities. The effects of disease, GCLC GAG-TNR polymorphism, age and gender on mPFC GSH level, GPx and GR enzymatic activity were investigated using generalized linear model. The correlation of brain GSH levels with GPx/GR ratio was evaluated. ***Results*** : mPFC GSH levels, GPx and GR activities were not significantly different between patients and controls. Subjects with the GAG-TNR high-risk genotype had lower GSH levels ($p=0.006$) as compared to those with low risk genotype. No correlation was found between medication dose and GSH, GPx, GR activity. Since GR activity is different between male and female ($p=0.009$), the correlation between GSH and the ratio of GPx/GR was investigated in separated gender groups. GSH levels were inversely correlated with GPx/GR activity in male patients ($p=0.02$) and such correlation was not observed in male controls and female subjects. ***Conclusions***: We show for the first time that GAG-TNR of GCLC gene predicts mPFC GSH levels, with high-risk genotype associated with lower GSH, extending to CNS previous results from fibroblasts. Moreover, mPFC GSH demonstrated a negative correlation with blood redox profile markers in EP patients but not in control subjects: low GSH brain levels are associated with more oxidative state of the blood redox profile, thus paving the way for the search of central and peripheral markers.

Disclosures: **L. Xin:** None. **R. Mekle:** None. **C. Ferrari:** None. **P.S. Baumann:** None. **L. Alameda:** None. **H. Moser:** None. **M. Fournier:** None. **P. Conus:** None. **R. Gruetter:** None. **K.Q. Do:** None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.07

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: CIHR

NIH

NARSAD

Stanley Foundation

RUSK Foundation

Title: Decoupling of transcription and translation in schizophrenia

Authors: *J. LAVOIE[1], T. TSUJIMURA[1], H. JAARO-PELED[1], K. ISHIZUKA[1], N. T. INGOLIA[2], A. SAWA[1];
[1]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Univ. of California, Berkeley, Berkeley, CA

Abstract: Identification of molecular signatures and cellular susceptibilities associated with psychiatric disorders, such as schizophrenia (SZ) and bipolar disorder (BP), is crucial to understand their pathophysiology and discover novel therapeutic targets. Recent advances in human cell technologies have provided us opportunities to use neuronal cells from patients, such as olfactory epithelium (OE)-derived neuronal cells, which show immature neuronal traits and have been enriched to near homogeneity from biopsied OE. High- throughput deep sequencing techniques allow the monitoring of physiological processes including transcription and translation. Among these techniques, RNA sequencing (RNA-seq) is used to investigate gene expression and ribosome profiling (Ribo-seq) assesses global measurement of ribosome-associated RNAs and the regions of the transcriptome that are actually translated. In this pilot study, we have performed RNA-seq and Ribo-seq with OE-derived neurons taken from age-, gender- and smoking status-matched 3 controls, 3 SZ and 3 BP subjects. To minimize confounding effects of medications, we selected patients with SZ and BP who took antipsychotics. The same cell lysate from each subject was used for both RNA-seq and Ribo-seq. By comparing fold change at the transcriptional level (RNA-seq) and at the translational level (Ribo-seq) in individual genes, we found translational alterations between controls and SZ subjects, but almost no mRNA transcriptional changes were observed. We did not find similar deviation between controls and BP subjects. These observations suggest that a decoupling of transcription and translation for certain gene products is associated with SZ. Profiling with additional SZ and control subjects is under way to validate this initial working hypothesis.

Further mechanistic studies are also warranted to investigate the origins of the translational perturbations reported in OE-derived neuronal cells from SZ patients.

Disclosures: J. Lavoie: None. **T. Tsujimura:** None. **H. Jaaro-Peled:** None. **K. Ishizuka:** None. **N.T. Ingolia:** None. **A. Sawa:** None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.08

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: The Uehara Memorial Foundation

Title: Trio-based exome sequencing identified de novo non-synonymous missense mutations in schizophrenia

Authors: *A. NISHI[1], S. NUMATA[1], A. TAJIMA[2,3], M. KINOSHITA[1], S. SHIMODERA[4], S. ONO[5], S. OCHI[6], N. KUROTAKI[5], A. IMAMURA[5], S. UENO[6], I. IMOTO[3], T. OHMORI[1]; [1]Psychiatry, Tokushima Univ., Tokushima, Japan; [2]Dept. of Bioinformatics and Genomics Grad. Sch. of Med. Sci., Kanazawa Univ., Ishikawa, Japan; [3]Dept. of Human Genet., Tokushima Univ. Grad. Sch., Tokushima, Japan; [4]Dept. of Neuropsychiatry, Kochi Med. Sch., Kochi, Japan; [5]Dept. of Neuropsychiatry, Nagasaki Univ. Grad. Sch. of Biomed. Sci., Nagasaki, Japan; [6]Dept. of Neuropsychiatry, Ehime Univ. Grad. Sch. of Med., Ehime, Japan

Abstract: Object: It is well known that schizophrenia has a strong genetic component. Despite its high heritability, there are many patients with no family history of schizophrenia, who are regarded as sporadic cases. The purpose of the present study was to detect de novo non-synonymous mutations in sporadic schizophrenia patients by a trio-based exome sequencing in the Japanese population. Methods: We collected 18 family trios consisting of a patient with schizophrenia and two unaffected parents from Tokushima University, Ehime University, Kochi University, and Nagasaki University in Japan. The diagnosis of schizophrenia was made according to DSM-IV criteria. Exome enrichment was conducted by TruSeq DNA Sample Prep Kits and TruSeq Exome Enrichment Kit (Illumina). We performed paired-end (2 × 100 bp) exome sequencing with HiSeq1000/1500 (Illumina). The sequencing reads obtained were mapped to the human reference genome (build hg19) by using the Burrows-Wheeler Aligner (BWA v0.5.9). We analyzed the mapped sequence data with the Genome Analysis Toolkit (GATK, v2.6-4 and v2.6-5) software. Candidate de novo mutations were validated by the Sanger

method of DNA sequencing. Result: We obtained average 15.4 GB of raw sequence data per sample, and 96.9 % of these data was mapped to the reference genome. We found 82 de novo single-nucleotide variants and 354 de novo insertion/deletion mutations in 18 proband-parent trios. Among these de novo mutations, 28 were predicted to be non-synonymous mutations. Of the 28 de novo non-synonymous mutations, we performed the Sanger sequencing of 17 candidate mutations, and validated 9 de novo non-synonymous mutations from 8 trio families. Conclusion: Our results suggest that de novo non-synonymous mutations may be involved in the pathology of schizophrenia.

Disclosures: **A. Nishi:** None. **S. Numata:** None. **A. Tajima:** None. **M. Kinoshita:** None. **S. Shimodera:** None. **S. Ono:** None. **S. Ochi:** None. **N. Kurotaki:** None. **A. Imamura:** None. **S. Ueno:** None. **I. Imoto:** None. **T. Ohmori:** None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.09

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH R01 MH102365,

Alfred P. Sloan Fellowship

Whitehall Foundation grant

NARSAD Young Investigator award

Smith Family Award for Excellence in Biomedical Research

Jane Coffin Fellowship

Title: Age-dependent role of Nrg1-ErbB4 signaling in GABAergic interneurons

Authors: *R. BATISTA-BRITO[1], D. VULLHORST[3], A. BUONANNO[3], J. A. CARDIN[2]; [1]Neurobio., [2]Yale Univ., New Haven, CT; [3]Natl. Inst. of Child Hlth. and Human Develop., Bethesda, MD

Abstract: Neuregulin1 (Nrg1) is a diffusible trophic factor in the brain that activates a tyrosine kinase receptor, ErbB4. Genetic studies have shown a strong correlation between schizophrenia and mutations in the genes Nrg1 and ErbB4. Studies in mice further indicate that loss of Nrg1 or

ErbB4 results in schizophrenia-like phenotypes. Previous work suggests that Nrg1-ErbB4 signaling is necessary for the function of GABAergic, parvalbumin-expressing inhibitory interneurons (PV-INs) in the brain. Disruption of the inhibitory-excitatory balance at different ages may result in different behavioral deficits and is likely related to the onset and severity of developmental pathologies in psychiatric diseases such as schizophrenia. However, it is unclear whether Nrg1-ErbB4 signaling is important only during specific developmental periods or throughout life. In order to understand the temporal role of ErbB4 in inhibitory function in cortical networks, we removed ErbB4 either during embryonic development or in adult mice. To assess how Nrg1-ErbB4 signaling affects cortical activity patterns, we recorded spontaneous and visually evoked activity in the primary visual cortex (V1) of awake or lightly anesthetized animals. We observed altered firing rates in both excitatory and inhibitory neurons, as well as altered spontaneous and visually evoked local field potential (LFP) activity when ErbB4 was removed either at early or late ages. Disrupted LFP activity could be rescued by restoring ErbB4 expression during the critical period of visual plasticity (P20) but not at later ages (P150). However, altered LFP activity could be rescued at mature ages (P150) by optogenetic enhancement of mutant interneuron activity.

Disclosures: **R. Batista-Brito:** None. **D. Vullhorst:** None. **A. Buonanno:** None. **J.A. Cardin:** None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.10

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: DIM Cerveau et Pensée

Prix Marcel Dassault

Title: Functional analysis of mutations in CADPS identified in patients with early onset bipolar disorder

Authors: ***J. SITBON**[1,2,3], C. KAPPELER[1,2,3], A. NICOLAS[1,2,3], A. HENRION[1,2,3], J. S. RHEE[4], M. LEBOYER[1,2,3,5], S. JAMAIN[1,2,3];
[1]Dept. of Neuropsychiatry, INSERM U955, Psychiatrie Translationnelle, Créteil, France; [2]Univ. Paris Est, Faculté de Médecine, Créteil, France; [3]Fondation FondaMental, Créteil, France; [4]Dept.

of Mol. Neurobiology, Max Planck Inst. of Exptl. Med., Göttingen, Germany; [5]AP-HP, Hôpital H. Mondor – A. Chenevier, Pôle de Psychiatrie, Créteil, France

Abstract: With a prevalence of 1% in general population, bipolar disorder is one of the most severe and common psychiatric diseases. Many studies suggest a preponderant role for genetic factors in bipolar disorder, mainly in early-onset form of the disease. However molecular mechanisms underling this disorder remains unclear. We identified missense variations and one deletion in a gene encoding the calcium-dependent activator protein for secretion (CADPS) in patients with early-onset bipolar disorder. CADPS is an essential regulator of synaptic and large dense core vesicles exocytosis in mammalian neurons and neuroendocrine cells, respectively. Moreover, CADPS promotes vesicular catecholamine uptake and storage mediated by vesicular monoamine transporters. In the current study, we showed that some of the mutations identified in patients altered the expression level of the protein due to protein stability impairment. In addition, we showed that two mutations impaired significantly the ability of CADPS to facilitate the monoamine vesicular uptake *in vitro*. Finally, mutant mice for Cadps (Cadps+/-) exhibited modification in anxiety-related behaviors as well as in behavioral despair, suggesting an altered sensitivity for these animals to mild acute stress, as compared to wild-type littermates. Altogether, our results suggest that impairment in CADPS function may affect the behavior of mutant subjects and such mutations may thus increase the vulnerability to early-onset bipolar disorders in humans.

Disclosures: J. Sitbon: None. **C. Kappeler:** None. **A. Nicolas:** None. **A. Henrion:** None. **J.S. Rhee:** None. **M. Leboyer:** None. **S. Jamain:** None.

Nanosymposium

282. Neuropathology: Mechanisms and Biomarkers

Location: S102

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 282.11

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Methamphetamine-induced locomotor sensitization alters the expression of proteins associated with energy metabolism, oxidative stress and GABAergic neurotransmission in the rat ventral hippocampus: Implications for psychosis

Authors: *M. K. SAUER[1], M. MIRZAEI[2], T. A. WEARNE[1], A. K. GOODCHILD[3], P. A. HAYNES[2], J. L. CORNISH[1];
[1]Dept. of Psychology, [2]Dept. of Chem. and Biomolecular Sci., [3]Australian Sch. of Advanced Med., Macquarie Univ., Sydney, Australia

Abstract: Methamphetamine (METH; “crystal”, “ice”) is a widely abused psychostimulant drug that can induce psychosis that is indistinguishable from schizophrenia. Repeat administration of METH in rodents induces a sensitized locomotor response that is thought to model the neurochemical changes that underlie psychoses. Previous findings of neurochemical alterations in the ventral hippocampus (VHipp) in schizophrenia and psychoses indicate that this region may be involved in the development and maintenance of positive symptoms of psychoses. However, the molecular mechanisms underlying this dysfunction in the VHipp are largely unknown. The current study used proteomic analysis to examine alterations in protein expression in the VHipp following METH-induced locomotor sensitization. Using a 2x2 experimental design, male Sprague Dawley rats (n=48) were treated with METH (1mg/kg i.p. on days 1 & 7; 5mg/kg on days 2-6) or saline (1mg/kg i.p.) for 7 days, followed by 14 days withdrawal. Rats then received acute METH (1mg/kg i.p.) or saline (1mg/kg i.p.) challenge. Locomotor activity was measured for 60 minutes after challenge, before rats were euthanized and the VHipp was dissected out for label-free quantitative shotgun proteomics (n=12). Statistical analysis of behavioural data showed that METH challenge resulted in a significant sensitized locomotor response in rats pre-treated with METH, compared to all other groups ($p<0.05$). Triplicate analysis of the VHipp proteome identified 596 differentially expressed proteins across the four groups, with 370 proteins uniquely altered in METH-sensitized rats. Changes in protein expression in METH-sensitized rats were associated with multiple biological functions, including energy metabolism (e.g., ENO1 and ENO2 proteins), oxidative stress (e.g., OXSR1 and HYOU1 proteins) and GABA neurotransmission (e.g., GAD67 and GABRG2 proteins). These data highlight the importance of the VHipp in METH-induced locomotor sensitization and further our understanding of changes to this region in the positive symptomatology of psychotic disorders.

Disclosures: **M.K. Sauer:** None. **M. Mirzaei:** None. **T.A. Wearne:** None. **A.K. Goodchild:** None. **P.A. Haynes:** None. **J.L. Cornish:** None.

Nanosymposium

283. Perception and Auditory Cortex

Location: S402

Time: Monday, October 19, 2015, 8:00 AM - 10:15 AM

Presentation Number: 283.01

Topic: D.02. Auditory System

Support: Wellcome Trust WT091681MA

NIH R01-DC04290

NIH UL1RR024979

Hoover Fund

Title: Direct recordings of oscillatory activity in the human brain during working memory for tones

Authors: *P. E. GANDER[1], S. KUMAR[2,3], K. V. NOURSKI[1], H. OYA[1], H. KAWASAKI[1], M. A. HOWARD[1], T. D. GRIFFITHS[2,3];
[1]Dept. of Neurosurg., Univ. of Iowa, Iowa City, IA; [2]Inst. of Neurosci., Newcastle Univ., Newcastle upon Tyne, United Kingdom; [3]Wellcome Trust Ctr. for Neuroimaging, Univ. Col. London, London, United Kingdom

Abstract: Working memory is the capacity to hold and manipulate behaviourally relevant information in mind in the absence of ongoing sensory input. Here we explored the hypothesis that working memory for tones requires a network of oscillatory activity in auditory cortex, frontal cortex, and hippocampus [Kumar et al., 2015, SfN], and examined the form of such activity in neuronal ensembles. We recorded local field potentials from six human subjects undergoing invasive monitoring for pre-surgical localization of epileptic foci. The subjects were implanted with depth electrodes along the axis of Heschl's gyrus (HG) containing primary cortex in the medial part, and subdural electrodes over temporal and frontal cortex. Following a visual alert subjects were presented with a pair of tones (0.5 s duration, 750 ms ISI) belonging to two different categories ('Low': 300-570 Hz; 'High': 2000 -2800 Hz). A visual cue (750 ms) then informed the subjects which tone (first or second) to keep in mind. A 3 s retention period was followed by a tone which could be the same or different (frequency difference ±20%) from the tone held in mind. The subjects made a same/different decision by pressing a button. A total of 160 trials (80 each of 'Low' and 'High' tone retention) were presented. We measured average ERPs and carried out single-trial time-frequency analysis using a wavelet transform. During perception, both the magnitude of ERPs (~100 ms after stimulus onset) and gamma-band (60-120 Hz) power in electrodes located in HG and lateral superior temporal gyrus (STG) showed category-specific responses. High tones elicited stronger responses in medial HG and low tones in lateral HG. During retention, sustained induced low frequency power in the delta/theta-band (2-8 Hz) was observed in HG, frontal cortex (inferior and superior gyri), and hippocampus. Sustained low frequency activity was observed in all contacts that showed gamma-band responses during perception. Low-frequency power during retention also showed a recency effect: a greater response in HG electrodes was observed for the most recently presented (second) tone. On the STG, however, the opposite effect was observed: a greater 2-8 Hz power for retention of the first compared to the second tone. The data demonstrate: 1) a network of brain regions during auditory working memory that includes auditory, frontal, and hippocampal cortex 2) theta-band correlates of tone retention in auditory cortex in the same neural ensembles that are active in the gamma band during perception 3) neural bases in the auditory cortex for interference effects within tonal working memory.

Disclosures: **P.E. Gander:** None. **S. Kumar:** None. **K.V. Nourski:** None. **H. Oya:** None. **H. Kawasaki:** None. **M.A. Howard:** None. **T.D. Griffiths:** None.

Nanosymposium

283. Perception and Auditory Cortex

Location: S402

Time: Monday, October 19, 2015, 8:00 AM - 10:15 AM

Presentation Number: 283.02

Topic: D.02. Auditory System

Support: NIH R01-DC04290

NIH UL1RR024979

Hoover Fund

Title: Electrocorticographic activation within and beyond auditory cortex during dialogue-based language and cognitive testing

Authors: ***M. STEINSCHNEIDER**[1], K. V. NOURSKI[2];
[1]Neurol., Albert Einstein Col. of Med., Bronx, NY; [2]Neurosurg., The Univ. of Iowa, Iowa City, IA

Abstract: The ventral pathway for language processing is envisioned to encode ever more complex and abstract features of speech (Rauschecker & Scott, Nat Neurosci 12:718-24, 2009; Poeppel et al, Philos Trans R Soc Lond B Biol Sci 363:1071-86, 2008). For instance, superior temporal gyrus (STG) is thought to be engaged in acoustic-phonetic mapping, while middle temporal gyrus (MTG) represents a sound-meaning interface. We examined this model using a dialogue-based paradigm, wherein subjects performed the Mini Mental Status Examination and other neuropsychological tests that assessed language and memory functions. Subjects were neurosurgical patients undergoing chronic invasive monitoring for medically refractory epilepsy. Studies were approved by the University of Iowa Institutional Review Board and NIH, and subjects could rescind their consent for participation at any time without affecting their clinical evaluation. Electrocorticography (ECoG) recordings were made simultaneously from auditory and auditory-related temporal cortex of Heschl's gyrus (HG), STG, MTG, superior temporal sulcus (STS), supramarginal gyrus (SMG), and mesial temporal structures including parahippocampal gyrus (PHG). High gamma (70-150 Hz) ECoG power was calculated using an FIR filter implemented in MATLAB. Responses were related to listening to the instructions of the interviewer and to the subject's verbal responses. As expected, posteromedial HG was

activated during both listening and speaking regardless of the task. In contrast, STG was differentially affected by the tasks, with areas adjacent to the transverse temporal sulcus generally suppressed during self-initiated speech. STS and MTG were strongly activated during tasks involving lexical retrieval. While SMG is envisioned to be a major auditory-motor hub within the dorsal processing pathway, its anterior portion was generally activated during listening and suppressed during speaking. PHG was strongly activated during memory-based tasks. The amygdala was maximally activated in tasks possessing an emotional valence to the subjects. We conclude that models of speech and language processing need to incorporate brain regions outside classically defined auditory and auditory-related areas that subserve more general cognitive processes (e.g., memory retrieval, emotional valence) that are actively engaged in real-life conversations. These patterns of cortical activation observed during performance of neuropsychological tests will need to be further characterized using more structured experimental paradigms.

Disclosures: **M. Steinschneider:** None. **K.V. Nourski:** None.

Nanosymposium

283. Perception and Auditory Cortex

Location: S402

Time: Monday, October 19, 2015, 8:00 AM - 10:15 AM

Presentation Number: 283.03

Topic: D.02. Auditory System

Title: Systematic investigation of auditory rhythmic regularity processing in behaviour and EEG

Authors: ***M. GRUBE**[1,3], I. STURM[1,4], A. BEKIUS[5], T. COPE[6], K.-R. MUELLER[2]; [2]Machine Learning Group, [1]TU Berlin, Berlin, Germany; [3]Inst. of Neurosci., Newcastle Univ., Newcastle-upon-Tyne, United Kingdom; [4]Sch. of Main and Brain, Humboldt Univ., Berlin, Germany; [5]Univ. of Amsterdam, Amsterdam, Netherlands; [6]Univ. of Cambridge, Cambridge, United Kingdom

Abstract: The perception of music and speech relies on the specialized use of neural processing of different degrees of temporal regularity in auditory stimuli. Previous research established margins of tolerance for the perception of a regular pulse in acoustic sequences (Madison & Merker 2002 Psych Res) and discrimination thresholds for perfectly regular or highly irregular sequences in normal controls and neurological patients (Grube et al. 2010 PNAS; Cope et al. 2014 Neuropsychologia). First reports on neural correlates also either used perfectly regular or randomly timed sequences (Nozaradan et al. 2011 J Neurosci; Fujioka et al. 2012 J Neurosci). This study examines both discrimination limens and subjective ratings of systematically varied

regularity, in correlation with EEG measures analysed by a machine learning approach. Stimuli consisted of sequences of 9-11 tones with different tempi (340, 400, 460 ms) and different degree of regularity. Discrimination limens were measured for perfectly regular (0% jitter) and highly irregular sequences (30% jitter). Subjective ratings of regularity were measured for 5 levels (classes) of jitter (0, 7.5, 15, 22.5, 30%), using a Likert scale of 1-4, while EEG was recorded (36 trials per combination of tempo and jitter). The EEG analysis in this multi-class setting is based on the adaptation of techniques from Brain-Computer-Interface (BCI) research to identify components that reflect the degree of regularity at the individual level. The first aim here is to define fine-grained differences in event-related potentials (ERPs) that reflect a gradual change in the processing of tones as a function of the systematic manipulation of degree of regularity. Initial analyses demonstrate a significant difference in N1 amplitude for 0 vs. 30% jitter, which is in line with previous literature. Significance at single-subject level motivated a Machine Learning based single-trial EEG approach to differentiate in detail the neural correlates of rhythmic regularity in this multi-class setting. Spatio-temporal filtering techniques from BCI research are applied to enhance the signal-to-noise-ratio and enable us to seek fine-grained differences in ERPs to behavioural responses as a function of regularity at the level of the individual. On-going analyses including those of oscillatory activity will allow to further our understanding of timing functions and regularity processing in the human brain in relation to subjective rhythm perception, which together provide the basis for neural and behavioural "entrainment" with acoustic stimuli from music to speech.

Disclosures: **M. Grube:** None. **I. Sturm:** None. **A. Bekius:** None. **T. Cope:** None. **K. Mueller:** None.

Nanosymposium

283. Perception and Auditory Cortex

Location: S402

Time: Monday, October 19, 2015, 8:00 AM - 10:15 AM

Presentation Number: 283.04

Topic: D.02. Auditory System

Support: BMBF 01EV0712

Title: Cortical network activation during conscious sound-pattern perception with and without informational masking

Authors: ***A. GUTSCHALK**, K. WIEGAND;
Univ. of Heidelberg, Heidelberg, Germany

Abstract: Conscious detection of a regular tone sequence comprised in a multi-tone, informational masker is accompanied by surface-negative activity in the auditory cortex time locked to each single tone (Gutschalk et al 2008, PLoS Biol 6:e138). Here, we evaluated how other areas are involved using fMRI. In Experiment 1, 15 participants listened to an ongoing, random multi-tone masker. Listeners were required to indicate whether or not they had detected a target in the preceding interval upon each color change of a square they continuously fixated. Targets were four isochronous tones of the same frequency. The average hit rate was 70% (8% false alarms). Activity for detected-versus-missed targets was observed in bilateral pre-frontal cortex (PFC), inferior parietal cortex (IPC), the intra-parietal sulcus (IPS), and the anterior insular cortex (aIC). Within the temporal lobe, only activity in the posterior right superior temporal sulcus (pSTS) was observed in the voxel-wise analysis. The detected-versus-correct-rejection contrast additionally revealed activity in auditory cortex on the superior temporal plane (STP). Experiment 2 was performed to explore if the fronto-parieto-insular network was related to the target-reporting task or to the perception of the target itself (14 participants). To this end, a similar setup was used but targets were presented without masker. Targets were generally perceived in this setup (confirmed by subsequent interview), and thus intervals with and without a targets were compared, only. In contrast to experiment 1, listeners received three different instructions in subsequent trials: First, they were asked to fixate the cross in the middle of the screen. Second, they were asked to indicate by pressing a response button whether the cue (a triangle) was pointing up or down upon each color change. Third, listeners were required to indicate whether a target was present in the interval since the last reversal or not. The target-present-versus-target-absent contrast revealed prominent activity in the auditory cortex, extending to the right pSTS for all three trials. In contrast, the fronto-parieto-insular network was only active in the third trial, where listeners were required to report target presence. While Experiment 1 might suggest that the fronto-parieto-insular network is required for perceptual awareness, Experiment 2 casts some doubt on this conclusion. Potentially, activity in the extended network is rather related to accompanying processes, such as updating working memory with the detected target or focused attention required to segregate the target from the masker.

Disclosures: A. Gutschalk: None. **K. Wiegand:** None.

Nanosymposium

283. Perception and Auditory Cortex

Location: S402

Time: Monday, October 19, 2015, 8:00 AM - 10:15 AM

Presentation Number: 283.05

Topic: D.02. Auditory System

Support: NIH R01-DC04290

NIH UL1RR024979

The Hoover Fund

Title: The "where" auditory processing pathway in the human: Insights from intracranial electrophysiology

Authors: *K. V. NOURSKI[1], M. STEINSCHNEIDER[2], A. E. RHONE[1], M. A. HOWARD, III[1];
[1]Dept. of Neurosurg., The Univ. of Iowa, Iowa City, IA; [2]Departments of Neurol. and Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: Auditory cortical processing is envisioned to include a posterodorsal "where" pathway subserving sound localization (Rauschecker & Scott, Nat Neurosci 12:718-24, 2009). Originally described in Old World monkeys, it has been identified in the human primarily using non-invasive neuroimaging techniques. This model predicts that variations in sound location will maximally activate posterior regions of the auditory cortex of the superior temporal gyrus (STG) corresponding to monkey caudal belt and parabelt regions (e.g. area CL). We tested this prediction in humans using invasive electrocorticographic (ECoG) recordings. Subjects were neurosurgical patients undergoing invasive monitoring for medically intractable epilepsy. Studies were approved by the University of Iowa Institutional Review Board and NIH, and subjects could rescind their participation consent at any time. Speech syllables /ba/, /da/ and /ga/ were presented using one of three free-field speakers (-60, 0 +60 degrees azimuth, equidistant from the subject, eye level). Tasks included syllable detection, sound source detection or their combination. ECoG data were recorded simultaneously from Heschl's gyrus (HG) and STG using multicontact depth electrodes and subdural grid arrays, respectively. Cortical activity was analyzed in the high gamma (70-150 Hz) frequency range. Syllables elicited robust responses throughout the auditory cortex. HG did not exhibit contralateral ear dominance, and short-latency responses to stimuli presented from all three locations were nearly identical. Target stimuli were associated with late increases in high gamma power that overlapped with behavioral responses. Within the most posterior portion of the STG, contralaterally presented stimuli elicited larger responses compared to ipsilateral or midline sources. These differences were enhanced in response to target stimuli. More anterior sites on STG had stronger responses to target than non-target stimuli, yet were not affected by sound location. The lack of contralateral ear dominance within HG is surprising given that monkey primary auditory cortex (A1) is generally more responsive to contralateral stimuli (Ahissar et al, J Neurophysiol 67:203-15, 1992). The finding that location sensitivity is greater on posterior STG parallels the greater sensitivity to sound location in area CL when compared to A1 in the monkey (Recanzone et al, J Neurophysiol 83:2723-39, 2000). Our findings provide the first human ECoG confirmation of the hierarchical

model incorporating differential location sensitivity within relatively early stages of cortical sound processing.

Disclosures: K.V. Nourski: None. **M. Steinschneider:** None. **A.E. Rhone:** None. **M.A. Howard:** None.

Nanosymposium

283. Perception and Auditory Cortex

Location: S402

Time: Monday, October 19, 2015, 8:00 AM - 10:15 AM

Presentation Number: 283.06

Topic: D.02. Auditory System

Support: Wellcome Trust Investigator Awards (CIP; WT092606AIA; TDG, PEG; WT091681MA)

BBSRC (CIP; BB/J009849/1)

NIH (MAH, AER, KN; R01-DC04290)

NIH intramural contract (CIP/YK)

Japanese NeuroCreative Award (YK)

Title: Rule-based sequences of nonsense words elicit similar nested oscillations in intracranial recordings from human and monkey auditory cortex

Authors: *Y. KIKUCHI[1], A. E. RHONE[2], K. V. NOURSKI[2], P. E. GANDER[2], A. ATTAHERI[1], C. KOVACH[2], H. KAWASAKI[2], T. D. GRIFFITHS[1,2,3], M. A. HOWARD III[2], C. I. PETKOV[1];
[1]Newcastle Univ. Med. Sch., Newcastle Upon Tyne, United Kingdom; [2]Human Brain Res. Laboratory, Dept. of Neurosurg., The Univ. of Iowa, Iowa City, IA; [3]Wellcome Trust Ctr. for Neuroimaging, Univ. Col. London, London, United Kingdom

Abstract: Neuronal oscillations entrain to environmental events and are thought to play an important role in segmenting sensory input. For instance, a prominent model of speech segmentation based, in part, on human intracranial recordings from auditory cortex suggests that theta oscillations (4-7 Hz) entrain to speech content and couple with gamma (50-120 Hz) amplitude (Giraud & Poeppel, Nat Neurosci 15:511-7, 2012). The extent to which such processes are uniquely human or evolutionarily conserved remains unclear, requiring more direct

comparisons between humans and animal models. Here we ask which auditory cortical oscillations respond to sequences of nonsense words in intracranial recordings from Rhesus macaques and human neurosurgical patients. We used an Artificial Grammar (AG) learning paradigm where the monkeys and humans were first exposed to representative rule-based sequences of nonsense words generated by the AG. In a subsequent testing phase, we presented the participants with sequences that were either consistent with the AG or created a specific violation to the AG ordering relationship. This allowed us to study the cortical oscillations in response to the nonsense words (regardless of sequencing context) and how rule-based sequencing relationships affect these responses. As the participants listened to the testing sequences, we recorded local field potentials from auditory cortex in the monkeys and from depth electrodes along Heschl's gyrus (HG) in humans. In the two monkeys we observed prominent nested oscillations in the form of theta phase coupling with gamma amplitude (recording sites with significant coupling, $P < 0.05$, Bonferroni corrected: 101/145, 70%). Violations of the AG ordering relationships further modulated the strength of the theta-gamma coupling over time (81/101, 80 %). Initial results from human recordings show similar theta-gamma coupling ($P < 0.05$) in response to the nonsense word in medial HG, which is associated with human primary auditory cortex, but not in lateral HG. We provide evidence that monkey auditory neural responses show theta-gamma coupling in response to sequences of nonsense words, in ways that are strikingly similar to results reported elsewhere (Canolty et al, Science 313:1626-8, 2006) and as seen in the results from our more direct comparisons with human intracranial recordings. The findings suggest that nested oscillations reflect general auditory segmentation processes that are unlikely to have, at least at this general level, uniquely specialised in humans, opening the door for more systematic study of neuronal processes in animal models and direct comparisons to human auditory neural processes.

Disclosures: **Y. Kikuchi:** None. **A.E. Rhone:** None. **K.V. Nourski:** None. **P.E. Gander:** None. **A. Attaheri:** None. **C. Kovach:** None. **H. Kawasaki:** None. **T.D. Griffiths:** None. **M.A. Howard III:** None. **C.I. Petkov:** None.

Nanosymposium

283. Perception and Auditory Cortex

Location: S402

Time: Monday, October 19, 2015, 8:00 AM - 10:15 AM

Presentation Number: 283.07

Topic: D.02. Auditory System

Support: ANR Grant ANR-11-BSH2-001-01 to BT and AC

Title: Pitch-responsive cortical regions in subjects with congenital amusia

Authors: *S. V. NORMAN-HAIGNERE[1], P. ALBOUY[2], A. CACLIN[2], N. KANWISHER[1], J. H. MCDERMOTT[1], B. TILLMANN[2];
[1]Brain and Cognitive Sci., MIT, Cambridge, MA; [2]Lyon Neurosci. Res. Centre, CNRS, Lyon, France

Abstract: Congenital amusia is characterized by a life-long deficit in music perception, thought to reflect an underlying impairment in the perception of pitch. One might expect that the cortical regions implicated in pitch representation in typical individuals would be absent or reduced in amusic individuals, but this remains to be tested. We addressed this issue by measuring fMRI responses in 11 subjects with congenital amusia and 11 matched controls to a stimulus contrast that reliably localizes pitch regions in non-amusic individuals: harmonic tones versus frequency-matched Gaussian noise. Surprisingly, amusic participants exhibited clusters of pitch-selective voxels that were comparable in extent, selectivity, and anatomical location to those of control participants. Our findings are broadly consistent with prior findings of abnormal anatomical connectivity between auditory and frontal cortex in amusics, despite apparently normal responses to sound in auditory cortex. The ability to identify regions in congenital amusics specifically responsive to pitch will enable their response properties and connectivity to be explored in future studies.

Disclosures: S.V. Norman-Haignere: None. **P. Albouy:** None. **A. Caclin:** None. **N. Kanwisher:** None. **J.H. McDermott:** None. **B. Tillmann:** None.

Nanosymposium

283. Perception and Auditory Cortex

Location: S402

Time: Monday, October 19, 2015, 8:00 AM - 10:15 AM

Presentation Number: 283.08

Topic: D.02. Auditory System

Support: NIDOCD DC009259

Title: Downregulation of cortical inhibition but not map reorganization underlies tinnitus

Authors: *S. YANG[1,2], A. MIYAKAWA[3], S. BAO[4];
[1]Univ. of California at San Francisco, San Francisco, CA; [2]Dept. of Biomed. Sci., City Univ. of Hong Kong, Kowlong, Hong Kong; [3]Helen Wills Neurosci. Institute, Univ. of California at

Berkeley, Berkeley, CA 94720, CA; [4]Dept. of Physiol., Univ. of Arizona, Tucson, AZ 85724, AZ

Abstract: Hearing loss is the biggest risk factor for tinnitus and hearing loss-related pathological changes in the auditory pathway have been hypothesized as the mechanism underlying tinnitus. However, due to the comorbidity of tinnitus and hearing loss, it has been difficult to differentiate between neural correlates of tinnitus and consequences of hearing loss. In this study, we dissociated tinnitus and hearing loss in FVB mice, which exhibit robust resistance to tinnitus following noise-induced hearing loss. Furthermore, knockdown of glutamate decarboxylase 65 (GAD65) expression in auditory cortex by RNA interference gave rise to tinnitus in normal-hearing FVB mice. We found that tinnitus was correlated with down-regulation of GAD65 in the auditory cortex. By contrast, cortical map distortions, which have been hypothesized as a mechanism underlying tinnitus, were correlated with hearing loss but not tinnitus. Our findings suggest new strategies for the rehabilitation of tinnitus and other phantom sensation, such as phantom pain.

Disclosures: **S. Yang:** None. **A. Miyakawa:** None. **S. Bao:** None.

Nanosymposium

283. Perception and Auditory Cortex

Location: S402

Time: Monday, October 19, 2015, 8:00 AM - 10:15 AM

Presentation Number: 283.09

Topic: D.02. Auditory System

Support: United States-Israel Binational Science Foundation Grant 2013400 (A.G.)

Rothberg Research Award in Human Brain Imaging (R.R.)

Title: The role of auditory cortex in mid-level audition

Authors: *A. S. GREENBERG[1], R. RANDALL[2];
[1]Dept. of Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI; [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Regions of the auditory cortex are associated with many stages of processing, from low-level analysis of sound information all the way to stream segregation. It is largely accepted that while auditory cortex supports the construction of streams and auditory perceptual organization, frontoparietal regions are needed for cognitive processing such as decision-making, memory, and emotional sound content. Here we explore the role auditory cortex plays in

judgments of musicality, a psychological construct that may be considered mid-level (possibly equivalent to face/scene processing in vision). Musicality is neither directly related to auditory object representations, nor is it considered part of higher-order cognition (i.e., concepts, attention, problem-solving). It is, therefore, an open question as to whether musicality judgments rely on frontoparietal cortex or can be computed in auditory cortex. In Exp. 1, subjects evaluated 50 ten-tone sequences according to how musical they judged them to be. A unique corpus was designed that controlled for timbre, pitch content, pitch range, rhythm, note and sequence length, and loudness. Musicality ratings were on a scale of one (not musical) to five (very musical). Stimulus ratings showed significantly distinct groupings of musical versus non-musical sequences. To test the degree to which low-level organizational parameters affect musicality ratings, in Exp. 2 we manipulated the 7 most musical and 7 least musical sequences by changing auditory scene analysis (ASA) cues for a subset of tones. Changes in Amplitude and Timbre lead to a significant reduction in musicality ratings, whereas changes in the Attack of the tone onsets increased the musicality ratings. These results suggest that ASA cues have a direct influence over music processing. In an effort to explore whether similar neural structures are involved in processing music versus ASA cues, in Exp. 3 we used fMRI during a one-back memory task on the same stimuli from Exp. 2. We found that differences in processing musical versus nonmusical sequences correlated with a large area of auditory cortex and almost no frontoparietal regions. However, our ASA manipulations evoked activation in a set of dorsolateral areas including MFG, SMA, and supramarginal gyrus. These data suggest that auditory cortex supports judgments of musicality without significant contributions from frontoparietal regions. Mid-level auditory representations may, thus, be confined to the superior temporal lobe where attention, memory, and motor systems can act upon them.

Disclosures: A.S. Greenberg: None. **R. Randall:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.01

Topic: D.04. Vision

Support: ESRC grant ES/I01135X/2

Title: Form- and motion-based face spaces encoded in the human brain

Authors: *N. FURL[1,2], M. LOHSE[2,3];
[1]psychology, Royal Holloway, Univ. of London, Egham, United Kingdom; [2]MRC Cognition and

Brain Sci. Unit, Cambridge, United Kingdom; [3]Oxford Neurosci., University of Oxford, United Kingdom

Abstract: In static photographs, facial identities and expressions can be recognized accurately based only on form and shape. In real-world settings, identity and expression perception is robust, and sometimes even facilitated, in the presence of facial motion. We aimed to understand the contributions of form and motion to facial perception and to reveal the coding of these attributes in the brain. In particular, we focused on the information carried by oscillatory responses. We employed a "face space" approach, which characterizes face representations as distances in a dissimilarity space. We obtained dissimilarities behaviorally by asking participants to judge either form- or motion-based dissimilarity for 36 videos (2 sec each) of six facial identities who expressed six possible emotional expressions. These form-based dissimilarities accounted for differences in identity (and, to a lesser extent, expression) while motion-based dissimilarities accounted only for differences in facial expression. We then identified brain responses with similar face space structure to the behaviorally-measured form- and motion-based dissimilarities. We obtained magnetoencephalography (MEG) scans in 17 of the same participants and computed dissimilarities based on correlations between the sensor responses to the 36 faces. These dissimilarities were then tested for correspondence with the behavioral form- and motion-based face spaces using representation similarity analysis. We found that form-based spaces (which primarily distinguished identities) were expressed by evoked responses during the M170 component and in induced beta power between 150-1000 msec. Motion-based spaces (which distinguished emotional expressions) manifested in induced beta power between 300 and 1000 msec. While some past studies have suggested a role for sustained beta power in coding for fearful expressions, we show that it indexes population coding of basic information used to perceive identities and expressions in realistically dynamic contexts.

Disclosures: **N. Furl:** None. **M. Lohse:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.02

Topic: D.04. Vision

Support: NIH R01 EY 020834

Title: A neural basis of facial action recognition in humans

Authors: *R. SRINIVASAN[1], J. D. GOLOMB[2], A. M. MARTINEZ[1];
[1]Electrical and Computer Engin., [2]Dept. of Psychology, The Ohio State Univ., Columbus, OH

Abstract: By combining different facial muscle actions, called action units, humans can produce an extraordinarily large number of facial expressions. Computational models and studies in cognitive science and social psychology have long hypothesized the brain needs to visually interpret these action units to understand other people's actions. Surprisingly, no studies have identified the neural basis of the visual recognition of these action units. Here, using functional Magnetic Resonance Imaging and an innovative machine learning analysis approach, we identify a consistent and differential coding of action units in the brain. Crucially, in a brain region thought to be responsible for the processing of changeable aspects of the face, multi-voxel pattern analysis could decode the presence of specific action units in an image. This coding was found to be consistent across people, facilitating the estimation of the perceived action units on participants not used to train the multi-voxel decoder. Furthermore, this coding of action units was identified when participants attended to the emotion category of the facial expression, suggesting an interaction between the visual analysis of action units and emotion categorization as predicted by the computational models mentioned above. These results provide the first evidence for a representation of action units in the brain and suggest a mechanism for the analysis of large numbers of facial actions and a loss of this capacity in psychopathologies.

Disclosures: R. Srinivasan: None. **J.D. Golomb:** None. **A.M. Martinez:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.03

Topic: D.04. Vision

Support: David and Lucile Packard Foundation Grant

Title: Parts-based representations of perceived face movements in the superior temporal sulcus

Authors: *B. M. DEEN, R. SAXE;
MIT, Cambridge, MA

Abstract: Facial motion is a primary source of social information about other humans, regarding their emotional state, direction of attention, and vocal utterances. Prior fMRI studies have identified regions of the superior temporal sulcus that respond specifically to perceived face

movements (termed fSTS), but little is known about the nature of motion representations in these regions. Do neural responses in fSTS contain information about specific perceived face movements? If so, does this region represent complex face movements holistically, or in terms of component movements of different parts of the face? The present study addresses these questions using fMRI and multivoxel pattern analysis. Participants (N=24) viewed a set of dynamic face movements, including four eye/eyebrow movements, four mouth movements, and combinations of these, performed by one of two actors and presented in one of four visual positions. Our results demonstrate that fSTS response patterns contain information about face movements, including subtle distinctions between types of eye and mouth movements. These representations generalize across the actor performing the movement, and across small differences in visual position. Critically, patterns of response to combined movements could be well predicted by linear combinations of responses to individual eye and mouth movements, pointing to a parts-based representation of complex face movements. These results indicate that the fSTS plays an intermediate role in the process of inferring social content from visually perceived face movements, containing a representation that is sufficiently abstract to generalize across low-level visual details, but still tied to the kinematics of face part movements.

Disclosures: B.M. Deen: None. **R. Saxe:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.04

Topic: D.04. Vision

Support: research supported by the NIMH IRP

Title: Dorsal stream contribution to the configural processing of faces

Authors: *V. ZACHARIOU[1], Z. N. SAFIULLAH[2], L. G. UNGERLEIDER[2];
[1]LBC:Section on Neurocircuitry, [2]Lab. of Brain and Cognition, NIH/NIMH, Bethesda, MD

Abstract: Human face recognition and face individuation are often attributed to configural processing (Maurer et al., 2002). That is, processing of the spatial relationships among the shape features of a face, such as the distance between the eyes, nose and mouth. The configural processing of faces is thought to be mediated by brain regions within the ventral visual pathway, more specifically brain regions involved in face perception such as the fusiform face area (Zhang, Liu & Xu, 2015). Configural processing, however, likely involves visuospatial

mechanisms, which raises the question of whether brain regions within the dorsal visual pathway, the main location-processing network of the brain, contribute to this process and, if so, whether the dorsal stream is necessary for the configural processing of faces. Here, we explored this issue in human adults performing a same-different face task while undergoing functional magnetic resonance imaging (n = 21) and, in a separate experiment, while undergoing transcranial magnetic stimulation (TMS; n = 20). Two face exemplars presented simultaneously on a screen could differ in terms of the shape (*featural differences*) or the spatial configuration of their shape features (*configural differences*). Differences (featural/configural) were matched in difficulty (RT and accuracy), number and pattern of eye-fixations. Within a-priori localized, dorsal stream regions (identified using an independent, distance-estimation localizer), configural differences led to significantly stronger activation compared to featural differences and the magnitude of this activation correlated with behavioral performance. Further, bilateral transcranial magnetic stimulation centered at the most active voxel of the distance-estimation localizer task (identified separately for each participant within dorsal cortex) significantly impaired participants performance on configural but not featural difference detections between faces, in comparison to no TMS trials and TMS on the vertex (the control site). We conclude that location-processing mechanisms within the dorsal visual pathway process the configuration of face features and, further, appear to be necessary for the configural processing of faces.
References Maurer, D., Le Grand, R., & Mondloch, C. J. (2002). The many faces of configural processing. *Trends in cognitive sciences*, *6*(6), 255-260. Zhang, J., Liu, J., & Xu, Y. (2015). Neural Decoding Reveals Impaired Face Configural Processing in the Right Fusiform Face Area of Individuals with Developmental Prosopagnosia. *The Journal of Neuroscience*, *35*(4), 1539-1548.

Disclosures: V. Zachariou: None. **Z.N. Safiullah:** None. **L.G. Ungerleider:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.05

Topic: D.04. Vision

Support: NIH Grant R01MH091848

Title: Social-affective dimensions underlie cortical tuning to face images in the human brain

Authors: *A. COWEN[1], S. A. ABDEL-GHAFFAR[2], J. L. GALLANT[1], S. J. BISHOP[2]; [2]Psychology, [1]UC Berkeley, Berkeley, CA

Abstract: Information about faces is represented in occipital temporal (OT) regions, including occipital face area (OFA), fusiform face area (FFA), and posterior superior temporal sulcus (pSTS). A dominant view has been that structural information is represented in OFA, identity-related features such as gender and race in FFA, and expression-related features in pSTS (Haxby et al., Trends in Cogn Sci 4:223-33, 2000). However, other studies have reported representation of expression in FFA and of identity in pSTS (Fox et al., Neuroimage 44:569-80, 2009). These conflicting reports may to some extent reflect the small stimulus sets typically used in fMRI experiments on faces. Here we used a large naturalistic stimulus set and multi-feature voxel-wise encoding models (Kay et al., Nature 452:352-5, 2008) to better recover the representations of face-related information in the brain. We collected BOLD data from 6 subjects while they viewed 941 face images. We then used regularized linear regression to fit 3 separate feature spaces to individual voxel timecourses: [1] a Gabor wavelet model, [2] a model describing the locations of 66 structural landmarks (e.g. corners of the eyes), and [3] a model based on 102 semantic features. Model fit was validated on a voxel-wise basis by assessing prediction accuracy using a separate dataset. In non-retinotopic OT cortex including OFA, FFA, and pSTS, the semantic model predicted activity more accurately than the other two models, suggesting these regions are more tuned to semantic than low-level or structural information. Next we performed independent component analysis on the semantic model weights to explore tuning to semantic features across OT cortex. Three independent components (ICs) emerged consistently across subjects. To interpret these ICs, we correlated them with hypothetical dimensions derived from separate behavioral ratings of the images. The ICs were highly correlated with [1] positive (vs. negative) expressions and social value of traits (e.g. attractiveness), [2] arousal, and [3] dominance (vs. submissiveness), respectively. A t-test contrasting identity- vs. expression-related feature coefficients was significant only for IC2, which had greater loadings on expression-related features. ICs 1 and 3 closely resembled joint expression and social trait dimensions derived by Oosterhof and Todorov (PNAS 105:11087-92, 2008) from behavioral ratings. In summary, our findings indicate widespread tuning to semantic face features across OT cortex, with complex representation of social-affective information crossing boundaries of identity and expression.

Disclosures: **A. Cowen:** None. **S.A. Abdel-Ghaffar:** None. **J.L. Gallant:** None. **S.J. Bishop:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.06

Topic: D.04. Vision

Support: NIMH IRP

Title: Imaging amygdala connections to the monkey face-processing system using electrical stimulation

Authors: *A. MESSINGER, J. M. SEIDLITZ, R. B. H. TOOTELL, L. G. UNGERLEIDER; Lab. of Brain and Cognition, NIMH, Bethesda, MD

Abstract: In both human and monkey imaging studies, the amygdala responds more to emotional facial expressions than neutral expressions. We hypothesized that the amygdala conveys information about the emotion a face is expressing to regions of the monkey inferior temporal cortex, called face patches, that respond significantly more to images of faces than non-face objects. To map where the amygdala projects, we electrically stimulated the amygdala in two rhesus monkeys and used functional MRI (fMRI) to identify regions functionally activated by projections arising in the amygdala. The pattern of functional activation was strongly dependent on which part of the amygdala was stimulated. Stimulation of both the lateral nucleus and the ventral (parvicellular) subdivision of the basal nucleus of the amygdala resulted in activation of the stimulated amygdala, some subcortical targets, and a few higher order sensory areas in the stimulated hemisphere. There was little or no significant activation of any of the face or object patches, which had been previously mapped in these animals using fMRI. In contrast, stimulation in the dorsal and intermediate subdivisions of the basal nucleus resulted in widespread bilateral activation of frontal, insular, auditory, and visual cortex. In particular, stimulation of these subdivisions significantly activated both face and object patches in the ventral visual stream. To quantify the relative strength of these projections, we averaged the stimulation-induced signal change across all voxels in the face and object patches. In the stimulated hemisphere, there was significantly stronger activation of the face patches than the object patches in both monkeys (2.0% vs 1.3%, 1-tailed t-test, $p<0.005$). Even in the contralateral hemisphere, where the effects of stimulation were weaker overall, projections to the face patches were stronger than to the object patches (1.1% vs. 0.6%, $p<0.002$). Thus, feedback from the amygdala to visual areas involved in form processing preferentially target areas selective for face processing over areas selective for processing of inanimate objects. These amygdala projections to the face patches are likely important for deciphering the emotional state of other from their facial expressions.

Disclosures: A. Messinger: None. **J.M. Seidlitz:** None. **R.B.H. Tootell:** None. **L.G. Ungerleider:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.07

Topic: D.04. Vision

Support: NSERC Individual Discovery Grant

Connaught New Researcher Award

Title: The time course of human face identification - a pattern analysis of EEG signals

Authors: *D. NEMRODOV[1], M. NIEMEIER[2], J. N. Y. MOK[2], A. NESTOR[2];
[1]Univ. of Toronto Scarborough, Scarborough, ON, Canada; [2]Dept. of Psychology at Scarborough, Univ. of Toronto, Toronto, ON, Canada

Abstract: An extensive body of work documents the time course of neural face processing in human visual cortex. However, the majority of this work focuses on specific temporal landmarks, such as N170 and N250 ERP components, derived through univariate analyses of EEG data. Here, we re-evaluate the functional significance of these landmarks as we attempt to move beyond the leading theoretical and methodological framework by the application of pattern analyses to EEG data. Specifically, we investigate the time course of stimulus discriminability as related to identity recognition as well as to gender and expression recognition. To this end, we used 64 electrodes (10-20 system) to record electrophysiological activity from the scalps of 10 participants while they viewed images of 4 different individuals displaying different emotional expressions. Pattern classification was then conducted both in time (for each electrode) and in space (across electrodes) to investigate the spatiotemporal profile of face discrimination. Our results confirm the significance of traditional ERP components in face processing. At the same time though, they support the idea that the temporal profile of face recognition is incompletely described by such components. First, we show that signals associated with different facial identities can be discriminated from each other outside the scope of these components, as early as 100ms following stimulus presentation. Next, electrodes associated with traditional ERP components as well as, critically, those not associated with such components are shown to contribute valuable information to stimulus discriminability. And last, the levels of EEG-based pattern discrimination are found to correlate significantly with recognition accuracy across subjects confirming the relevance of these methods for bridging brain and behavior data. Altogether, the current results shed new light on the fine-grained time course of neural face processing and showcase the value of novel methods for pattern analysis to investigating fundamental aspects of visual recognition.

Disclosures: **D. Nemrodov:** None. **M. Niemeier:** None. **J.N.Y. Mok:** None. **A. Nestor:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.08

Topic: D.04. Vision

Support: a Grant-in-Aid for Scientific Research on Innovative Areas, Sparse Modeling (25120004), from the Japan Society for the Promotion of Science (JSPS)

a Grant-in-AID for Scientific Research 26240021

Title: Principles for mapping view tuned neurons in the face selective region of anterior inferotemporal cortex revealed by dense neural recordings

Authors: A. SASAKI[1,2], C.-P. LIN[1,3], M. MATSUDA[1,2], T. SATO[1], G. UCHIDA[1], C. HUNG[4,3], *M. TANIFUJI[1,2];
[1]Riken BSI, Saitama, Japan; [2]Dept. of Complexity Sci. and Engin., The Univ. of Tokyo, Chiba, Japan; [3]Institue of Neuroscience, Brain Res. Ctr., Natl. Yang-Ming Univ., Taipei, Taiwan; [4]Dept. of Neurosci., Georgetown Univ., Washington, DC

Abstract: In macaque inferior temporal (IT) cortex, multiple face selective regions were identified by fMRI (Freiwald and Tsao, 2010). They reported that one of face selective regions (AL patch; spanning for several millimeters) included neurons that were tuned to mirror symmetric views of faces. However, the spatial arrangement of these neurons within the face region is not well understood. Here, we used electrode arrays and identified a face region (potentially corresponding to AL patch) in anterior IT cortex by Face Selective Index (FSI) (for FSI, see Freiwald and Tsao, 2010) (Fig.1, left panel). Then, we investigated spatial arrangement of neurons with respect to preferred viewing angles in the face region. The electrode arrays consisted of 8 shanks (spacing, 200 μm) with 8 electrical contacts each (spacing, 200 μm). We found that (1) neurons were view selective, (2) there was no representation for viewing angles more than 90 degree from the front face, (3) neurons responded to mirror-symmetric viewing angles, and (4) preferred viewing angles gradually shifted from shank to shank making viewing angles to be continuously mapped (Fig. 1, right panel). Modeling of functional maps with the preferred viewing angles from the discrete samples of neural responses suggested that the face region contained multiple maps where preferred views were mapped continuously around 90 degree representation (Fig. 2). In this way, the face region was covered by the maps without discontinuity. Thus, there are two principles for functional organization of facial views in the face region, local continuity and global continuity across the maps. These maps may imply

functionally distinct sub-regions within the face region such as distinct functions between V1 and V2. Previously identified columnar regions with systematic arrangement of preferred viewing angles (spanning for ~0.5 x 1.2 mm) in anterior IT cortex (Wang et al. 1996, 1998) may consist of a part of view maps within the face selective region.

Fig.1 Face selective sub-region determined by FSI (Left panel) and mapping of preferred viewing angle within the region (Right panel). Here, left and right views were combined together for averaging since responses were mirror symmetric. Each circle indicates the location of the shank penetrated. Colors indicate FSI (Left) and the preferred viewing angle of each shank-averaged response (Right).

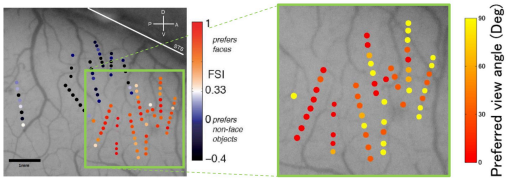
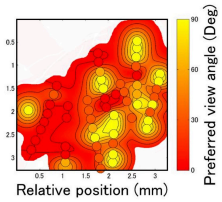


Fig. 2 Kernel modeling predicted a possible functional map within face-selective region based on preferred viewing angles (color-coded).



Disclosures: **A. Sasaki:** None. **C. Lin:** None. **M. Matsuda:** None. **T. Sato:** None. **G. Uchida:** None. **C. Hung:** None. **M. Tanifuji:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.09

Topic: D.04. Vision

Support: NSF-STC-1231216

Title: Unsupervised learning of invariant face representations from natural video in a model of the macaque face processing system

Authors: Q. LIAO[1], *J. Z. LEIBO[2], T. POGGIO[1];
[1]MIT, Cambridge, MA; [2]DeepMind Technologies Ltd, London, United Kingdom

Abstract: Populations of neurons in the anterior medial (AM) face patch maintain an explicit code for face identity that also tolerates transformations like position, scale, and viewing angle. This work develops a biologically plausible model of the processing in the macaque face patches leading up to AM. The model is trained in an unsupervised fashion using natural videos collected from YouTube. It exploits the temporal continuity of the visual world by assuming that frames from nearby times will have invariant identity content. By associating frames in this manner, a representation that tolerates whatever transformations occurred in the video can be achieved. Intriguingly, this model recapitulates several otherwise mysterious aspects of the macaque face patch system.

Disclosures: Q. Liao: None. **J.Z. Leibo:** None. **T. Poggio:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.10

Topic: D.04. Vision

Support: PFV/10/008;

Odysseus G.0007.12N

IUAP VII/11

FWO

Title: Two parallel streams for face- and body processing

Authors: *E. PREMEREUR[1], J. TAUBERT[1], P. JANSSEN[1], W. VANDUFFEL[1,2,3], R. VOGELS[1];
[1]KU Leuven, Leuven, Belgium; [2]Harvard Med. Sch., Boston, MA; [3]Athinoula A. Martinos Ctr. for Biomed. Imaging, Boston, MA

Abstract: Face patches in macaque inferotemporal (IT) cortex (e.g. Tsao et al., 2003, 2008) form an interconnected network as shown in combined electrical microstimulation (EM) - fMRI experiments (Moeller et al., 2008). More recent research showed the existence of body patches in macaque IT, adjacent to and even partially overlapping with regions more activated by faces (e.g. Pinsk et al., 2005; Popivanov et al., 2012, 2014). We aimed to directly compare the effective connectivity of face patches ML and AL with that of the mid STS body patch using fMRI-EM (Ekstrom et al., 2008). We first identified face and body patches based on fMRI and single-unit recordings in two macaque monkeys (G and D). During the subsequent anesthetized fMRI-EM experiments, EM blocks were interleaved with no-EM blocks. In EM blocks, the individual patches were stimulated at 1 mA using a platinum-iridium electrode (impedance: 40-150 kΩ) inserted in a recording grid. EM lasted for 250 ms (pulsewidth: 0.48 ms, frequency: 200 Hz) and was repeated on average every 2 seconds. Both monkeys were injected with a contrast agent and scanned on a 3T Siemens MR scanner with an 8-channel phased-array coil. Data were acquired in two sessions per animal for every EM-site. Corroborating previous research (Moeller et al., 2008), EM of AL and ML caused increased fMRI activations in both animals throughout the face patches in IT. EM of the mid STS body patch elicited increased activation in a network of IT areas, which was largely segregated from the network activated by AL-EM ($p < 0.05$, FWE corrected). A conjunction analysis only showed a few voxels co-activated by AL-EM and body-EM. We also obtained a negative correlation between the voxel's t-score values for the contrasts AL-EM vs no -EM and body-EM vs no-EM (Spearman rank correlation, monkey D: -0.35, monkey G: -0.35), indicating that voxels significantly driven by one contrast were not activated by the other. Furthermore, ML-EM and body-EM also increased activation in two separate networks in anterior IT ($p < 0.05$, FWE corrected), although co-activated voxels were found in posterior IT (conjunction analysis, $p < 0.05$, FWE corrected). The latter finding may be due to the very close proximity of both patches and spill-over of the EM effect from the target to the neighbouring patch. Finally, similar to EM of the face patches, body-EM increased activation throughout the body-selective regions. These results suggest that face and body patches form two interconnected hierarchical networks that are largely separated within monkey IT.

Disclosures: E. Premereur: None. **J. Taubert:** None. **P. Janssen:** None. **W. Vanduffel:** None. **R. Vogels:** None.

Nanosymposium

284. Visual Processing: Representation of Faces and Bodies

Location: S401

Time: Monday, October 19, 2015, 8:00 AM - 10:45 AM

Presentation Number: 284.11

Topic: D.04. Vision

Title: Decoding neural activity in response to approaching familiar and unfamiliar people in face and body selective areas

Authors: ***C. HAHN**[1], P. PHILLIPS[2], A. J. O'TOOLE[1];
[1]Behavioral and Brain Sci., The Univ. of Texas At Dallas, Richardson, TX; [2]Natl. Inst. of Standards and Technol., Gaithersburg, MD

Abstract: The goal of this study was to examine the neural correlates of naturalistic,, real world recognition of a person approaching from a distance. We investigated the time course of neural response differentiation for familiar and unfamiliar people across a network of face- and body-selective brain regions in the dorsal and ventral visual processing streams. Specifically, we applied pattern classification analysis to discriminate these neural activity patterns at multiple time points in the approach, with time points corresponding to different viewing distances. First, human participants (N = 12) were visually familiarized with identities using multiple, diverse videos. Next, in a 3T fMRI scanner, they viewed 8s videos of people (half familiar/half unfamiliar) approaching a camera from a distance of ~13.6m. A pattern classifier was applied to voxels in face- and body-selective ROIs to discriminate neural responses to familiar and unfamiliar people. Classification accuracy (d') was computed separately across the 4-TR video timeline of the approach, from the most distant view (TR1) to the closest view (TR4). The neural responses to familiar and unfamiliar people were discriminable during TR3 ($M = 0.77$, $SE = 0.17$, $p = .001$) in an ROI that contained body-selective voxels in ventral-temporal cortex (bodies > objects + scrambled images, $p < .0001$, uncorrected). With analogously defined face-selective voxels, classification was not above chance for any TR. In classically defined face- and body-selective regions, accuracy also peaked in TR3 in the left fusiform face area ($M = 0.45$, $SE = 0.11$, $p = .001$) and right fusiform body area ($M = 0.55$, $SE = 0.14$, $p = .003$). Notably, in both the right fusiform face area (rFFA) ($M = 0.50$, $SE = 0.16$, $p = .009$) and in the anatomically defined right posterior superior temporal sulcus (rpSTS) ($M = 0.54$, $SE = 0.21$, $p < .0001$), classifier accuracy was highest at the most distant view (TR1). In lower-order visual areas, including the occipital face area and extrastriate body area, classification was at chance for all TRs. In conclusion, a neural familiarity signal is detectable for people viewed from a distance in both the dorsal (rpSTS) and ventral (rFFA) visual streams. At closer distances, only ventral face- and body-selective areas signaled familiarity. Notably, body-selective areas differentiated the neural response to familiar and unfamiliar people more accurately than face-selective areas. In the context of previous studies, these findings suggest the importance of motion in triggering differential responses to familiar and unfamiliar people.

Disclosures: **C. Hahn:** None. **P. Phillips:** None. **A.J. O'Toole:** None.

Nanosymposium

285. Energy Metabolism and Cardiovascular Regulation

Location: S405

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 285.01

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Title: A1 and A3 adenosine receptors mediate hypothermia via distinct mechanisms

Authors: *J. CARLIN[1], D. K. TOSH[2], A. PANYUTIN[3], R. A. PIÑOL[4], K. A. JACOBSON[2], O. GAVRILOVA[3], M. L. REITMAN[4];
[1]DEOB, Natl. Inst. of Hlth., Bethesda, MD; [2]Lab. of Bioorganic Chem., NIH, Bethesda, MD; [3]Mouse Metabolism Core, [4]Diabetes, Endocrinology, Obesity Br., NIDDK/National Inst. of Hlth., Bethesda, MD

Abstract: Introduction: Pharmacological activation of adenosine receptors in mice and rats causes torpor, which is characterized by reduced body temperature (hypothermia) and reduced physical activity. The current experiments examined the role of adenosine agonists at the A_1AR and A_3AR in eliciting these effects. Methods: Adenosine agonists were administered intraperitoneally (i.p.) or intracerebroventricularly (i.c.v.) and core body temperature and physical activity were monitored by telemetry in freely active wild type, *Adora1-/-*, and *Adora3-/-* mice. Results: All agonists tested i.p. (MRS5474; N^6-cyclopentyladenosine, CPA; N^6-cyclohexyladenosine, CHA; 5'-chloro-5' deoxy-ENBA, Cl-ENBA; and MRS5698) caused dose-dependent hypothermia and decreased physical activity in wild type mice. Hypothermia induced by A_3AR agonist MRS5698 was abolished in *Adora3-/-*, but not in *Adora1-/-,* mice, demonstrating that MRS5698 (10 mg/kg) is selective for A_3AR. A_3AR agonist, but not A_1AR agonists induced hypothermia was prevented by pretreatment with histamine H_1 antagonists (i.p.). Interestingly, the hypothermia elicited by commonly used A_1AR agonists CPA and CHA was at least partially reduced in the *Adora3-/-* . We found CPA (0.3 mg/kg), CHA (0.05 mg/kg), and Cl-ENBA (3 mg/kg), at doses that are in the range typically used to study A_1AR function, to also cause hypothermia via an A_3AR mechanism. Conclusions: These results demonstrate that activation of both A_1AR and A_3AR can cause hypothermia through independent mechanisms. Our results also suggest that nucleoside derivatives commonly used as selective A_1AR agonists may also activate the A_3AR *in vivo*, at the doses used to produce hypothermia.

Disclosures: J. Carlin: None. **D.K. Tosh:** None. **A. Panyutin:** None. **R.A. Piñol:** None. **K.A. Jacobson:** None. **O. Gavrilova:** None. **M.L. Reitman:** None.

Nanosymposium

285. Energy Metabolism and Cardiovascular Regulation

Location: S405

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 285.02

Topic: E.04. Autonomic Regulation

Title: Brain endothelial MYD88-dependent signaling in inflammation-induced fever

Authors: *E. MIRRASEKHIAN[1], D. ENGBLOM[2];
[1]Linköping Universitet, Linköping, Sweden; [2]Linköping Univ., Linköping, Sweden

Abstract: Circulating cytokines play a pivotal role in immune-to-brain signaling, particularly in brain mediated adaptive response such as fever. We have previously shown that brain endothelial prostaglandin E2 is an essential mediator for the febrile response and that pyrogenic interleukin 6 (IL-6) mediates prostaglandin E2 induction via brain endothelial IL-6 receptor α and Signal Transducer and Activator of Transcription 3 (STAT-3). However, IL-6 injected peripherally is not sufficient to induce fever, which indicates that other circulating mediators are also involved. Cytokines of the IL-1 family and toll-like receptor ligands such as lipopolysaccharide are obvious candidates. We generated two mouse lines with selective deletion of myeloid differentiation primary response gene 88 (MYD88), an intracellular protein in the TLR4/IL-1R signaling pathway, in the brain endothelium and in myeloid cells. Upon immune challenge with lipopolysaccharide, mice lacking MYD88 in brain endothelium showed strongly attenuated febrile responses whereas mice lacking MyD88 in myeloid cells displayed normal fevers. Our findings show that MyD88-dependent signaling in the brain endothelium is critical for the febrile response.

Disclosures: E. Mirrasekhian: None. **D. Engblom:** None.

Nanosymposium

285. Energy Metabolism and Cardiovascular Regulation

Location: S405

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 285.03

Topic: E.04. Autonomic Regulation

Title: Thermogenic effects of bombesin receptor subtype-3 (BRS-3) activation in selective brain nuclei

Authors: *R. A. PINOL, S. H. ZAHLER, C. XIAO, M. L. REITMAN;
NIDDK, NIH, Bethesda, MD

Abstract: Bombesin receptor subtype-3 (BRS-3) is an orphan G protein-coupled receptor expressed in several brain regions, including hypothalamic areas such as the paraventricular nucleus of the hypothalamus (PVH), dorsomedial hypothalamus (DMH), and arcuate nucleus (Arc). BRS-3 regulates energy homeostasis since its agonists stimulate brown adipose tissue (BAT) activation through sympathetic activation and suppress food intake. We measured BAT temperature in urethane anesthetized mice and probed brain regions with stereotactic injections of the BRS-agonist MK-5046 (1 mg/ml). Large volume (700 nl) intrahypothalamic injections of MK-5046 raised BAT temperature by 0.75 ± 0.11 vs 0.08 ± 0.14 °C after vehicle. Small volume (25 nl), nucleus-targeted MK-5046 injections in the DMH and Arc, but not in the PVH, raised BAT temperature. These results confirm that hypothalamic activation of BRS-3 increases BAT temperature. More specifically, these results suggest that the thermogenic effects of BRS-3 activation occur selectively, mediated by a subset of BRS-3-expressing neurons.

Disclosures: **R.A. Pinol:** None. **S.H. Zahler:** None. **C. Xiao:** None. **M.L. Reitman:** None.

Nanosymposium

285. Energy Metabolism and Cardiovascular Regulation

Location: S405

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 285.04

Topic: E.04. Autonomic Regulation

Support: NIH Grant HL127975

NIH Grant HL007284

NIH Grant HL28785

NIH Grant HL74011

Title: Blood pressure regulation by the C1 neurons determined by optogenetic acute loss of function in conscious rats

Authors: *I. C. WENKER, C. ABE, R. L. STORNETTA, P. G. GUYENET;
Pharmacol., Univ. of Virginia, Charlottesville, VA

Abstract: The C1 neurons of the rostral ventrolateral medulla (RVLM) have a mixed catecholaminergic and glutamatergic phenotype, are activated by stressors such as hypoxia, hypotension and hemorrhage and regulate sympathetic tone to cardiovascular organs. In anesthetized animals C1 neurons are extremely active and probably essential to maintain BP but their contribution to BP regulation in conscious animals is unclear. Optogenetic C1 cell activation, using Channelrhodopsin, increases blood pressure (BP) and sympathetic nerve activity (SNA) in conscious rats but selective destruction of these neurons alters BP very little. The lack of effect of these lesions could be explained by adaptive changes to C1 cell lesion or by the fact that the C1 neurons contribute little to BP at rest. In order to measure the contribution of the C1 cells to BP in intact conscious animals we decided to examine the effect produced by transient, bilateral and reversible inhibition of these neurons. To do this C1 neurons were bilaterally transduced to express the light-driven proton pump Archaerhodopsin (ArchT) (lentiviral vector, PRSx8 promoter). Single-unit recordings in 3 anesthetized rats revealed that a majority (7/11) of putative C1 neurons (i.e. barosensitive) were reversibly inhibited by laser (530 nm, 3-4 mW) light (82.6 ± 11.6 % reduction in action potential firing, $p = 0.01$). For conscious loss of function studies, C1 neurons of 5 rats were bilaterally transduced to express ArchT and fiberoptic/ferrule assemblies were implanted. Four to six weeks later, telemetric BP probes were implanted. After recovery, rats were placed in a plethysmography chamber on top of a wireless receiver, to record ventilation and BP. Bilateral inhibition for 10 s had virtually no effect on BP in conscious unstressed rats under normoxic conditions (21% FiO_2). However, the ArchT-induced hypotension increased significantly during hypoxia (-11.4 ± 1.9 mmHg in 10% O_2 versus -2.9 ± 0.9 mmHg in 21% O_2, $p = 0.001$). By contrast, ArchT-induced hypotension was unchanged by normoxic hypercapnia (6% $FiCO_2$; -3.5 ± 1.2 mmHg vs. -2.9 ± 0.9 mmHg without added CO_2, $p = 0.465$). The addition of 3% $FiCO_2$ to 10% FiO_2 reduced ArchT-induced hypotension (7.4 ± 1.0 mmHg vs. 11.4 ± 1.9 mmHg in hypoxia alone, $p = 0.035$). In conclusion, the C1 neurons seem relatively inactive in normoxic unstressed rats. During hypoxia, these neurons are activated and prevent BP from falling, presumably by increasing SNA. The hypoxic activation of the C1 neurons could be intrinsic, directly mediated by peripheral chemoreceptors or may be partly arousal- or stress-dependent.

Disclosures: **I.C. Wenker:** None. **C. Abe:** None. **R.L. Stornetta:** None. **P.G. Guyenet:** None.

Nanosymposium

285. Energy Metabolism and Cardiovascular Regulation

Location: S405

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 285.05

Topic: E.04. Autonomic Regulation

Support: CNPq

BIDMC

CAPES

FAPEMIG

PMF NS073613

Title: Dorsal hypothalamic area neurons mediate psychological stress-induced hyperthermia in conscious mice

Authors: *N. L. MACHADO[1,2], S. B. G. ABBOTT[2], P. M. FULLER[2], M. P. FONTES[1], C. B. SAPER[2];
[1]Federal Univ. of Minas Gerais, Boston, MA; [2]Beth Israel Deaconess Med. Ctr. – Harvard Med. Sch., Boston, MA

Abstract: Background/Aims: The dorsomedial hypothalamic region is thought to be critical in adaptive thermoregulatory responses such as psychological stress-induced hyperthermia, though the neural pathways and neurotransmitters are not fully understood. We hypothesize that stress-induced hyperthermia is dependent on glutamatergic neurons in the dorsal hypothalamic area that innervate the raphe pallidus. The aim of the present study was to determine the neurochemical phenotype of RPA-projecting DHA neurons that are active during psychological stress. Further, we determined if chemogenetic inhibition of DHA neurons is capable of preventing stress-induced hyperthermia in conscious mice. Methods and Results: Male VGLUT2-IRES-Cre/GFP (n=4) and VGAT-IRES-Cre/GFP (n=4) were used in these studies. First, anesthetized mice were stereotaxically injected with retrograde tracer, cholera toxin subunit b (CTb), in the RPa. Seven days after CTb microinjections, mice were exposed to a psychological stress: singly housed mice were switched to an empty cage previously occupied by a singly housed male. After two hours, mice were euthanized and processed for immunostaining for CTB and CFOS, a marker of neuronal activation. A majority of CTB immunostained neurons in the DHA were glutamatergic (83%, N=4), with virtually no GABAergic colocalization (N=4). Psychological stress induced a large increase the number of CTB+/VGLUT2+ neurons expressing CFOS (control: 12%, N=2; stress: 34%, N=2). In a separate series of experiments, we bilaterally injected a mixture of AAV-Cre and AAV-Flex-hGlyR-mCherry in the DHA of male C57BL/6 mice. HGlyR is a mutated human glycine receptor in which Ivermectin (hGlyR ligand) (IVM) gates a chloride channel. Two weeks after virus injection, core temperature (Tc) data loggers were implanted in the peritoneal cavity. Following recovery, mice were exposed to psychological stress after vehicle and VM (5mg/kg i.p.). Treatment with IVM reduced the hyperthermic response to psychological stress in mice with injections bilaterally targeted in the DHA (Δ°C 2.67 ± 0.24 after vehicle vs.

1.03 ± 0.35 after IVM, n=3), but had no effect in mice with off-target injections (n=4), or in controls (n=6). Conclusion: These experiments support the idea that a direct glutamatergic projection from DHA to the RPa is required for the hyperthermic response to psychological stress.

Disclosures: N.L. Machado: None. **S.B.G. Abbott:** None. **P.M. Fuller:** None. **M.P. Fontes:** None. **C.B. Saper:** None.

Nanosymposium

285. Energy Metabolism and Cardiovascular Regulation

Location: S405

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 285.06

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: MH078823

MH104506

MH099658

T32NS073547

Title: Hippocampal neurons utilize multiple energy sources during metabolic challenges

Authors: *C. SOBIESKI, A. A. TAYLOR, S. J. MENNERICK;
Dept of Psychiatry, Washington Univ. In St Louis, Saint Louis, MO

Abstract: Neurons are energetically demanding cells; however neurons do not store glycogen or other reserves and require a continuous monosaccharide or monocarboxylate supply. Although debated, neurons may prefer mitochondrial oxidative processing of astrocyte-supplied monocarboxylates over glycolysis. To test preferred fuels, we first investigated effects of energetic challenges on neuronal survival in mixed neuron/astrocyte microcultures. We incubated cells overnight in unsupplemented, glucose-free saline, while blocking glutamate receptors to inhibit excitotoxic contributions. As rated by observers naïve to experimental conditions, neurons survived overnight glucose deprivation but died when further challenged with overnight incubation with additional 30 mM extracellular potassium, meant to deplete ATP reserves. Neuronal survival was increased by the addition of glucose or by pyruvate, suggesting that cell damage reflected metabolic factors. Blocking monocarboxylate transport with 100 μM 4-CIN in glucose-free saline resulted in extensive neuronal death, but survival was improved

with glucose. These results suggest that glucose and astrocyte-derived monocarboxylates can sustain neurons during overnight metabolic stress. To further investigate the effects of astrocyte metabolic support on neuronal function, we studied neurotransmission in microcultures containing or lacking astrocytes (+astrocyte, -astrocyte respectively) maintained overnight in glucose-free saline with or without 15 mM KCl, conditions that permitted survival. In all conditions, key elements of neurotransmission remained functional, assessed by evoked EPSCs. We further challenged glutamatergic neurons with 90 mM extracellular KCl for 30 s to depolarize cells and induce ATP-demanding vesicle recycling. Although we did not detect a significant effect of the overnight 15 mM K^+ treatment on EPSC recovery following acute challenge, an ANOVA revealed that –astrocyte EPSCs recovered less completely than +astrocyte EPSCs ($p<0.01$, $n = 21, 22$). When overnight medium and recording solutions were supplemented with glucose, -astrocyte glutamatergic neurons still exhibited deficient recovery. In summary, neurons are surprisingly resilient to overnight glucose deprivation in mixed cell cultures, and this resilience is mediated by astrocyte-derived monocarboxylates. Although glucose alone can directly improve neuronal survival in the absence of astrocyte-derived monocarboxylates, glucose appears unable to rescue neurotransmission following a combined subchronic and acute energetic challenge in the absence of astrocytes.

Disclosures: C. Sobieski: None. **A.A. Taylor:** None. **S.J. Mennerick:** None.

Nanosymposium

285. Energy Metabolism and Cardiovascular Regulation

Location: S405

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 285.07

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: MH41256

MH041256-26s1

Title: Modulation of voltage-dependent anion channel 1 (VDAC1) in CB1 receptor knockout mice

Authors: *N. P. BOWLES, J. L. QUINTERO, B. S. MCEWEN;
Neurosci., Rockefeller Univ., New York, NY

Abstract: Recently it has been suggested that the endocannabinoid system regulates the function of mitochondria, which play a vital role in supplying cellular energy, inter-organelle

communication, ageing, and signaling cell death. Centrally, mitochondria dysfunction such as bioenergetics defects, mitochondrial DNA mutations, and altered mitochondrial dynamics have been identified as central causal factors in the pathogenesis of neurodegenerative disorders. Activation of the CB1R has been shown to regulate mitochondria biogenesis, alter mitochondrial morphology and physiology, and modulate components of the electron transport chain. Previously it has also been demonstrated that voltage-dependent anion channel 1 (VDAC1), a channel located in the mitochondrial outer membrane and a pivotal component in mitochondria-mediated apoptosis, is a target of cannabidiol. Cannabidiol is not a classical agonist of the CB1R and its functional mechanism remains unknown. Therefore, we investigated the role of CB¬1R signaling on VDAC1 abundance using CB1R knockout mice. Three cohorts of male CB1R knockout mice (c57BL6 background) and their wild-type littermates were generated for this study. For the initial cohort mice were perfused for immunocytochemistry. In the second and third cohorts, the whole hippocampus was extracted for qRT-PCR, western blot, and mitochondrial membrane permeability analysis. Initial findings indicate increased measures of VDAC1 protein in CB1R knockout mice in the CA1, dentate gyrus, and CA3; however, protein levels did not reach significance in the latter. Whole hippocampus mRNA expression of Bax was increased in CB1R knockout mice, whereas expression of Parp1, Parp2, and Apaf-1 was decreased. There were no significant changes in expression of TNFR1 or TNFR2. Collectively these findings demonstrate that CB1R deficient mice have increased mitochondrial membrane permeability and potentially an increased metabolite flux through the VDAC channel. There were no indications in the gene expression of DNA damage in the basal state suggesting increased energy regulation without apoptosis. Results add to current literature that suggests a regulatory role for endocannabinoid signaling in moderating mitochondria permeability.

Disclosures: **N.P. Bowles:** None. **J.L. Quintero:** None. **B.S. McEwen:** None.

Nanosymposium

285. Energy Metabolism and Cardiovascular Regulation

Location: S405

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 285.08

Topic: E.04. Autonomic Regulation

Support: CNPQ

CAPES

FAPEMIG

UFOP

Title: Food restriction changes GABAA and angiotensin II AT1 receptors activity within the paraventricular nucleus of the hypothalamus of female Fisher rats

Authors: *R. C. MENEZES[1], A. M. A. SOUZA[2], L. G. B. T. SANTOS[2], D. A. CHIANCA, Jr[2]; [2]Biol. Sci., [1]Federal Univ. of Ouro Preto- UFOP, Ouro Preto, Brazil

Abstract: Food restriction (FR) model has been widely used as an animal model of the nutritional aspect of anorexia nervosa. Dietary restriction can trigger the development of cardiovascular dysfunctions such as ventricular hypertrophy, hypotension, bradycardia and cardiac arrhythmias. In a recent study, we observed that rats submitted to FR presented an increased activity of endothelial α1 adrenergic receptors, as well as an increased brain angiotensin II AT1 receptor activity. Moreover, it is well known that the PVN is an important brain nucleus that regulates the sympathetic nervous system and can be influenced by the AT1 receptors. Therefore, the goal of this study was to evaluate the blockade of GABAergic and AT1 receptors within the PVN on basal blood pressure and heart rate (HR) of rats submitted to food restriction. Fischer female rats, weighing 220g, were submitted to FR receiving 40% (± 6.0g) of the average intake of the control group for 14 days. On the seventh day of food restriction the rats were submitted to bilateral guide cannula implantation in the PVN. After 7 days, they were catheterized with a polyethylene tube in the femoral artery for recording cardiovascular parameters; mean arterial pressure (MAP) and heart rate (HR). We began the experimental procedures 48 hours after the last surgical procedure. After 14 days, there was a reduction in body weight of approximately 26g in the FR group (C: 201.6g ± 1.8, n=13 vs. FR: 176.1g ± 2.1, n=14; $p<0.05$). Injection of muscimol, a $GABA_A$ agonist, into the PVN increased MAP (C: Δ 1.7 ± 1.6 mmHg, n=6 vs. FR: Δ 9.7 ± 2.2 mmHg, n=7, p=0.0163) and HR (C: Δ -1.2 ± 14.9 bpm, n=6 vs. FR: Δ 80.7 ± 12.8 bpm, n=7, p = 0.0015) in food restricted animals when compared to control. In another experiment we found that the blockade of AT1 receptors within the PVN, with losartan, induced an increase in blood pressure in rats subjected to FR when compared to the control (C: Δ 1.6 ± 1.4 mmHg, n=7 vs. FR: Δ 9.9 ± 3.5 mmHg, n=7; 0.0496). It also led to a reduction in HR in these animals (C: Δ 17.0 ± 11.8 bpm, n=7 vs. FR: Δ -29.7 ± 14.2 bpm, n=7; p = 0.0263). These results suggest that the increase in sympathetic activity in rats with FR may result from changes in $GABA_A$ and AT1 receptors activity within the PVN.

Disclosures: R.C. Menezes: None. **A.M.A. Souza:** None. **L.G.B.T. Santos:** None. **D.A. Chianca:** None.

Nanosymposium

285. Energy Metabolism and Cardiovascular Regulation

Location: S405

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 285.09

Topic: E.04. Autonomic Regulation

Support: Commonwealth of Kentucky Challenge for Excellence Trust Fund

Leona M. and Harry B. Helmsley Charitable Trust

NIH Grant 5 P30 GM103507

Craig H. Neilsen Foundation

University of Louisville Foundation

Jewish Hospital and St. Mary's Foundation

Kentucky Spinal Cord Injury Research Center

Title: Characterizing cardiovascular autonomic dysfunction in individuals with spinal cord injury

Authors: *S. WANG[1], S. ASLAN[1,2], C. FERREIRA[1], J. GUNTER[1], J. WYLES[1], D. WANG[1], S. HARKEMA[1,2];
[1]Dept. of Neurolog. Surgery, Univ. of Louisville, Louisville, KY; [2]Neurosci. Collaborative Ctr., Frazier Rehab Inst., Louisville, KY

Abstract: Recognizing the pattern of autonomic control of the heart and blood vessels is a prerequisite for an effective treatment of abnormal blood pressure (BP) regulation in individuals with spinal cord injury (SCI). The goal of this study was to characterize short-term BP and heart rate (HR) responses to orthostatic stress (sit-up test) in individuals with SCI independent of their diagnoses of sensory-motor impairment scale and level. Continuous finger BP and HR were recorded from 20 subjects with AIS scale graded A, B, C or D, and neural level ranged from C3 to T11, during 15 minutes of supine rest followed by a quick passive sit-up and 15 minutes of quiet sitting. There were diverse BP and HR responses to orthostatic stress among individuals. Specifically, 1) two had normal increases in HR and BP in response to upright position. 2) Four developed orthostatic hypotension with a normal increase in HR. 3) Six had normal increases in HR but no or inadequate BP response. 4) Two had higher than normal HR response but inadequate BP response. 5) Five had no significant HR response but had a BP response. 6) One had no HR or BP response. 7) Finally, one had unstable systolic and diastolic BP responses. We further investigated sympathetic (SNS) and parasympathetic (PNS) control of HR and SNS control of peripheral vasomotion by using indirect indexes from spectral analysis. Results showed that 1) in the four with orthostatic hypotension, responses in index of SNS modulation of vasomotion (low-frequency power of diastolic BP) were lower than other subjects, indicating

impaired SNS control of vasomotion below injury level. 2) Responses in SNS modulation of vasomotion were correlated with responses in systolic BP among all subjects ($r = 0.46$, $p < 0.05$) but were not correlated with completeness of sensory-motor injury.3) In the five with no HR response but had a BP response, shift of cardiac sympatho-vagal balance to SNS dominance (low to high frequency ratio of HR power) were lower than other subjects, indicating impaired SNS control of HR in these subjects. 4) Responses in cardiac sympatho-vagal balance were correlated with HR responses among all subjects ($r = 0.64$, $p<0.004$) but were not correlated with completeness of sensory-motor injury. These results confirmed impaired SNS control of HR and peripheral vasomotion after SCI and the usefulness of indirect measures of autonomic functions to assess autonomic impairment, and also indicated the importance of recognizing the pattern of autonomic impairment in individuals with SCI independent of their diagnoses of AIS scale and neural level. Larger number of subjects is needed to further characterize the diverse pattern of autonomic regulation after SCI.

Disclosures: **S. Wang:** None. **S. Aslan:** None. **C. Ferreira:** None. **J. Gunter:** None. **J. Wyles:** None. **D. Wang:** None. **S. Harkema:** None.

Nanosymposium

285. Energy Metabolism and Cardiovascular Regulation

Location: S405

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 285.10

Topic: E.08. Biological Rhythms and Sleep

Support: AHA 14GRNT18370013

Title: Shift work-simulated disruption of circadian rhythms exacerbates pathological outcomes in an animal model of ischemic stroke

Authors: ***D. J. EARNEST**[1,2], J. COFFMAN[3], N. NEUENDORFF[3], S.-M. KIM[2], A. SELVAMANI[3], F. SOHRABJI[3];
[1]Neurosci & Exp. Therapeut., Texas A&M Hlth. Sci. Ctr. Col. of Medicin, Bryan, TX; [2]Biology, Ctr. for Biol. Clocks Res., Texas A&M Univ., College Station, TX; [3]Neurosci & Exp. Therapeut., Texas A&M Hlth. Sci. Ctr. Col. of Med., Bryan, TX

Abstract: At perimenopause, women show increasing incidence of ischemic stroke and poor prognosis for recovery, suggesting that declining ovarian steroid levels alter the risk for neurovascular disease. Peripheral circadian clocks throughout the body may provide integral links between cycling levels of estrogen and neuroprotective responses. Circadian rhythm

disruption may be a key factor coupling risk factors (ie, diabetes, obesity) to cardiovascular pathologies. In middle-aged females, decreased levels and damped oscillations in ovarian hormones may disrupt coordination among peripheral clocks, leading to altered regulation of growth factors that mediate neuroprotective responses to brain injury. Thus, the present study used an ischemic stroke model to determine whether environmental disruption of circadian rhythms in young adult female rats modulates estrous cyclicity and induces corresponding increases stroke volume and functional deficits similar to that observed in middle-aged females. Adult (5mo) female rats were exposed for 8wks to either a fixed or shifted (12hr advance/5d) LD 12:12 cycle and then subjected to middle cerebral artery occlusion (MCAo). Pre and post sensorimotor testing was performed to assess functional deficits. Brains were collected at 5d post MCAo and processed for histological analysis of infarct volume. Before and after experimental manipulations, estrous cyclicity was assessed via vaginal smears in parallel groups of animals. Circadian activity rhythms stably entrained to the fixed LD cycle but were severely disrupted in shifted LD rats. In contrast to the regular estrous cycles (~7d) in fixed-LD animals, cyclicity was abolished and persistent estrous was evident in all shifted-LD rats. The disruption of estrous cyclicity in shifted-LD rats was associated with an increase in serum estradiol levels. Exposure to the shifted LD paradigm had a significant effect in increasing total infarct volume (cortex and striatum) relative to that observed in fixed-LD rats. Similar to infarct volume, MCAo-induced sensorimotor deficits were significantly greater in shifted-LD rats than fixed-LD controls. These results suggest that the loss of estrous cyclicity in young females due to circadian disruption exacerbates stroke outcomes, supporting the hypothesis that in females, middle-age may precipitate circadian disturbances that link reproductive aging to pathological changes in neuroprotective responses to injury.

Disclosures: **D.J. Earnest:** None. **J. Coffman:** None. **N. Neuendorff:** None. **S. Kim:** None. **A. Selvamani:** None. **F. Sohrabji:** None.

Nanosymposium

286. Blood Brain Barrier, Blood Flow, and Imaging

Location: S404

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 286.01

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Title: Angiopoietin-2 blockade prevents microaneurysm formation and maintains blood-retinal barrier integrity even in the absence of pericyte

Authors: *J. LEE[1], J.-Y. KOH[2], A. UEMURA[3], G. Y. KOH[4], Y. H. YOON[1];
[1]Dept. of Ophthalmology, Div. of Vitreoretina, Asan Med. Ctr., Seoul, Korea, Republic of;
[2]Neural Injury Res. Center, Dept. of Neurol., Asan Inst. for Life Sciences, Asan Med. Center, Univ. of Ulsan Col. of Med., Seoul, Korea, Republic of; [3]Grad. Sch. of Med. Sci., Nagoya City Univ., Nagoya, Japan; [4]Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: Keywords: pericyte, blood retinal barrier, microaneurysm, angiopoietin-2 Pericyte, a key component of neurovascular unit, stabilizes the integration of blood retinal barrier (BRB) and blood brain barrier. Loss of pericyte leads to the disruption of the neurovascular barriers, microaneurysms formation, and subsequent neurodegenerative changes in retina and brain. However, the underlying mechanisms are yet to be clearly defined. The purposes of this study are to evaluate structural and functional changes of retinal vessels in the absence of pericyte, and to find out growth factors involved in the formation of microaneurysms and disruption of BRB. Using anti-PDGFRβ antibody, we have developed a novel pericyte-deficient mouse model, which follows sequential pathophysiological cascades of human diabetic retinopathy. Expressions of angiogenic genes were analyzed using transgenic reporter mice, in-situ hybridization, and immunofluorescence. To evaluate the role of angiopoietin-2 (Ang2) in microaneurysm formation, anti-Ang2 antibody was administrated into the vitreous of either eye in the pericyte-deficient mouse model. We confirmed that systemic administration of anti-PDGFRβ antibody effectively induced pericyte dropout in the mouse retina. In this mouse, we observed microaneurysms, retinal hemorrhage and edema, which are characteristic findings of BRB breakdown. Ang2 is selectively expressed in pericyte-free endothelial cells of microaneurysms in this mouse. VEGF-A promoted Ang2 expression in pericyte-free endothelial cells. When Ang2 is inhibited, microaneurysms were markedly diminished and retinal edema and hemorrhage were prevented even in the absence of pericyte. In conclusion, loss of pericyte induces VEGF-A-mediated Ang2 expression in endothelial cells, which destabilize blood vessels leading to microaneurysm formation and vascular leakage. Therefore, Ang2 is crucial for the formation of microaneurysm and could be a direct therapeutic target preventing pericyte-related neurovascular disruption.

Disclosures: J. Lee: None. **J. Koh:** None. **A. Uemura:** None. **G.Y. Koh:** None. **Y.H. Yoon:** None.

Nanosymposium

286. Blood Brain Barrier, Blood Flow, and Imaging

Location: S404

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 286.02

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: R37NS34467

R37AG23084

Title: Endothelial LRP1 controls cerebrovascular integrity and neuronal survival via the CycA-MMP9-NFkB pathway

Authors: *Z. ZHAO[1], A. M. NIKOLAKOPOULOU[2], S. V. REGE[2], A. MONTAGNE[2], Q. MA[2], A. SAGARE[2], Y. WANG[2], J. MAKSHANOFF[2], A. AHUJA[2], G. SI[2], N. C. OWENS[2], J. HERZ[3], B. V. ZLOKOVIC[2];
[1]Physiol. & Biophysics, [2]USC, Los Angeles, CA; [3]UT Southwestern Med. Ctr., Dallas, TX

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease, which is characterized by the accumulation of amyloid beta (Aβ) and its plaque deposition in brain tissue, neuronal and synaptic loss, and cognitive impairment that inevitably leads to dementia. In the normal brain, Aβ is predominantly produced in neurons and eliminated through several routes including receptor-mediated transportation across the blood-brain barrier (BBB) into the peripheral circulation, proteolytic degradation in glial cells or perivascular fluid drainage. Human and animal studies in AD have shown that Aβ aggregation in the brain is increased due to reduced levels of the endothelial low- density lipoprotein receptor-related protein 1 (LRP1) that prevents Aβ accumulation by regulating Aβ efflux from the brain to blood. In our studies, we used a mouse model, where LRP1 has been ablated from endothelial cells, to examine BBB integrity, neuronal survival and cognitive function. Our results show that endothelial LRP1 depletion increases BBB permeability at early stages (~1m old) as identified by IgG and fibrin deposits, and neuronal cadaverine accumulation, and causes cerebrovascular degeneration. Furthermore, LRP1 deficiency promoted Cyclophilin A (CypA) upregulation and downstream metalloproteinase-9 (MMP9) activation, the latter participating in the degradation of capillary basement membrane and tight junction proteins. At later stages (~4m old), lack of endothelial LRP1 causes neuronal degeneration, memory deficits and cerebral blood flow (CBF) changes. Treatment with Cyclospirine A, a drug that blocks CypA upregulation, showed inhibition of the CypA-MMP9 activation pathway by downregulating both CypA and MMP9 expression in the brain, and repaired BBB breakdown evidenced by lack of cadaverine, IgG and fibrin depositions. Preventive therapy from early stages with long-term cyclosporine A administration ameliorated CBF, BBB leakage and neuronal survival, while completely reversed cognitive dysfunction. Taken together, our data show that endothelial LRP1 is crucial for BBB preservation, neuronal survival and cognitive function. Cyclosporine A could be proven to be a beneficial drug in AD protecting against BBB leakage and neuronal death caused by CypA upregulation, while at the same time it may ameliorate cognitive impairment.

Disclosures: **Z. Zhao:** None. **A.M. Nikolakopoulou:** None. **S.V. Rege:** None. **A. Montagne:** None. **Q. Ma:** None. **A. Sagare:** None. **Y. Wang:** None. **J. Makshanoff:** None. **A. Ahuja:** None. **G. Si:** None. **N.C. Owens:** None. **J. Herz:** None. **B.V. Zlokovic:** None.

Nanosymposium

286. Blood Brain Barrier, Blood Flow, and Imaging

Location: S404

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 286.03

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: FWO Grant G032015N

Title: Connexin and Ca^{2+} signaling in glial and endothelial cells is implicated in inflammation-induced blood-brain barrier permeability changes *in vivo*

Authors: ***M. DE BOCK**, V. VAN HAVER, E. DECROCK, L. LEYBAERT;
Ghent Univ., Ghent, Belgium

Abstract: Aim/Hypothesis. Situated between the circulation and the brain, the blood-brain barrier (BBB) protects the cerebral tissue from circulating toxins while securing a specialized environment for neuro-glial signaling. BBB function is maintained by signaling interactions with blood cells, astrocytes, pericytes and neurons that occur in the neurogliovascular unit (NGVU). BBB integrity is compromised in a multitude of pathologic conditions, including exposure to systemic endotoxins that are associated with an inflammatory response and adverse effects on nervous tissue functioning. Previous work from our lab demonstrated that the endothelial cytoplasmic Ca^{2+} concentration ($[Ca^{2+}]_i$) is an important factor determining the functional state of the BBB and that connexin hemichannels (CxHCs), small aqueous pores in the plasma membrane, contribute to $[Ca^{2+}]_i$ dynamics and BBB alterations. Astrocytes, the central components of the NGVU, are also well-known for exhibiting connexin-dependent Ca^{2+} signaling in physiological as well as pathological conditions. We hypothesize that bidirectional signaling interactions between astrocytes and endothelial cells, that rely on connexins and Ca2+, contribute to BBB dysfunction in inflammatory conditions. **Methods.** We here used intraperitoneal injection of lipopolysaccharide (LPS) in mice to trigger an in time and severity expanding increase in BBB permeability. **Results.** We demonstrate that the LPS-induced BBB permeability increase is prevented by intravenous injection of the Ca^{2+} chelator BAPTA-AM and of Cx channel blocking peptides *in vivo*. At the abluminal side, the BBB endothelium is in contact with astrocytic endfeet and we find that buffering astrocytic $[Ca^{2+}]_i$ changes and blocking astroglial CxHCs by applying BAPTA-AM or Cx channel-targeting peptides directly to the

exposed cortex overcomes prevents the LPS-induced barrier breach. Work with inducible Cx43 knockout mice and mice carrying an astrocyte-specific deletion of Cx43 confirmed the protective potential of Cx-targeting strategies and pointed to a crucial role of Cx43 as a target. **Conclusion.** Collectively, our results demonstrate that BBB malfunctioning in response to inflammatory mediators is mediated by $[Ca^{2+}]_i$ dynamics and CxHC signaling in both endothelial cells and astrocytes. Further work is needed to establish the role of the signaling pathways in astrocyte-endothelial interactions, but our results bring up Cx channels as interesting targets with therapeutic potential.

Disclosures: M. De Bock: None. **V. Van Haver:** None. **E. Decrock:** None. **L. Leybaert:** None.

Nanosymposium

286. Blood Brain Barrier, Blood Flow, and Imaging

Location: S404

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 286.04

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: CIHR FRN93603

Queen Elizabeth II/Heart & Stroke Foundation Graduate Scholarship in Science & Technology

Title: Chronic Vasculotide treatment in a mouse model of Alzheimer's disease

Authors: *M. LYNCH[1,2], P. VAN SLYKE[4], D. DUMONT[1,3], I. AUBERT[1,2];
[1]Biol. Sci., Sunnybrook Res. Inst., Toronto, ON, Canada; [2]Lab. Med. & Pathobiology, [3]Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada; [4]Vasomune Therapeut., Toronto, ON, Canada

Abstract: Cerebrovascular dysfunction in Alzheimer's disease (AD) has been gaining support as a key mediator of neurodegeneration and cognitive decline. It is suggested that vascular dysfunction precedes the clinical presentation of AD. Decreased vascular health in the AD brain can be related to several factors, including cerebral amyloid angiopathy, blood-brain barrier (BBB) leakage, morphological and functional alterations of blood vessels, all of which can impair blood flow and lead to hypoperfusion of the brain. Vasculotide (VT) is a synthetic angiopoietin-1 mimetic peptide, which activates the Tie2 signaling cascade known to promote vascular stability and cell survival in peripheral organs. VT has been shown to improve

endothelial barrier function thereby reducing vascular leakage in lungs and kidney. The effects of VT in cerebrovascular health, particularly in presence of AD pathology, are unknown. Using a transgenic (Tg) mouse model of amyloidosis and their non-Tg littermates, VT was given as chronic intraperitoneal injections, every 48 hours for 3.5 months. We identified proteins for which levels of expression were influenced by VT in Tg and non-Tg. Amyloid pathology was also evaluated in response to VT. Behavioural tests were also done in Tg and non-Tg mice treated with VT and with a saline control. Preliminary data evaluating nest construction suggests that Tg-mice treated with VT have improved performance of daily living compared to saline-injected Tg-mice. This research evaluates the activation of Tie2 signaling using VT as a novel treatment for AD. **Funding:** CIHR (FRN93603) Queen Elizabeth II/Heart & Stroke Foundation Graduate Scholarship in Science & Technology

Disclosures: **M. Lynch:** None. **P. Van Slyke:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on granted and submitted patents relating to Vasculotide. **D. Dumont:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on granted and submitted patents relating to Vasculotide. **I. Aubert:** None.

Nanosymposium

286. Blood Brain Barrier, Blood Flow, and Imaging

Location: S404

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 286.05

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: CIHR (FRN93603)

Weston Brain Institute

Title: The effects of MRI-guided focused ultrasound in a mouse model of Alzheimer's disease

Authors: *K. A. MARKHAM-COULTES[1], M. LYNCH[1,3], M. O'REILLY[2], M. KAWAJA[5,6], K. HYNYNEN[2,4], I. AUBERT[3,1];
[1]Biol. Sci., [2]Physical Sci., Sunnybrook Res. Inst., Toronto, ON, Canada; [3]Lab. Med. and Pathobiology, [4]Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada; [5]Biomed. and Mol. Sci., [6]Ctr. for Neurosci. Studies, Queen's Univ., Kingston, ON, Canada

Abstract: The blood-brain barrier (BBB) is a specialized structure of the central nervous system that controls the passage of substances from the blood to the brain. MRI-guided focused ultrasound (MRIgFUS), in presence of microbubbles injected in the bloodstream, transiently induces BBB permeability. This technology can be used for the delivery of therapeutics, injected intravenously, to the targeted areas of the brain in a minimally invasive manner. FUS application in presence of microbubbles, independent of therapeutics, is gaining support as a method to reduce amyloid pathology and improve cognitive functions in mouse models of Alzheimer's disease (AD). We have previously demonstrated that the internalization of amyloid-beta is increased by astrocytes and microglia after FUS treatment where normally circulating antibodies can enter the brain in FUS-targeted areas to improve amyloid-beta clearance. Here, we evaluate proteins, which may be associated with FUS-mediated reduction of amyloid pathology. Furthermore, it is of critical importance to establish the properties of the BBB in presence of amyloid pathology and in response to FUS. Using a transgenic (Tg) mouse model of amyloidosis and their non-Tg littermates, we used FUS to induce transient increases in BBB permeability. The entry of gadolinium in the brain was monitored by MRI and quantified at 6, 12 and 20 hours post-FUS. MATLAB quantification of gadolinium enhancement demonstrated no significant difference between Tg and non-Tg mice. The initial enhancement and pressure to induce BBB permeability was similar in Tg and non-Tg mice. Additionally, using T2-weighted MR images we did not find any significant edema after application of FUS. Our research provides a better understanding of the effects of FUS, in the brain and on the properties of the BBB. These studies are required before translation to the clinic in AD patients where the brain, vasculature and BBB are afflicted by amyloid pathology. To date, our results are promising in supporting MRIgFUS treatment strategies for AD.

Disclosures: K.A. Markham-Coultes: None. **M. Lynch:** None. **M. O'Reilly:** None. **M. Kawaja:** None. **K. Hynynen:** None. **I. Aubert:** None.

Nanosymposium

286. Blood Brain Barrier, Blood Flow, and Imaging

Location: S404

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 286.06

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: CIHR (FRN93603)

Weston Brain Institute

Canadian Blood Services

Health Canada

Title: Focused ultrasound-mediated delivery of natural antibodies to the brain enhances neurogenesis and cognition in a mouse model of amyloidosis

Authors: *S. DUBEY[1,3], A. BURGESS[2], J. MCLAURIN[1,3], D. BRANCH[3], K. HYNYNEN[2,4], I. AUBERT[1,3];
[1]Biol. Sci. Res., [2]Physical Sci. Res., Sunnybrook Res. Inst., Toronto, ON, Canada; [3]Lab. Med. and Pathobiology, [4]Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada

Abstract: Background/Hypothesis: Alzheimer's disease (AD) is characterized by several pathological hallmarks including the accumulation of amyloid beta peptides (Aβ), cellular death and cognitive decline. To date, there is no treatment that halts disease progression. Intravenous immunoglobulins (IVIg), natural antibodies collected from the plasma of thousands of healthy blood donors, have been shown to improve some AD-related pathologies when administered intravenously in murine models of AD. Despite these promising results, a recent Phase III clinical trial suggests limited efficacy of IVIg in improving cognition in AD patients. One possible factor contributing to the suboptimal effects of IVIg treatments may be the restricted ability of antibodies to get through the blood-brain barrier (BBB). Here, we propose using transcranial focused ultrasound (FUS), guided by magnetic resonance imaging (MRI), to temporarily increase BBB permeability and deliver IVIg to brain regions most affected by Aβ pathology. Our hypothesis is that combination of FUS with IVIg therapy will reduce amyloid pathology, enhance neurogenesis and attenuate cognitive decline. If effective, these data will represent a novel therapeutic approach for IVIg delivery and an alternative for lowering the dosage requirements for IVIg treatment efficacy. Experimental Method: Using a mouse model of amyloidosis, we administered IVIg intravenously, with or without application of FUS. FUS was performed once a week, for two consecutive weeks, and was targeted bilaterally to the hippocampus. After treatment, cognitive function was tested using behavioural paradigms and post-mortem immunohistochemistry was used to evaluate neurogenesis and amyloid pathology. Results/Conclusion: Our data demonstrates that IVIg is delivered to the brain using FUS. Furthermore, we found that compared to animals treated with FUS or IVIg alone, FUS and IVIg treated animals had reduced Aβ pathology, increased neurogenesis and improved cognitive performance. Our findings suggest that IVIg drug delivery to the brain by FUS enhances the beneficial effects of IVIg therapies related to Alzheimer's disease.

Disclosures: S. Dubey: None. **A. Burgess:** None. **J. McLaurin:** None. **D. Branch:** None. **K. Hynynen:** None. **I. Aubert:** None.

Nanosymposium

286. Blood Brain Barrier, Blood Flow, and Imaging

Location: S404

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 286.07

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: CIHR (FRN93603)

Weston Brain Institute (TR130117)

Title: MRI-guided focused ultrasound gene delivery to the brain using chimeric adeno-associated virus

Authors: *D. WEBER-ADRIAN[1], Z. NOROOZIAN[1], J. SILBURT[1], K. SHAH[2], A. BURGESS[2], S. KÜGLER[3], K. HYNYNEN[2], I. AUBERT[1];
[1]Brain Sci. Research, Biol. Sci., [2]Physical Sci., Sunnybrook Res. Inst., Toronto, ON, Canada; [3]Neurol., Univ. of Med. Göttingen, Göttingen, Germany

Abstract: Background: Gene therapy shows potential for the treatment of neurological disorders; however, the presence of the blood brain barrier (BBB) remains a challenge for non-surgical delivery of a gene construct. An additional consideration is viral serotype and promoter selection, which influences cell tropism, and could thereby limit gene expression in non-targeted organs after systemic delivery *in vivo*. Here, we describe non-invasive delivery of a green fluorescent protein (GFP) reporter gene from a chimeric adeno-associated virus (AAV) serotype under control of 3 different promoters in wild-type C57BL/6 mice. Hypothesis: AAV-mediated gene delivery under control of cell-specific promoters will result in gene expression in the brain, while preventing expression in non-target organs after systemic delivery. Methods/Results: Non-invasive gene delivery was mediated by magnetic resonance imaging-guided focused ultrasound (MRIgFUS), which transiently and locally permeabilizes the BBB and allows for gene constructs, delivered intravenously, to enter the brain. Results indicated that the glial fibrillary acidic protein promoter is selective for gene expression in astrocytes in the central nervous system (CNS). However, this promoter allowed for considerable gene expression in the liver after systemic delivery. Gene expression under control of the synapsin promoter showed neuron-specificity in the brain, and did not result in gene expression in the liver or kidney. Conclusion: Chimeric AAV gene expression under control of the synapsin promoter leads to neuron-specific expression in the CNS after systemic delivery, and MRIgFUS-mediated delivery to the brain.

Disclosures: D. Weber-Adrian: None. **Z. Noroozian:** None. **J. Silburt:** None. **K. Shah:** None. **A. Burgess:** None. **S. Kügler:** None. **K. Hynynen:** None. **I. Aubert:** None.

Nanosymposium

286. Blood Brain Barrier, Blood Flow, and Imaging

Location: S404

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 286.08

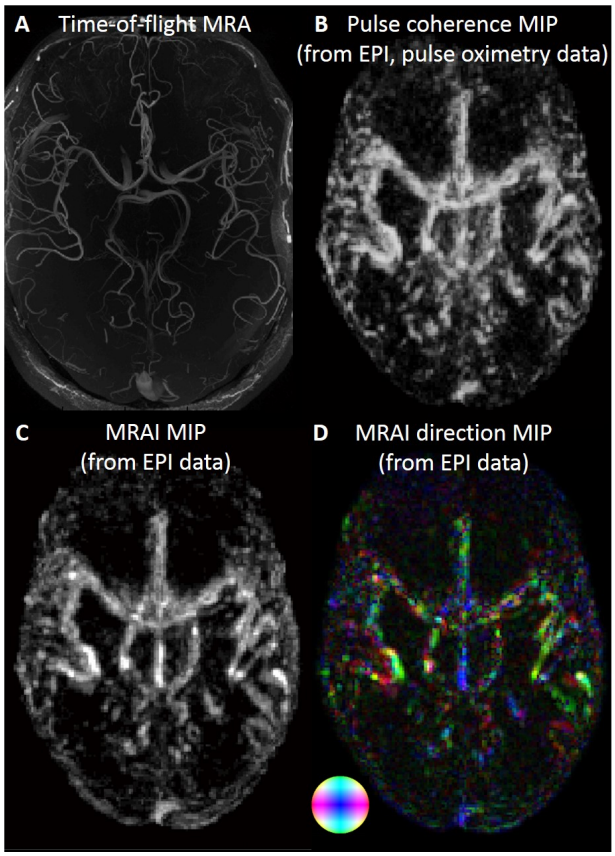
Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: NSF Grant 0956306

Title: Mapping cerebrovascular dynamics with magnetic resonance advection imaging (MRAI): modeling challenges and estimation bias

Authors: *H. U. VOSS[1], J. P. DYKE[1], K. TABELOW[3], N. D. SCHIFF[2], D. J. BALLON[1]; [1]Radiology, [2]Neurol., Weill Cornell Med. Col., New York, NY; [3]Weierstrass Inst., Berlin, Germany

Abstract: Objectives: Magnetic Resonance Advection Imaging (MRAI, [1,2]) provides velocity maps of cerebrovascular dynamics from dynamic EPI data. It delivers precisely localized information about vascular dynamics, which might aid the interpretation of (resting state) fMRI experiments affected by vascular anatomy [3,4]. Here we demonstrate MRAI on a public fMRI data set and discuss possible sources of estimation bias. Methods: It is assumed that the EPI signal $\rho(r,t)$ in a small domain around r obeys the advection equation $\partial\rho(r,t)/\partial t + u \bullet \text{grad}\, \rho(r,t) = 0$. Velocity parameters and pulse coherence maps were estimated from a public data set of natural stimulation fMRI-EPI data [5] by multiple regression [6,7]. Numerical simulations were performed in Matlab. Results: 1. MRAI and pulse coherence maps partially reproduce the anatomy of main cerebral arteries (Figure). MRAI has lower resolution than angiographic flow-based images but contains information about the pulsatory part of cerebrovascular dynamics. 2. Simulations show that traveling wave velocities can be estimated reliably for weak noise and slow waves. For spatially modulated velocity fields, or mis-specified models, estimation biases in magnitude and direction of velocities are found. Conclusions: MRAI maps show clear signs of vascular anatomy. Spatially modulated waves and noisy data cause estimation bias. The possibility of these biases should be kept in mind in interpretations of MRAI maps that are based on the simple advection model used here. It is an interesting question whether MRAI can be improved by using alternative model fitting or pulse sequences. 1. H. U. Voss et al., OHBM - Human Brain Mapping, 2436 (2015). 2. H. U. Voss et al., BRAIN/PET 2015, 0141 (2015). 3. J. T. Webb et al., PloS one 8 (2013). 4. R. M. Birn, NeuroImage 62, 864 (2012). 5. M. Hanke et al., Sci. Data 1:140003 1(2014). 6. H. U. Voss et al., Phys. Rev. Lett. 83, 3422 (1999). 7. H. U. Voss and N. D. Schiff, Entropy 16, 3689 (2014).



Disclosures: **H.U. Voss:** None. **J.P. Dyke:** None. **K. Tabelow:** None. **N.D. Schiff:** None. **D.J. Ballon:** None.

Nanosymposium

286. Blood Brain Barrier, Blood Flow, and Imaging

Location: S404

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 286.09

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

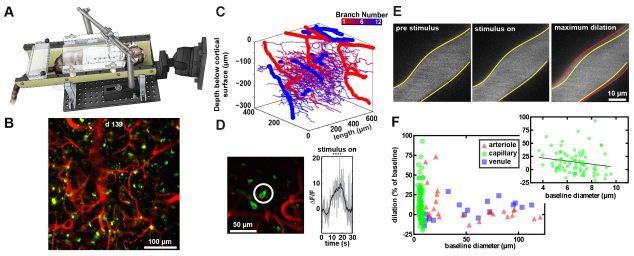
Support: NIH Intramural Research Program

NINDS Competitive Fellowship

Title: Quantification of cerebral hemodynamics and neural activity in awake and anesthetized marmoset by two-photon imaging

Authors: *T. P. SANTISAKULTARM[1], C. J. KERSBERGEN[1], D. K. BANDY[2], D. C. IDE[2], S.-H. CHOI[1], A. C. SILVA[1];
[1]Natl. Inst. of Neurolog. Disorders and Stroke, [2]Natl. Inst. of Mental Hlth., NIH, Bethesda, MD

Abstract: Cerebral blood flow is precisely controlled to maintain homeostasis during neural activation when metabolic demand is heightened. This neurovascular coupling at the cellular level can be visualized with two-photon microscopy (2PM). Often, optical imaging is performed in anesthetized animals albeit the unclear influence of the anesthetic agents. Here, we aim to quantify the effects of a common anesthesia, isoflurane, on cortical vessels and neural activation in marmosets with 2PM. Marmosets were acclimated to awake imaging. A cranial chamber was implanted over the somatosensory cortex (**Fig 1A**). To visualize functional activity, AAV1-GCaMP5G was injected for optical detection of calcium influx during neural firing (**Fig 1B**). After recovery, 2PM revealed vascular topology and enabled measurement of blood cell motion in individual vessels for over 6 months (**Fig 1C**). The vascular characteristics, along with neural responsiveness (**Fig 1D-E**), were quantified in both awake and anesthetized states. Under isoflurane, blood vessels of all classes dilated, especially for smaller microvessels, resulting in a median capillary dilation of 10%. Arterioles and venules displayed smaller diameter changes of 2.8 and 5.6%, respectively (**Fig 1 F**). Flow speed in pial arterioles was reduced by 24% in isoflurane-anesthetized condition compared to while awake. The fraction of stalled capillaries was 2.4% in awake marmosets, suggesting robust cortical perfusion. In contrast, 11% of capillaries had stalled blood flow while marmosets were under isoflurane. Finally, 19% of neurons were activated following stimulation, compared to 0% while anesthetized. These results suggest significant alterations in hemodynamics and neural activity under isoflurane, and highlight the importance of studying brain function without anesthesia's confounding effects. This work provides an imaging technique to assess neurovascular coupling at the cellular level in awake non-human primates, and allows for longitudinal investigation of critical mechanisms in neurological disorders.



Disclosures: T.P. Santisakultarm: None. **C.J. Kersbergen:** None. **D.K. Bandy:** None. **D.C. Ide:** None. **S. Choi:** None. **A.C. Silva:** None.

Nanosymposium

286. Blood Brain Barrier, Blood Flow, and Imaging

Location: S404

Time: Monday, October 19, 2015, 8:00 AM - 10:30 AM

Presentation Number: 286.10

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: ARC DP120100614

ARC DP130100437

ARC CE140100007

ARC FL140100025

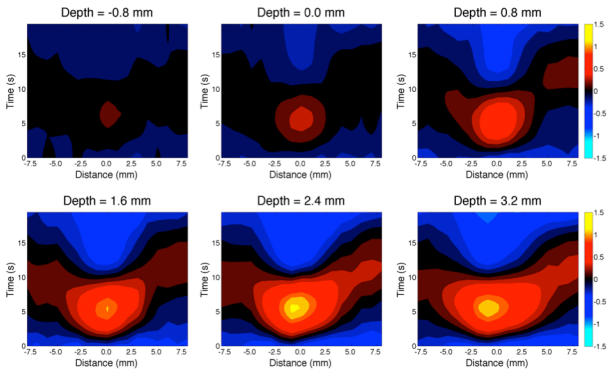
UOW SIM funding

Title: Three-dimensional spatiotemporal stHRF for laminar analysis of fMRI

Authors: *M. M. SCHIRA[1,2], A. M. PUCKETT[1], K. M. AQUINO[2,3], P. A. ROBINSON[3,4], M. J. BREAKSPEAR[5];
[1]Univ. of Wollongong, Wollongong, Australia; [2]Brain Structure and Fuction, Neurosci. Res. Australia, Randwick, Australia; [3]Sch. of Physics, [4]Cooperative Res. Ctr. for Alertness, Safety, and Productivity, Univ. of Sydney, Sydney, Australia; [5]QIMR-Berghoffer, Herston, Australia

Abstract: Background: The gray matter of human cortex is marked by depth-dependent differences in neuronal activity and connections as well as in the associated vasculature. Recent advances in imaging hardware have pushed the resolution limits of functional magnetic resonance imaging (fMRI) below a millimeter, permitting these differences to be measured in awake and behaving human subjects. Here, we present a prerequisite for such endeavors, a detailed, three-dimensional hemodynamic response function (HRF) reconstructed through the use of submillimeter fMRI. Methods: Functional MRI data were acquired using a 3T scanner and 0.8 mm isotropic resolution. Several high-resolution T1 scans were averaged to a volume with 0.4 mm resolution and carefully segmented. A surface at the gray/white boundary and parallel surfaces (0.8mm apart) were constructed using CARET. Subjects viewed a simple visual stimulus consisting of a single, thin (1 pixel = 0.03 deg), black and white, flickering (250 ms) ring stimulus ('ON' for 4 seconds) with a radius of 1 degree alternated with a uniform gray field ('OFF' for 16.5 s). Stimulus onset was varied with respect to the MRI timing to yield an effective resolution of 500ms. Spatiotemporal HRF responses were measured by averaging time-course responses based on the distance of the responses from the centerline of activation. Results: A fully three-dimensional HRF is obtained, which describes the response vs. time and two spatial dimensions: one tangential and one perpendicular to the cortical surface. The response depends significantly on depth. As expected, there is virtually no response at z = -0.8 mm (that is 0.8 mm below the gray/white boundary, Fig. 1, first panel). At more superficial

depths the response is stronger and broader. Moreover, at all depths part of the response propagates as a traveling wave, in accord with theory, evident as increasingly delayed BOLD away from the stimulus location. The quantification of the 3D spatiotemporal structure of the HRF provided is a crucial prelude to using fMRI to infer layer-specific neuronal responses.



Disclosures: **M.M. Schira:** None. **A.M. Puckett:** None. **K.M. Aquino:** None. **P.A. Robinson:** None. **M.J. Breakspear:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.01

Topic: F.01. Human Cognition and Behavior

Support: NIH RO1 MH097085

1K99MH106719-01

Title: The effect of acute stress on fear generalization

Authors: ***J. E. DUNSMOOR**, A. R. OTTO, E. A. PHELPS;
New York Univ., New York, NY

Abstract: Stress affects the ability to regulate emotional responses. Using fear conditioning models, prior studies indicate that acute stress impairs retrieval of the extinction (safety) memory. These effects mirror deficits in emotion regulation following stress and identified in patients with posttraumatic stress disorder (PTSD), providing a link between laboratory models of stress effects and clinical translational research. Here, we investigated whether acute stress

was associated with overgeneralization of conditioned fear. Fear generalization occurs when threat-related responses to a conditioned stimulus (CS), paired with an aversive unconditioned stimulus (US), transfer to other stimuli that have never been paired with the US. Generalization tends to decrease as similarity to the CS diminishes, but is enhanced in certain anxiety and stress-related disorders, i.e., overgeneralization. In a 2 X 2 between subjects factorial design, healthy adult subjects first underwent differential fear conditioning to a pure tone (CS+; 500 Hz or 1000 Hz, counterbalanced) paired with shock, while another tone was presented without shock (CS-; 1000 Hz or 500 Hz, counterbalanced respectively). Stress administration (cold-pressor) followed fear conditioning either on the same day (Stress-Immediate), or 24 hours later (Stress-Delay). A fear generalization test, consisting of a range of tones that varied in pitch between the CS+ and CS-, was conducted 15 minutes after stress administration. Other subjects received a control task prior to the generalization test either on the same day (Control-Immediate), or 24 hours after fear conditioning (Control-Delay). Fear conditioning and the stress manipulation were successful in all cases, as assessed by conditioned skin conductance responses (SCR) and cortisol, respectively. All groups exhibited generalization gradients of SCRs and trial-by-trial ratings of shock expectancy that peaked at the CS+ and diminished as a function of perceptual similarity along the frequency continuum. These gradients were unaffected by the stress manipulation immediately after conditioning. However, gradients were affected by stress after a delay, such that stress induced broad overgeneralization to unreinforced tones 24 hours after fear conditioning. These findings show that acute stress can lead to broad generalization of a remote (but not a recent) fear memory, and have clinical relevance to understanding overgeneralization characteristic of anxiety and stress-related disorders.

Disclosures: J.E. Dunsmoor: None. **A.R. Otto:** None. **E.A. Phelps:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.02

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R21MH91550

NIH Grant R01MH81884

NIH Grant R01MH46729

NIH Grant P50MH84051

NIH Grant P50MH100031

NIH Grant R21MH092581

HealthEmotions Research Institute

Title: The neural substrates of anxious temperament in young rhesus monkeys

Authors: *A. S. FOX[1], A. J. SHACKMAN[2], J. A. OLER[3], R. M. BIRN[3], A. A. ALEXANDER[3], S. E. SHELTON[3], R. J. DAVIDSON[3], N. H. KALIN[1];
[1]Psychiatry, Univ. of Wisconsin, Madison, WI; [2]Univ. of Maryland, Col. Park, College Park, MD; [3]Univ. of Wisconsin-Madison, Madison, WI

Abstract: Anxious temperament (AT) is a stable trait-like tendency to respond to novelty and potential threat with fear and reticence. In humans, extreme AT is a risk-factor for the development of anxiety and depressive disorders. To study the biology of this risk, we developed and validated a non-human primate model of AT. Due to their relatively recent evolutionary divergence, non-human primates share similarities in brain function and structure with humans, including an enlarged prefrontal cortex. These similarities are thought to underlie parallels in cognitive and emotional behavior, rearing methods, and psychosocial development, which contribute to variation in AT. Mirroring human AT, we quantify AT as increased freezing, decreased vocalizations, and increased cortisol in response to a potentially threatening human intruder presenting their profile to the monkey while making no eye contact (NEC). In a large familial sample of 592 young rhesus monkeys (327M/265F; Age:μ=1.88,sd=0.78, roughly equivalent to 3-12 year old humans), we measured brain metabolism during exposure to the NEC context using ^{18}fluorodeoxyglucose positron emission tomography (FDG-PET). We performed MRI scans to assess brain structure and resting functional connectivity (rsfMRI). rsfMRI analyses (n=339) used seed regions in the central nucleus of the amygdala (Ce) and bed nucleus of stria terminalis (BST), which are part of the extended amygdala. Voxelwise regressions assessed the relationship between neuroimaging measures and AT while covarying for age, sex and other potentially confounding variables. Results demonstrated significant relations between metabolism and AT ($p<.05$ Sidak corrected) in regions of the orbitofrontal (OFC) and anterior insular (AI) cortices (including cytoarchitectonic areas 11/13/47, and OPro), anterior hippocampus, extended amygdala (including Ce and BST), and midbrain regions that encompass the PAG. rsfMRI analyses at a $p<.005$, uncorrected, revealed inverse relationships between AT and the strength of connectivity between extended amygdala and prefrontal regions (e.g. Ce-DLPFC, and BST-OFC/AI). These findings identify a network of AT-related brain regions, many of which causally contribute to AT, including: OFC/AI areas involved in emotional valuation; extended amygdala, an interface between emotions and their behavioral and physiological expression; and downstream brain stem effectors required for the expression of defensive responses (e.g. PAG). Moreover early-life rsfMRI data are consistent with an altered prefrontal capacity for emotion regulation in extreme AT.

Disclosures: **A.S. Fox:** None. **A.J. Shackman:** None. **J.A. Oler:** None. **R.M. Birn:** None. **A.A. Alexander:** None. **S.E. Shelton:** None. **R.J. Davidson:** None. **N.H. Kalin:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.03

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant MH091864

Dana Foundation Grant

Title: Effects of early life stress on neural mechanisms of fear learning

Authors: *J. A. SILVERS[1], D. S. LUMIAN[2], L. GABARD-DURNAM[1], D. GEE[3], B. GOFF[4], D. S. FARERI[1], C. CALDERA[4], J. FLANNERY[5], E. H. TELZER[6], K. L. HUMPHREYS[7], N. TOTTENHAM[1];
[1]Psychology, Columbia Univ., New York, NY; [2]Univ. of Denver, Denver, CT; [3]Weill Cornell Med. Col., New York, NY; [4]UCLA, Los Angeles, CA; [5]Univ. of Oregon, Eugene, OR; [6]Univ. of Illinois, Urbana-Champaign, Urbana-Champaign, IL; [7]Tulane Sch. of Med., New Orleans, LA

Abstract: Early life stress can profoundly influence fear behavior in childhood and beyond. As members of an altricial species, there is perhaps no early life stressor more disruptive for humans than parental deprivation, which has been shown to alter amygdala and hippocampal development and associated fear learning in rodents. However, it has yet to be demonstrated how parental deprivation alters prefrontal-subcortical circuitry that supports fear learning in humans, who typically remain dependent on caregivers longer than any other species. To address this issue, we compared 46 previously institutionalized (PI) youth (33F/13M; 7-16 years) to 44 comparison youth who had never experienced institutional care (22F/22M; 7-16 years). To assess prefrontal-amygdala-hippocampal circuitry associated with fear learning, participants completed a conditioning paradigm while undergoing functional neuroimaging wherein visual cues were paired with either a neutral or aversive tone (CS- and CS+, respectively). Both PI and comparison youth showed robust behavioral evidence of fear learning that was supported by CS+ > CS- discrimination in the amygdala. However, compared to same-aged controls, PI children showed greater CS+ > CS- discrimination in the hippocampus. Within PI children, higher trait anxiety was associated with better CS+>CS- discrimination behavior, an effect that was mediated by prefrontal recruitment. These data build on existing evidence showing adult-like

amygdala and hippocampal function in juveniles following parental deprivation and are suggestive of ontogenetic acceleration of fear learning circuitry following parental deprivation.

Disclosures: **J.A. Silvers:** None. **D.S. Lumian:** None. **L. Gabard-Durnam:** None. **D. Gee:** None. **B. Goff:** None. **D.S. Fareri:** None. **C. Caldera:** None. **J. Flannery:** None. **E.H. Telzer:** None. **K.L. Humphreys:** None. **N. Tottenham:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.04

Topic: F.01. Human Cognition and Behavior

Support: NIMH early experience, stress, and neurodevelopment center seed grant

UCLA Staglin center for cognitive neuroscience seed grant

NSF GRFP

Title: Childhood as a sensitive period for human medial prefrontal cortex learning

Authors: ***L. GABARD-DURNAM**, N. TOTTENHAM;
Columbia Univ., New York, NY

Abstract: The medial prefrontal cortex (mPFC) is critical to the integration and regulation of affective stimuli, but the timing and mechanisms of the human functional ontogeny of this region remain largely uncharacterized. Recent evidence in the rodent suggests that there is a sensitive period before puberty, when complex stimuli (e.g., music) can be encoded by mPFC. In adulthood, these stimuli effectively increase mPFC activity and reduce anxiety. The present study aimed to examine whether a homologous sensitive period for mPFC learning occurs during human childhood, when a developmentally-unique mPFC phenotype has been identified. Pop music was used as the environmental signal as there is discrete temporal exposure to specific pop songs during development (as a noted by placement on Billboard charts). Two groups of adults, those raised in the USA with varying exposure to pop during childhood (n =42), and individuals who immigrated to the USA in adulthood (and had no exposure to USA pop during childhood (n = 29)), were given a baseline music preference test where they could choose between listening to childhood or adolescence music, followed by a modified Trier stress test and then a second music preference test. After exposure to the stressor, only the childhood-exposed group preferred to listen to the childhood music ($p < 0.001$), which was accompanied by reduced reported

anxiety ($p < 0.04$). Galvanic skin response analyses confirmed that only childhood songs for the childhood-exposed group lowered arousal levels during this period ($n = 40$, $p < 0.035$). Adolescent music did not show any of these anxiolytic effects. Individuals without the childhood exposure to the childhood songs did not exhibit any of the anxiolytic effects for either song category. Functional resonance magnetic imaging revealed greater activation in the mPFC to childhood music relative to the adolescent music for the childhood-exposed group compared to the non-exposed group ($n = 29$, $p < 0.005$), and this mPFC activity was predictive of lower reported anxiety ratings following childhood songs for the childhood-exposed group ($p < 0.005$). Together, these behavioral, physiological, and fMRI results suggest that a human sensitive period may occur during childhood for mPFC learning with important implications for emotion regulation and mPFC function in adulthood. These findings are consistent with the mPFC learning period identified in the rodent and suggest that the mPFC learning sensitive period is a phylogenetically conserved phenomenon.

Disclosures: L. Gabard-Durnam: None. **N. Tottenham:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.05

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R01 MH077813

James J Peters VA Medical Center

Title: Can people be trained to be better emotion regulators? Evidence that longitudinal reappraisal training reduces self-reported negative emotion and amygdala activity and increases prefrontal cortex activity in borderline personality disorder patients

Authors: *B. T. DENNY[1], J. FAN[1,2,3], X. LIU[4], K. N. OCHSNER[5], S. MAYSON[1], L. RIMSKY[1], A. MCMASTER[1], H. ALEXANDER[1], A. S. NEW[1,6], M. GOODMAN[1,6], L. J. SIEVER[1,6], H. W. KOENIGSBERG[1,6];
[1]Psychiatry, Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Psychology, Queens College, City Univ. of New York, New York, NY; [4]Chinese Acad. of Sci., Beijing, China; [5]Psychology, Columbia Univ., New York, NY; [6]James J Peters VA Med. Ctr., Bronx, NY

Abstract: Substantial research has indicated the effectiveness of engaging reappraisal in order to reduce self-reported negative emotion via recruitment of prefrontal cortex and down-regulation of amygdala activity in individual sessions. However, there has been far less research into whether focused longitudinal training in reappraisal strategies can yield adaptive changes in brain and behavior over time, both in healthy populations and in populations for whom emotion regulation often fails. Borderline personality disorder (BPD) is the prototypical disorder involving emotion dysregulation. In this study, we assessed whether and via what neural mechanisms BPD patients could be trained to enhance reappraisal and reduce self-reported negative emotion via psychological distancing, which involves viewing stimuli as an impartial, objective observer. At each of five sessions, 14 BPD and 16 healthy control (HC) participants were shown negative social emotional images and given instructions to reappraise their responses to half ("Reappraise") and to look and respond naturally at the other half ("Look"). Emotion self-reports were obtained after each image presentation. Sessions 1-5 were spaced 1-2 days apart and afforded training through practice on novel images. fMRI data were acquired at Sessions 1 and 5. We found that BPD patients showed reductions in negative emotion self-reports over time. BPD patients also showed increasing attenuation of amygdala activity due to reappraisal (Reappraise Negative) relative to responding naturally (Look Negative) over time in a manner not attributable to habituation. Further, with training, BPD patients showed increased reappraisal-related recruitment of dorsolateral prefrontal cortex, a region engaged during reappraisal in HC's in this and prior studies. Taken together, these data suggest a potential neural mechanism for reappraisal training and represent the first evidence that longitudinal training can normalize reappraisal-related neural activity in any patient population. Further, these results suggest a potential translational role for reappraisal training in BPD treatment.

Disclosures: B.T. Denny: None. **J. Fan:** None. **X. Liu:** None. **K.N. Ochsner:** None. **S. Mayson:** None. **L. Rimsky:** None. **A. McMaster:** None. **H. Alexander:** None. **A.S. New:** None. **M. Goodman:** None. **L.J. Siever:** None. **H.W. Koenigsberg:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.06

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R01AG039283

Title: Stress exposure decreases cooperative behavior

Authors: *C. M. RAIO[1], O. FELDMANHALL[1], M. GAIKWAD[1], E. PHELPS[1,2];
[1]New York Univ., New York, NY; [2]Nathan Kline Inst., Orangeburg, NY

Abstract: In daily life, emotion regulation plays a key role in facilitating appropriate social behavior. This is especially evident in the context of prosocial decision-making, where individuals must choose between the self-interested desire to maximize personal gain and the desire to uphold social norms that promote cooperation with others despite the inherent personal cost. Given the central role of cooperation in human society, it is of considerable importance to characterize the conditions under which people are more or less likely to cooperate. However, the way that aversive emotional states, such as stress, influence such behavior remains unknown. Stress has been shown to engender reliance on habitual forms of behavior, suggesting that stress may enhance cooperation, which has been described as an automatic or intuitive response. Alternately, the aversive nature of stress exposure may enhance individuals' propensity to behave selfishly in order to secure additional resources, leading to less cooperation. Here, we sought to distinguish these possibilities by combining a well-characterized, classic behavioral economic game that measures cooperative decision-making behavior with an acute stress manipulation known to reliably engage sympathetic and neuroendocrine responses to stress. In two separate studies, participants underwent a stress induction task (i.e., cold pressor task) or control task before playing either the Prisoner's Dilemma (PD) game, in which participants could either cooperate with a partner for a lower monetary reward, or betray them for higher monetary gain, or a matched non-social lottery game. Our data revealed that stress exposure reduced prosocial behavior by decreasing cooperation and increasing individuals' propensity to betray their partners for higher earnings. This tendency was found irrespective of whether subjects played a one-shot version of the game that promotes lower cooperation since partners are never encountered more than once (Study 1), or an iterative version of the game that promotes cooperative tendencies since subjects repeatedly play with the same partner (Study 2). By studying the effect of an ecologically valid stress induction on cooperative decision-making, this work promises to situate our understanding of prosociality in a broader framework that reflects the influence of real-world conditions of stress exposure.

Disclosures: C.M. Raio: None. **O. FeldmanHall:** None. **M. Gaikwad:** None. **E. Phelps:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.07

Topic: F.01. Human Cognition and Behavior

Support: PO1 HL040962

R01 HL089850

R01 DA035484

R01 MH076136

Title: Reappraisal alters the construction the emotional experiences

Authors: *L. CHANG[1], P. J. GIANAROS[2], J. GROSS[3], S. B. MANUCK[2], T. D. WAGER[1]; [1]Psychology and Neurosci., Univ. of Colorado, Boulder, CO; [2]Dept. of Psychology, Univ. of Pittsburgh, Pittsburgh, PA; [3]Dept. of Psychology, Stanford Univ., Palo Alto, CA

Abstract: Successful regulation of emotions is important for maintaining our mental and physical health. Though many studies have reliably demonstrated that strategies such as reappraisal are effective in decreasing negative affective states, the precise mechanism of how this process unfolds remains unclear. One popular account argues that reappraisal directly attenuates the affective experience by recruiting executive control systems. Alternatively, reappraisal may not directly decrease the brain's reactivity to negative stimuli, but instead qualitatively changes the affective experience. Here we develop a sensitive and specific signature of negative affect elicited via negative arousing images and evaluate these competing hypotheses. We find that participants report lower negative affect ratings when instructed to reappraise, but interestingly, our negative affect signature systematically overestimates how people are feeling. Region of interest analyses suggest that this may be a consequence of processes in medial and lateral prefrontal cortex that are likely shared in both emotion generation and reappraisal, but are amplified during reappraisal. We used a whole-brain multivariate moderation analysis to test this hypothesis and find that the negative affect signature is reconfigured when reappraising compared to naturally reacting to negative stimuli. This is evidenced by increased weights in the dACC and decreased weights in the MPFC, left amygdala, and areas of the visual cortex. In addition, we identify a multivariate representation of reappraisal that can discriminate between reappraisal and reactive states with 91% accuracy in leave-one-subject out cross-validation. The most predictive weights of this reappraisal detector partially overlap with the moderation analysis (e.g., dACC) suggesting that cognitive reappraisal processes contribute to the change in emotional experience. Together, these results suggest that reappraisal recruits distinct neural circuitry from emotional reactivity and appears to alter the construction of the emotion experience.

Disclosures: L. Chang: None. **P.J. Gianaros:** None. **J. Gross:** None. **S.B. Manuck:** None. **T.D. Wager:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.08

Topic: F.01. Human Cognition and Behavior

Support: NIH IBSC center 1-P50-MH079485

Title: Brain mechanisms of worse than expected rewards

Authors: *J. MOLLICK[1], L. J. CHANG[1], A. KRISHNAN[1], G. FRANK[2], T. D. WAGER[1], R. O'REILLY[1];
[1]Dept. of Psychology, Univ. of Colorado Boulder, Boulder, CO; [2]Univ. of Colorado Denver, Denver, CO

Abstract: This talk will focus on the brain mechanisms involved in learning about unexpected omissions of reward, and outline a model of interactions between those regions. This account is distinct from traditional reinforcement learning theories, which treat both worse than expected and better than expected rewards similarly as differences in prediction error. However, we propose that learning about reward omissions draws on brain circuitry involved in negative valence and stress, in particular the lateral habenula, which drives dopamine dips for negative valence and reward omissions. Additionally, I will describe a computational model based on circuit-level research from animal models that proposes specific interactions between limbic brain regions such as the ventral striatum, amygdala, and lateral habenula in positive and negative valence conditioning tasks. As a test of these model predictions, we ran a conditioned inhibition fMRI study, where a CS paired with a juice reward was later paired with a Inhibitor, that caused omission of the expected juice reward. This conditioned inhibition procedure has previously been tested in monkey studies (Tobler, 2003), which have found that dopamine neurons respond with a dip to the Inhibitor that predicts a reward omission. Based on recent research showing that the lateral habenula plays an important role in causing dopamine dips, we predicted that the habenula would play a role in driving reduced VTA activity for the Inhibitor. In this study, we observed significantly more activity in the SN/VTA for the CS+ than the CS- ($p = .044$, $t(1,18)= 2.16$). Based on this result, we ran a whole brain functional connectivity analysis to look for brain regions where correlations with single-trial VTA estimates in each of our conditions varied across the different CS types. We found that lateral habenula activity was negatively correlated with activity in the VTA for the Inhibitor, but not the other CS types, supporting our model of the role that lateral habenula plays in signaling the VTA for predictors of reward omission. Additionally, I will discuss other predictions the computational model

makes about the involvement of the amygdala and ventral striatum in conditioned inhibition and how they are borne out by the data.

Disclosures: **J. Mollick:** None. **L.J. Chang:** None. **A. Krishnan:** None. **G. Frank:** None. **T.D. Wager:** None. **R. O'Reilly:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.09

Topic: F.01. Human Cognition and Behavior

Support: NIMH Grant F32 MH 098504

Title: Neural responses during vicarious reward predict enhanced well-being

Authors: ***S. MORELLI**, M. E. ARNN, J. ZAKI;
Psychology, Stanford Univ., Stanford, CA

Abstract: Individuals experience reward not only when directly receiving positive outcomes (e.g., food or money), but also when observing others receive such outcomes. This latter phenomenon, known as vicarious reward, is a perennial topic of interest among psychologists and neuroscientists. Despite a long-standing interest in vicarious reward, many characteristics of this phenomenon remain unclear. In particular, little is known about how vicarious reward relates to social and emotional well-being in our daily lives. To explore this question, we scanned 48 participants as they won money during a gambling game and also observed a close friend win money. These same participants also completed a 14-day diary study and reported on their loneliness, life satisfaction, and happiness each day. When observing a friend win five dollars (compared to zero dollars), increased reward-related activity in the ventral and dorsal striatum predicted decreased loneliness, but increased life satisfaction and happiness across 14 days. However, reward-related activity when winning money for the self did not relate to any of these daily outcomes. These findings suggest that sharing others' rewarding experiences is closely tied to well-being and may influence our sense of connectedness and happiness even more than personally rewarding experiences.

Disclosures: **S. Morelli:** None. **M.E. Arnn:** None. **J. Zaki:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.10

Topic: F.01. Human Cognition and Behavior

Support: R01 MH043454

T32 MH018931

P30 HD003352

John Templeton Foundation

Title: Variability in real-world daily emotion predicts lower well-being and is associated with increased variability in prefrontal BOLD engagement

Authors: *A. HELLER[1], A. S. FOX[2], E. K. WING[3], R. J. DAVIDSON[2];
[1]Univ. of Miami, Coral Gables, FL; [2]Univ. of Wisconsin - Madison, Madison, WI; [3]Univ. of Kansas, Lawrence, KS

Abstract: Rapid variation and instability in emotional states has been linked to reductions in well-being and increases the risk that an individual may develop a psychiatric illness. However, measuring such instability in emotion is difficult with most lab-based techniques as sampling periods are typically not long enough to gather sufficient data and participant's self-report about their own emotional instabilities are retrospective and prone to bias. Furthermore, how individual differences in such emotional instability is instantiated in the brain are not known. As a result, human participants performed two studies: First, individuals performed an experience sampling study in which they were asked to rate their current positive and negative affect several times a day over the course of ten days. Second, participants returned to the lab and were scanned with event-related fMRI while engaging in a card-guessing task in which they could win or not win money. Individuals who, in their daily self-report, experienced significantly greater emotional instability were those with more variable engagement in the dorsolateral prefrontal cortex - a brain region thought to underlie executive control. These individuals also self-reported lower levels of well-being on a traditional self-report measure. These results suggest that real-world emotional instability is associated with greater variability in engagement of executive control systems and is related to reduced well-being.

Disclosures: **A. Heller:** None. **A.S. Fox:** None. **E.K. Wing:** None. **R.J. Davidson:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.11

Topic: F.01. Human Cognition and Behavior

Title: The effects of orienting attention and action readiness on emotion regulation

Authors: *G. SURI;
Stanford Univ., Menlo Park, CA

Abstract: I describe an affective neuroscience framework - the Readiness-Attention-Motivation (RAM) framework - to test the proposition that emotion regulation is governed by readiness to engage in action (specifically, action readiness (AR), defined as the ease with which a new action can be launched, based upon prior instances of that action) and levels of attention (specifically, orienting attention (OA), defined as the application of top-down attention towards desired end-states associated with a behavior). According to the RAM framework, individuals are more likely to launch healthy emotion regulation strategies if they have previously done so in similar contexts, and/or they are directing top-down attention towards emotion regulation outcomes. In this work, we provide evidence for these predictions by describing behavioral effects under laboratory conditions, examining their associated neural mechanisms, and assessing their relevance to everyday life separately for action readiness, orienting attention, and for their interaction (ARxOA).

Disclosures: G. Suri: None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.12

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant DA027764

NSF Postdoctoral Fellowship 1305994

Title: Coping with setbacks: Emphasis on learning from setbacks counteracts effects of acute stress on persistence

Authors: *J. P. BHANJI, E. S. KIM, M. DELGADO;
Rutgers Univ., Newark, NJ

Abstract: The experience of a negative outcome while striving for a goal can cause negative affect, and requires one to cope with this setback in order to persist with the goal. For example, a negative performance evaluation may cause negative affect for an employee trying to earn a promotion. That setback may be exceptionally difficult to cope with if the employee is already experiencing stress from a situation at home. However, setbacks can also provide useful information to improve efforts to achieve a goal. For example, a negative evaluation can guide an employee's future performance towards a goal. In this study, we address two questions. First, we investigate how preexisting stress influences the ability to cope with setbacks. Second, we probe whether emphasizing the informative aspects of setbacks can promote better persistence with goals. Human participants played a game in which they encountered setbacks and made decisions to persist or give up on a goal after the setbacks. Increasing the informative properties of setbacks promoted better persistence after setbacks and diminished negative affect. Prior exposure to an acute cold water stressor (which elicited an increase in salivary cortisol) had a deleterious influence on such persistence behavior. Importantly, the decrease in persistence due to prior stress (compared to a control group) was only observed when uninformative (i.e., random) aspects of the setbacks were emphasized. When informative properties of the setbacks were emphasized, persistence deficits were not observed in the stress group. This is consistent with prior neuroimaging data (Bhanji & Delgado, 2014) demonstrating dissociable neural mechanisms underlying participants' responses to setbacks. Ventral striatal signal decreases were associated with using information from setbacks to correct mistakes and predicted greater persistence through the setbacks. Ventromedial prefrontal cortex (vmPFC) signal increases predicted persistence when setbacks were uninformative (i.e., random), and vmPFC signal changes mediated the relationship between increased negative affect and persistence behavior. Together these results suggest that preexisting stress can impair the ability to cope with negative affect elicited by setbacks, a process potentially associated with vmPFC function. However, coping with setbacks as a learning opportunity, which may rely on striatal mechanisms, can counter the effects of stress.

Disclosures: J.P. Bhanji: None. **E.S. Kim:** None. **M. Delgado:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.13

Topic: F.01. Human Cognition and Behavior

Support: NSF GRFP DGE-0707424

Wendell Jeffrey and Bernice Wenzel Term Chair in Behavioral Neuroscience (UCLA)

Title: Social support and safety: examining the role of social support figures as prepared safety stimuli

Authors: *E. HORNSTEIN, N. EISENBERGER;
Psychology, UCLA, Los Angeles, CA

Abstract: While fear conditioning research has demonstrated that certain stimuli that have threatened survival, namely *prepared fear stimuli,* are more readily associated with fearful events, little research has explored whether a parallel category exists for safety stimuli. We examined whether social support figures, who have typically promoted survival, are '*prepared safety stimuli*,' a category which has not been explored previously. First, we developed a definition of this category using the concept of conditioned inhibitors (learned safety signals that require in-lab training) from Pavlovian conditioning theory, and examined whether, without any lab-based training, social support figure stimuli pass the two tests of conditioned inhibitors. First, we examined whether social support figure stimuli passed a "retardation-of-acquisition test", less readily becoming associated with fear. Participants underwent a session of fear conditioning with three conditions: social support figure stimuli, stranger stimuli, and neutral stimuli. Results showed that while participants could acquire a conditioned fear response for both stranger and neutral stimuli, none was acquired for the social support stimuli (demonstrated by no significant difference in Skin Conductance Response (SCR) after a fear conditioning session, p=.696). Next, we examined whether social support figure stimuli passed a "summation test", inhibiting the conditioned fear response for another cue. Participants first acquired a conditioned fear response for three neutral stimuli, and each was then paired with either a social support figure, stranger, or neutral image to examine whether the conditioned fear response was inhibited. We found that no inhibition occurred when a conditioned stimulus was paired with a stranger or neutral image, but inhibition did occur when a conditioned stimulus was paired with a social support figure image (demonstrated by no significant differences in SCR, p=.314). Additional results demonstrated that this inhibition continued even after the social support stimulus was then removed (demonstrated by no significant difference in SCR, p=.649). These findings show that social support figures naturally, without any lab-based training, pass the tests of a conditioned inhibitor and possibly have other powerful safety signaling properties beyond those normally attributed to learned safety signals. Altogether, these data suggest that social support figures are one category

of prepared safety stimuli and imply that social support figures may have long-lasting effects on fear learning processes.

Disclosures: E. Hornstein: None. **N. Eisenberger:** None.

Nanosymposium

287. Stress and Negative Emotion

Location: N227

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 287.14

Topic: F.01. Human Cognition and Behavior

Support: NIMH Grant P50MH094258

Gordon and Betty Moore Foundation

German Research Foundation (DFG)

Title: An enhanced default approach bias following human amygdala lesions

Authors: *L. A. HARRISON[1], R. HURLEMANN[2], R. ADOLPHS[1];
[1]Caltech, Pasadena, CA; [2]Univ. of Bonn, Bonn, Germany

Abstract: Approach and avoidance constitute a basic dimension of all animal behavior. A large literature documents approach and avoidance elicited by specific sensory stimuli, yet comparatively little is known about default approach biases when stimulus information is reduced. The amygdala is well known to contribute to approach and avoidance behaviors in response to specific sensory stimuli, and here we test whether the amygdala's role might extend to situations where stimulus information is reduced. A novel task asked three rare patients with bilateral amygdala lesions to make approach-related judgments about photos of faces when intact, and with all internal facial features occluded. Direct comparisons of these stimuli isolated a stimulus-independent bias. The patients showed a greater tendency than controls to default to rating occluded faces as more approachable than whole faces. These findings suggest that the amygdala's role in approach behavior extends beyond responses to specific stimuli.

Disclosures: L.A. Harrison: None. **R. Hurlemann:** None. **R. Adolphs:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.01

Topic: G.04. Physiological Methods

Support: Star Family Fund

Fidelity Biosciences

Air Force Office of Scientific Research

Title: Syringe injectable macroporous electronics for *in vivo* electrophysiology

Authors: *C. M. LIEBER[1,2], T.-M. FU[2], G. HONG[2], T. ZHOU[2], T. SCHUHMANN[2], J. LIU[3]; [1]Dept. of Chem. and Chem. Biol., [2]Harvard Univ., Cambridge, MA; [3]Stanford Univ., Stanford, CA

Abstract: Traditional neural probes have limitations in long-term electrophysiology studies due to chronic immune response that leads to signal degradation over time. To meet present and future challenges of understanding complex neural networks calls for new paradigms for electronics that allow precise minimally-invasive delivery into targeted brain regions and subsequent 3D integration with the neural networks. Here we demonstrate the unique capabilities of syringe injectable ultra-flexible macroporous electronics, which have mechanical properties similar to brain tissue and feature sizes similar to neuronal networks, can overcome biocompatibility limitations of more rigid probes and yield *in vivo* electrophysiology data from anesthetized and awake rodents over extended time periods. Targeted delivery of mesh electronics with spatial precision of ca. 10 μm into specific brain regions has been achieved via a stereotaxic stage that locates the needle in the 3D brain coordinates. Post-injection chronic histology studies show that the mesh electronics exhibit unprecedented 'neurophilicity' as evidenced by the close proximity of neurons to and interpenetration neurofilaments with the mesh electronics probe structure. In addition, mesh electronics were stereotaxically-injected into the mouse hippocampus through needles with inner diameter as small as 100-micrometer. A 100% yield I/O connections to external electrical measurement system has been realized through conductive ink printing process, which allows for multiplexed *in vivo* brain electrophysiology recordings on free-moving animals. Multiplexed recordings from the injected electronic networks yielded well-defined LFPs with modulation amplitudes of 200-400 μV, and related spatiotemporal mapping revealed a characteristic hippocampal field activity. Importantly, single-unit spikes were observed and the average peak-to-peak amplitude steadily increased with time after surgery. This study demonstrates excellent biocompatibility of our injectable macroporous electronic sensor networks, and suggests our approach will be unique for future investigations of long-term electrophysiology-based brain activity mapping.

Disclosures: **C.M. Lieber:** None. **T. Fu:** None. **G. Hong:** None. **T. Zhou:** None. **T. Schuhmann:** None. **J. Liu:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.02

Topic: G.04. Physiological Methods

Title: Organized hydrogel scaffolds for promoting and directing neuronal growth

Authors: ***M. ANTMAN- PASSIG**[1,2,3], O. SHEFI[3,2,1];
[2]Inst. for Nanotechnology and Advanced Materials, [3]Fac. of Engin., [1]Bar-Ilan Univ., Ramat-Gan, Israel

Abstract: The ability to manipulate and direct neuronal growth has great importance in the field of tissue engineering, both for neuronal repair and potential medical devices. We have previously demonstrated that neurons grown on patterned nano-topographic cues develop neurites aligned with cues. We have also shown neurite growth is dependent on the material of substrate. However, these and other traditional systems manipulate neuronal growth in a planar 2D manner whilst in-vivo neurons grow and develop in a 3D extra cellular matrix (ECM). In order to address the challenge of directing neuronal growth in 3D we have developed a method to grow neurons in a 3D collagen hydrogel. The collagen hydrogel system was chosen as a 3D ECM analog to best mimic the natural environment of cells. We compared the neuronal growth in 3D to a 2D model and showed that neurons grown in 3D collagen gels develop significantly longer dendritic trees and neurites. We then manipulated the gel construct via inducing controlled uniaxial strain to align collagen matrix. We showed collagen fiber directionality by analysis of light microscope images via Fast Fourier transform and by SEM imaging. Using this method we were able to direct neuronal growth coinciding with collagen matrix orientation. To further direct neuronal growth in 3D we have enhanced the collagen hydrogel system to form a magnetic hydrogel containing cues of designed orientation. We have enriched the hydrogel neuronal culture with magnetic nanoparticles thus creating a magnetically responsive hydrogel. By employing an external magnetic field we were able to control magnetic particle orientation aligned with the magnetic field lines. Control over magnetic particle alignment was achieved by adjusting magnetic field strength, magnetic particle size and gel composition. To analyze neuronal growth in the magnetically aligned hydrogels we used primary leech (Hirudo medicinalis) neuronal culture and PC12 as a mammalian analog. We followed the growth of

single cells for a week. Cells were then immune-labeled and analyzed semi-automatically using imageJ software and an optimized MATLAB script. Our initial results show directed neuronal growth in magnetic hydrogels, without compromising dendritic tree length. These methods for directing neurite growth in 3D hold promise for applicable nerve repair therapies and biomedical technologies.

Disclosures: M. Antman- Passig: None. **O. Shefi:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.03

Topic: G.04. Physiological Methods

Support: BayBrain Initiative

Title: Tetherless upconverting nanocrystal light bulbs for targeted deep tissue nearinfrared optogenetic stimulation

Authors: *M. CHAMANZAR[1], D. J. GARFIELD[2], J. IAFRATI[3], V. SOHAL[4], E. CHAN[5], B. COHEN[5], P. SCHUCK[5], M. M. MAHARBIZ[1];
[1]Univ. of California Berkeley, Berkeley, CA; [2]the Mol. Foundry, Lawrence Berkeley Natl. Lab., Berkeley, CA; [3]the Univ. of California San Francisco, San Francisco, CA; [4]Univ. of California San Francisco, San Francisco, CA; [5]Mol. Foundry, Lawrence Berkeley Natl. Lab., Berkeley, CA

Abstract: Optogenetics is a powerful technique for stimulating neurons. Ion channels in specific cell-types that express light sensitive proteins (opsins) can be modulated in response to light. The absorption band of most of these opsins is in the visible range of spectrum. Tissue exhibits a high absorption in visible wavelength range. Moreover, light is diffracted and scattered as it propagates through the tissue. The combination of large absorption and beam spreading in the tissue results in the degradation of light intensity that rapidly falls below the excitation threshold of opsins. To compensate for this intensity drop, we need to increase the input light intensity at the surface of brain, which would cause excessive heat generation and damage to brain tissue. To reach deep regions of brain, fiber optics and light guides are inserted in the tissue, which can cause damage to the tissue and vasculature. Furthermore, steering light beam in the tissue would require physically moving the guides in the tissue, which is extremely invasive. Here, we present a novel approach to use NIR light (that can penetrate deep into the brain) and excite implanted micro light bulbs that emit visible light at the optogenetic wavelengths to locally stimulate

neighboring neurons. Our light bulbs are microfabricated polymer parylene C pillars that encapsulate lanthanide-doped upconverting nanocrystals (UCNPs). These core/shell UCNPs are optimized to absorb NIR and emit visible light locally. We will discuss ex-vivo experiments to show the power of this method for deep tissue optogenetic stmulation of neural activity in coronal brain slices from a mouse brain. We stereotactically inject the UCNP light bulbs into neocortex of 5-8 week old mice (heterozygous Thy1-ChR2-eYFP line 18 transgenic mice and also B6.Cg-Tg(Thy1-COP4/EYFP)18Gfng/J (Jackson Laboratories). In these mice, Channelrhodopsin-2 fused to enhanced Yellow Fluorescent protein is expressed under the control of Thy1 promoter and neuronal action potential firing happens following blue light illumination. After brain preparation from these mice, slices that include embedded UCNP light bulbs are incubated in artificial cerebrospinal fluid (ACSF) and then perfused (2 ml/min) with equilibrated ACSF at 32-35°C. Whole-cell patch-clamp and field EPSP (fEPSP) using glass pipette electrode are then recorded from neurons at the vicinity of UCNP light bulbs. In this presentation, we will discuss the nanofabrication of tetherless nanocrystal light bulbs and the details of our ex-vivo experiments to show we can reach deep regions of the brain and stimulate targeted clusters of neurons using NIR light.

Disclosures: **M. Chamanzar:** None. **D.J. Garfield:** None. **J. Iafrati:** None. **V. Sohal:** None. **E. Chan:** None. **B. Cohen:** None. **P. Schuck:** None. **M.M. Maharbiz:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.04

Topic: G.04. Physiological Methods

Support: Grant/Other Support: Medical Research Council (MC_UP_1202/5)

HFSP (RGP0048/2013)

Title: Efficiently scalable, modular *in vivo* neuronal recordings with a readout integrated circuit

Authors: ***M. KOLLO**[1], W. WRAY[1], R. R. RACZ[1], N. KISKIN[1], M. ANGLE[2], A. T. SCHAEFER[1,3];
[1]The Francis Crick Inst. Mill Hill Lab., London, United Kingdom; [2]Stanford Univ., Stanford, CA; [3]Univ. Col. London, Neuroscience, Physiology, Pharmacol, United Kingdom

Abstract: Computational functions of neuronal networks rely on the orchestrated activity of thousands to millions of neurons. In order to understand how sensory percepts or higher order cognitive structures arise from these patterns, it is essential to be able to monitor the electrical activity of a large proportion of the involved neurons individually at millisecond resolution. Therefore, to address such questions, an ideal electrophysiological recording technique would employ small electrodes in a highly scalable configuration, in order to record from many single neurons. Finally, to avoid the signal-to-noise problems often associated with small electrodes, each electrode should also be optimized for both low electrode-electrolyte interfacial impedance and low stray capacitance. Here we present an approach that addresses this challenge by combining bundles of insulated metal wires with arrays of highly sensitive amplifiers based on readout integrated circuits (ROICs) from high-speed infrared cameras. Glass-ensheathed metal wires with customizable metal core (2-15 um) and glass (10-40 um) diameters were assembled in bundles with 10-100.000 individual wires. The bundles were contacted to the ROIC of a Xenics Cheetah 640-CL1700 camera, incorporating over 300,000 capacitive transimpedance amplifier circuits with <10 fF feedback capacitance at a pixel pitch size of 20 um. Noise levels were less than 70 μm (SD) at 10 kHz sampling frequency and 14 bit signal resolution and a dynamic range of 3 mV. To further potentiate electrolyte-electrode coupling, iridium oxide was plated on the recording interface by electrochemical deposition, increasing interface capacitance to > 2 pF/μm. This resulted in recorded neuronal spike signals of up to 1.2 mV in anaesthetized mice *in vivo*. Our data suggests that the combination of bundles of insulated metal wires and high-speed ROICs provides a highly scalable approach to neuronal unit recordings.

Disclosures: **M. Kollo:** None. **W. Wray:** None. **R.R. Racz:** None. **N. Kiskin:** None. **M. Angle:** None. **A.T. Schaefer:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.05

Topic: G.04. Physiological Methods

Support: NIH 1U01MH106011-01

NIH 1R24MH106075-01

NIH 1DP1NS087724

Hertz Foundation Graduate Fellowship

Title: Optical reflectometry with capacitive signal enhancement for multiplexed neural recording

Authors: *S. G. RODRIQUES[1], A. H. MARBLESTONE[1], E. S. BOYDEN[2];
[2]Media Lab., [1]MIT, Cambridge, MA

Abstract: We introduce a fiber-optic architecture for neural recording without contrast agents, and study its properties. Our sensor design is inspired by electrooptic modulators, which modulate the refractive index of a waveguide by applying an electric field across an electrooptic core material, and allows neural recording over a 10 centimeter length of optical fiber with 30 micron axial resolution, with high sensitivity and a large dynamic range using commercially available optical reflectometers as readout devices. The key concept of the design is the ability to create an ``intensified'' electric field inside an optical waveguide by applying the extracellular voltage from a neural spike over a nanoscopic distance. Implementing this concept requires the use of ultrathin high-dielectric capacitor layers. If suitable materials can be found -- possessing favorable properties with respect to toxicity, ohmic junctions, and surface capacitance -- then such sensing fibers could, in principle, be scaled down to few-micron cross-sections. Custom-designed multi-material optical fibers, probed using a reflectometric readout, may therefore provide a powerful platform for neural sensing.

Disclosures: S.G. Rodriques: None. **A.H. Marblestone:** None. **E.S. Boyden:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.06

Topic: G.04. Physiological Methods

Support: Charles E. Smith and Prof. J. Elkes Laboratory for Collaborative Research in Psychobiology

EU FP7 MERIDIAN grants agreement No. 280778

EU FP7 FET program, “BRAINLEAP” grant No. 306502

EU FP7 Marie Curie ITG Grant agreement No. 264872

Title: Long-term, multisite, noninvasive, in-cell recordings by extracellular gold mushroom-shaped microelectrode array from *in vitro* bursting rat hippocampal neurons networks

Authors: *M. E. SPIRA, S. M. OJOVAN, N. RABIEH, N. SHMOEL, H. EREZ;
The Hebrew Univ. of Jerus, Jerusalem, Israel

Abstract: The development of multi-electrode array platforms for large scale recordings of individual neurons comprising a neuronal network is at the forefront of neuro-engineering research efforts. In past years our laboratory focused on developing a technological approach that merge the advantageous properties of noninvasive substrate integrated planar multi-electrode array with those of intracellular recording of sub threshold synaptic- and action-potentials by patch or sharp electrodes. Here we report on the use of the cell-noninvasive gold-mushroom-shaped microelectrode arrays (gMμEs) to simultaneously record from a large number of individual rat hippocampal neurons comprising a spontaneously bursting network in culture. As the gMμEs maintain extracellular position the gMμEs-hippocampal neurons configuration allows long-term in-cell recordings. In the presentation we: (a) analyze the physical parameters that define the expected electrical coupling coefficient levels formed between neurons and gMμEs. (b) Describe the electrophysiological signaling repertoire recorded by an 8x8 gMμE array and (C), analyze the mechanisms and origin of the in-cell recorded electrophysiological signaling repertoire. By comparing the estimated physical limits and the experimental results we define the physical, chemical and biological parameters that could be modified to further improve the electrical coupling coefficient between neurons and gMμE arrays. Based on the present results it is conceivable that the extracellular gMμE platforms could be beneficial also for *in vivo* studies.

Disclosures: M.E. Spira: None. **S.M. Ojovan:** None. **N. Rabieh:** None. **N. Shmoel:** None. **H. Erez:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.07

Topic: G.04. Physiological Methods

Support: NSF (CBET-1253890)

CMSE (DMR-0819762)

CSNE (ERC)

McGovern Institute for Brain Research

Title: Multimodal interrogation of brain circuits with thermally drawn flexible neural probes

Authors: *A. CANALES, X. JIA, U. P. FRORIEP, R. A. KOPPES, C. M. TRINGIDES, J. SELVIDGE, Y. FINK, P. ANIKEEVA;
MIT, Cambridge, MA

Abstract: Mapping neural circuits *in vivo* requires interacting with the diversity of the brain signaling modalities with high spatial resolution over extended periods of time. Neural probes are currently limited in their long-term utility due to the foreign-body response manifested in neuronal death and the formation of a glial scar around the probe, which lead to decreased signal-to-noise ratio (SNR) and loss of recorded neuronal units. It has been hypothesized that one of the responsible factors for this observed probe failure is the mismatch in elastic moduli between the neural tissue and the neural probes. In addition to longevity, many neurophysiological experiments require neural recording devices to incorporate other capabilities, such as optogenetic stimulation and drug delivery. However, incorporation of additional modalities often results in larger and stiffer devices, and is expected to further aggravate the tissue response to neural probes. Leveraging thermal drawing process, widely used in the telecommunications industry, we developed minimally invasive neural probes consisting of biocompatible polymers and polymer-metal composites. These probes are first designed and fabricated as macroscale templates, called preforms, incorporating different materials and functionalities in the desired geometry. These preforms are then heated and stretched into fibers with identical cross-sectional geometries and features reduced by 30-200 times and lengths of hundreds of meters. Using this method, we have fabricated flexible multielectrode probes as thin as 80 μm in diameter (comparable to a human hair) with individual electrodes sizes ~ 5 μm. These devices were used to record action potentials in freely moving mice with average SNR = 13. Fiber-drawing was also employed to produce multifunctional probes that seamlessly integrated recording electrodes, hollow channels for drug delivery and polymer waveguides for optogenetic stimulation. We demonstrated simultaneous operation of all three modalities by recording neural activity in response to optogenetic stimulation during injection of neuromodulatory compounds. Finally, we found that long term implantation of our probes results in little accumulation of glia, astrocytes and macrophages and minimal blood-brain barrier breach surrounding the electrodes. Consequently, we believe that fiber-based probes may provide a promising minimally-invasive tool for studying the complexity of the brain signaling modalities in the context of systems neuroscience.

Disclosures: A. Canales: None. **X. Jia:** None. **U.P. Froriep:** None. **R.A. Koppes:** None. **C.M. Tringides:** None. **J. Selvidge:** None. **Y. Fink:** None. **P. Anikeeva:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.08

Topic: G.04. Physiological Methods

Title: A storm is coming: The challenges of analyzing, modeling, and using huge volumes of data from nanoscale electrophysiological recordings

Authors: *G. A. SILVA;
Bioengineering, UCSD, La Jolla, CA

Abstract: There is currently tremendous interest (and significant funding) in existing and emerging nanotechnologies aimed at ultra high density electrical recording of neuronal activity in the brain. Much (almost all?) of the existing efforts and funding opportunities to date have focused on the development of novel and innovative neurotechnologies designed to achieve this. However, equally daunting and critical are related issues associated with the analyses, modeling and general use of the mountains of data expected to result from such recordings. These have received less attention although they are certainly recognized as being critical to the eventual success of this entire effort. In this talk we will discuss in particular two aspects of this problem: 1. How to extract the high volumes of data generated by such recordings in a meaningful way, which presumably will be in the tens if not hundreds of thousands simultaneously, and 2. what we might do with all of this data once we have it to understand neural dynamics with the ultimate goal of understanding how the brain works.

Disclosures: G.A. Silva: None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.09

Topic: G.04. Physiological Methods

Title: Cmos-nanoelectrode array for high fidelity, multiplexed interrogation of neuronal ensembles

Authors: *H. PARK;
Dept. of Chem. and Chem. Biol., Harvard Univ., Cambridge, MA

Abstract: Parallelization of intracellular recording/stimulation will revolutionize the field of neuroscience and neurotechnology. Combining the two tasks, intracellular and parallel, in one tool, however, has proven an outstanding challenge. Recent advances in nanoscale neuronal interfaces, in particular, vertical nanoelectrodes, offer a new line of attack to this long-standing parallel vs. intracellular dichotomy: the nanoelectrodes can enter live mammalian neurons for intracellular measurement/stimulation, yet they can be top-down defined by standard fabrication techniques into an large-scale array. In this presentation, I will describe our efforts to transform our first generation, passive nanoelectrode prototypes into a fully integrated, active CMOS-nanoelectrode array (CNEA) with significantly improved capability. Concretely, we are creating a large, high-density array --128×128 recording/stimulation sites -- of vertical nanoelectrodes on top of a CMOS integrated circuit (IC) that we will custom design. Nanoelectrodes at each site are operated by their own amplifier, stimulator, and memory in the underlying IC. These proximal electronics are pivotal in enabling the large array operation and for achieving the recording sensitivity on a par with the patch clamp technique. Our new nano-neuro interface should enable massively parallel, high-fidelity electrophysiological interrogation of complex neuronal ensembles *in vitro* and ex vivo, thereby providing a new experimental platform for high-throughput screening of new pharmaceutical candidates for neurological disorders as well as the interrogation and manipulation of the “functional connectome” of a complex neuronal network.

Disclosures: H. Park: None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.10

Topic: G.04. Physiological Methods

Support: NIH DP2-NS082125

NSF 1055112

Title: Nanoelectrodes for intracellular electrophysiology recording

Authors: *B. CUI, A. MCGUIRE, W. ZHAO;
Stanford Univ., Stanford, CA

Abstract: The rapidly evolving field of nanotechnology creates new frontiers for biological sciences. Recently, we and other groups show that vertical nanopillars protruding from a flat surface support cell survival and can be used as subcellular sensors to probe biological processes in live cells. In particular, we are exploring nanopillars as electric sensor, optical sensors, and structural probes. As an electrode sensor, nanopillars electrodes offer several advantages such as high sensitivity, subcellular spatial resolution, and precise control of the sensor geometry. We found that the 3D topology of the nanopillars electrodes is crucial for its enhanced signal detection. The high membrane curvature induced by vertical nanopillars significantly affects the distribution of curvature-sensitive proteins and stimulates several cellular processes in live cells. Our studies show a strong interplay between biological cells and nano-sized sensors, which is an essential consideration for future development of interfacing devices.

Disclosures: B. Cui: None. **A. McGuire:** None. **W. Zhao:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.11

Topic: G.04. Physiological Methods

Support: NSF award 1265055

DARPA award W911NF-14-1-0006

Title: Integrated neurophotonics: Precisely localized optogenetic stimulation via photonic neural nanoprobes

Authors: *E. SEGEV[1], J. REIMER[5], L. C. MOREAUX[1], T. M. FOWLER[1], D. CHI[1], A. FARAON[2], A. G. SIAPAS[3], A. S. TOLIAS[5], M. L. ROUKES[4];
[1]Kavli Nanoscience Inst. and Dept. of Physics, [2]T. J. Watson Lab. of Applied Physics, [3]Computation and Neural Systems, [4]Kavli Nanoscience Inst. and Dept. of Physics, Applied Physics, and Bioengineering, Caltech, Pasadena, CA; [5]Dept. of Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Computation and information processing in the brain arise from the coordinated activation of large assemblies of neurons distributed across the brain. Current methods for studying these assemblies lack the required ability to deliver precise, dense, and specific stimulation patterns across deep brain circuits, with high spatial and temporal resolution. We

have developed ultra-compact multi-pixel implantable silicon-based neural probes for optogenetic stimulation at arbitrary depths in brain tissue. Our probe design can be easily tailored for customized studies of specific brain areas, with arbitrary number of shanks spaced at arbitrary pitch, each containing specifically patterned arrays of photonic emitters. These probes are minimally invasive, with shanks having a cross-section roughly an order of magnitude smaller than previous state-of-the-art probes. Our fabrication process is fully compatible with semiconductor foundry mass-production methodologies; about 300 probes can be fabricated on a 4" wafer. The compact footprint of these probes is achieved through wavelength division multiplexing and demultiplexing. This enables a single optical fiber to carry a multiplicity of separately modulated wavelengths (signal channels), which are demultiplexed *in situ* to permit delivery of temporally patterned light to the many illumination points on the probes. A one-to-one mapping between the wavelength of the input light and the spatial location of the corresponding output emitting pixel is set by the probe design. Optical demultiplexing of the visible wavelength stimulation signals is achieved by embedded array waveguide gratings (AWG). We experimentally demonstrate AWGs working in the visible spectrum, with spectra centered on blue (473nm) wavelengths within the absorption band of the ChR2 family of optogenetic effectors. These AWGs are integrated at the base of the shanks; in our current design, each routes light to nine densely spaced illumination points located close to the tip of the shank. The scalability of this technology enables up to hundreds of independent stimulation points to be fabricated on each probe shank. We have experimentally characterized the functionality of these probes in a mammalian brain *in vivo*. Blue light delivered by the probe is used to excite neurons co-expressing ChR2-mCherry (ET-TC) and GCaMP6s in the cortex of a 16-week old C57/Bl6 female mouse 25 days after transfection. Neural activity is simultaneously measured using 2-photon imaging. Using our photonic nanoprobes we demonstrate the ability to pinpoint excitation to one individual neuron within an ensemble of optogenetically labeled neurons.

Disclosures: **E. Segev:** None. **J. Reimer:** None. **L.C. Moreaux:** None. **T.M. Fowler:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **D. Chi:** None. **A. Faraon:** None. **A.G. Siapas:** None. **A.S. Tolias:** None. **M.L. Roukes:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.12

Topic: G.04. Physiological Methods

Support: DARPA Young Faculty Award (D13AP00043)

NSF CAREER award (CBET-1253890)

MIT NSF MRSEC Shared Experimental Facilities DMR- 0819762

Title: Wireless magnetothermal deep brain stimulation

Authors: *R. CHEN[1,2], G. ROMERO[2], M. G. CHRISTIANSEN[1,2], A. MOHR[3], P. ANIKEEVA[1,2];
[1]Materials Sci. and Engin., [2]Res. Lab. of Electronics, [3]Chem. Engin., MIT, Cambridge, MA

Abstract: Electrical deep brain stimulation can ameliorate symptoms of treatment-resistant psychiatric and neurological disorders. However, mechanically-invasive implanted electrodes are required to deliver electrical impulses, often with variable results because the cellular mechanism is poorly understood. Next-generation neural stimulation technologies, such as optogenetics and transcranial ultrasound stimulation, also require conduits to deliver local stimuli into sub-cortical structures. Alternating magnetic fields (AMF) in the low-radiofrequency regime, a largely unexplored modality in neuroscience, can penetrate deep into tissue with little signal attenuation due to the body's low magnetic susceptibility. Magnetic nanoparticles undergo hysteretic heating in the presence of AMFs, an effect commonly employed for cell destructive therapies in cancer hyperthermia and recently explored for wireless control of cell signaling *in vitro* and glucose release in engineered xenographs. We have optimized the hysteretic power dissipation of magnetic nanoparticles at clinically relevant magnetic field amplitudes and frequencies (Chen, R. et al. ACS Nano 2013) for wireless magneothermal neural excitation. We first demonstrated synchronized and repeatable neural excitation with AMF pulses in primary hippocampal neural cultures incubated with magnetic nanoparticles and sensitized to heat via transfection with a thermally-sensitive capsaicin receptor TRPV1 (Chen, R. et al. Science 2015). We have also shown magnetothermal excitation of intact neural circuits chronically in mice. Lentiviral delivery of TRPV1 to excitatory neurons in the ventral tegmental area (VTA) followed by nanoparticle injection enabled neural excitation of VTA neurons as well as its projections into the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) a month later. Surface passivation of the nanoparticles with poly(ethylene glycol) reduced the foreign-body response to the ferrofluid injection in the brain as compared to a similarly-sized stainless steel implant. Our experiments illustrate that wireless control of heat-sensitized neural circuits *in vitro* and *in vivo* is possible with colloidal solutions of biocompatible magnetic nanoparticles. However, *in vivo* physiological recordings and modulation of behaviors remain to be explored. Further, this modality for neural stimulation, consisting of a simple injection into a targeted brain structure, may also enable triggering of thermally sensitive ion channels expressed endogenously.

Disclosures: **R. Chen:** None. **G. Romero:** None. **M.G. Christiansen:** None. **A. Mohr:** None. **P. Anikeeva:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.13

Topic: G.04. Physiological Methods

Support: NSF DMR-1254637

AFOSR FA9550-14-1-0175

Searle Scholars program

Title: Mesostructured silicon for enhanced biointerfaces

Authors: ***B. TIAN**;
Chem., The Univ. of Chicago, Chicago, IL

Abstract: Achieving tight integration of semiconductor-based medical devices with neuronal components is challenging. Natural skeletal elements or extracellular matrices have mesoscale features that are known to promote cellular interactions. Herein we develop a modular deposition-diffusion-incorporation approach for direct chemical synthesis of mesostructured skeleton-like spicules made of silicon. The spicules have three-dimensional tectonic motifs, reduced symmetries, and curvilinear open frameworks with gradient. Atom-probe tomography and other quantitative measurements indicate the existence and unexpected role of individual gold atoms in controlling patterned inorganic-inorganic interfaces and spicule formation. When interfacing with individual collagen fibers, synthetically enabled mesostructures in silicon lead to enhanced detachment force and work. Finally, we showed that silicon spicules form robust and flexible interfaces with single cells and exhibit improved electrical performance. Our work suggests new silicon-based electrode components for neuroscience and neuroengineering.

Disclosures: **B. Tian:** None.

Nanosymposium

288. Electrode Arrays II

Location: N228

Time: Monday, October 19, 2015, 8:00 AM - 11:30 AM

Presentation Number: 288.14

Topic: G.04. Physiological Methods

Support: NSF GRFP 0940902

DARPA Young Faculty Award D14AP00049

Title: Suspended nano-electrodes for high-throughput electrophysiological phenotyping of *C. elegans*

Authors: *D. L. GONZALES[1,2], K. N. BADHIWALA[3], B. W. AVANTS[2], J. T. ROBINSON[1,2,3,4];
[1]Applied Physics, [2]Electrical and Computer Engin., [3]Bioengineering, Rice Univ., Houston, TX; [4]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: The small size, fast generation time and genetic tractability of *C. elegans* in combination with its use as a model organism for human diseases have allowed researchers to perform a variety of high-throughput assays to study human diseases and reveal potential drug treatments. These assays include methods for imaging, protein expression, genetic sequencing, and behavioral profiling. However, the lack of a high-throughput technique for measuring electrophysiology hinders the accurate phenotyping of models for neurological diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS). A protocol for dissection and micropipette patch-clamp measurements in *C. elegans* exists, but the lack of scalability and laborious nature of this method falls short of the throughput needed to screen thousands of genetic perturbations and drug candidates when studying diseases. To facilitate the study of neurological diseases in small organisms, we invented a microfabricated device based on suspended nano-electrodes (SNEs) integrated into a microfluidic platform. This scalable technique records body-wall muscle electrophysiology in intact animals that remain viable post-measurement. Using this device, we can extract several electrophysiological metrics including waveforms, spike statistics, and power spectral densities to produce the first high-dimensional electrophysiological phenotypes of *C. elegans* models for AD, PD and ALS. In addition, we measured a rescue of normal electrophysiology in PD worms treated with a known neuroprotective drug. These results verify that SNEs measure both the changes in electrophysiology due to a diseased-state and the effects of drug treatments on these disease models. Furthermore, because our device is fabricated using semiconductor manufacturing processes we can array more than a dozen recording chambers on the same chip and rapidly screen for drugs that help recover regular electrophysiological phenotypes. Overall, SNE

technology represents a new paradigm for high-throughput electrophysiological studies of small organism models for neurological diseases.

Disclosures: D.L. Gonzales: None. **K.N. Badhiwala:** None. **B.W. Avants:** None. **J.T. Robinson:** None.

Nanosymposium

368. New Progresses in Nerve Regeneration and Transplantation

Location: S102

Time: Monday, October 19, 2015, 1:00 PM - 3:15 PM

Presentation Number: 368.01

Topic: A.07. Transplantation and Regeneration

Support: NIH Grant 1K99NS088211-01

NIH Grant 2R37NS040929

NIH Grant EY010688-19

Howard Hughes Medical Institute

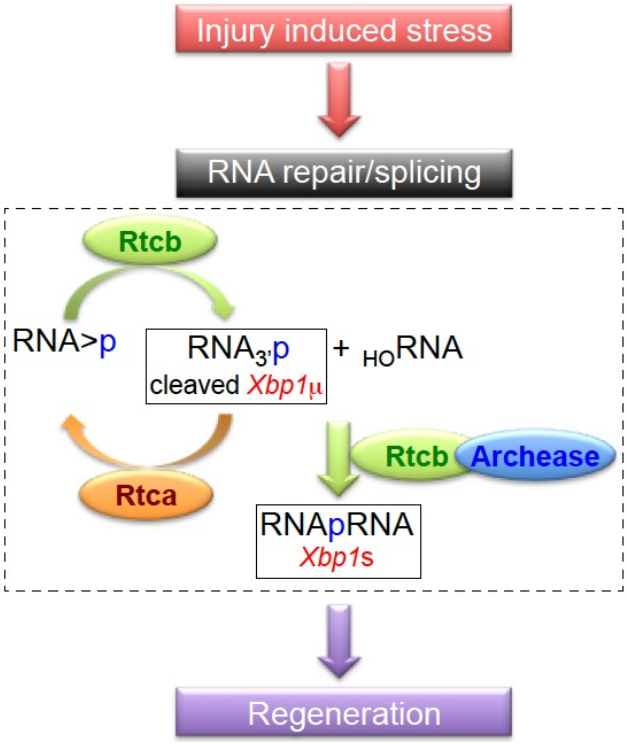
UC Irvine-Roman Reed grant P0045665

Title: Evolutionarily conserved regulation of axon regeneration by the RNA repair/splicing pathway

Authors: *Y. SONG[1], D. SRETAVAN[2], L. JAN[1], Y. JAN[1];
[1]Physiol., [2]Ophthalmology, Univ. of California, San Francisco, San Francisco, CA

Abstract: Mechanisms governing a neuron's regenerative ability are important but not well understood. We identified Rtca, RNA 3'-terminal phosphate cyclase, as an inhibitor for axon regeneration. Removal of dRtca cell-autonomously enhanced axon regrowth in the *Drosophila* central nervous system, whereas its overexpression reduced axon regeneration in the periphery. Rtca along with the RNA ligase Rtcb and its catalyst Archease operate in the RNA repair/splicing pathway important for stress induced mRNA splicing, including that of Xbp1, a cellular stress sensor. Rtca and Archease had opposing effects on Xbp1 splicing, and deficiency of Archease or Xbp1 impeded axon regeneration in *Drosophila*. Indicative of evolutionary conservation of Rtca function, overexpressing mammalian Rtca in cultured rodent neurons reduced axonal complexity *in vitro*, whereas reducing its function promoted retinal ganglion cell axon regeneration after optic nerve crush in mice. Our study thus links axon regeneration to

cellular stress and RNA metabolism, revealing new potential therapeutic targets for treating nervous system trauma.



Disclosures: **Y. Song:** None. **D. Sretavan:** None. **L. Jan:** None. **Y. Jan:** None.

Nanosymposium

368. New Progresses in Nerve Regeneration and Transplantation

Location: S102

Time: Monday, October 19, 2015, 1:00 PM - 3:15 PM

Presentation Number: 368.02

Topic: A.07. Transplantation and Regeneration

Support: Craig H. Neilsen Foundation

Title: PARG and PARP genes are novel regulators of axon regeneration

Authors: ***A. B. BYRNE**[1], R. MCWHIRTER[2], D. M. MILLER[2], M. HAMMARLUND[3]; [1]Dept. of Genet., Yale Univ. Sch. of Med., New Haven, CT; [2]Vanderbilt Univ., Nashville, TN; [3]Genet., Yale Univ., New Haven, CT

Abstract: Few of the intrinsic mechanisms that regulate axon regeneration after injury are known. To identify genes that regulate axon regeneration, we compared gene expression profiles of FACS-sorted *C. elegans* GABA motor neurons with high regenerative capacity (conferred by overexpression of DLK-1 MAPKKK) to wild type GABA motor neurons. We detected robust upregulation of both poly(ADP-ribose) glycohydrolases (PARGs), *parg-1* and *parg-2*, in neurons with high regenerative capacity. These data suggest PARG activity might promote axon regeneration. To test this hypothesis, we performed laser axotomy in *parg-1* and *parg-2* loss-of-function mutants and we found that regeneration is impaired in both mutants. Therefore, PARGs are regeneration-promoting factors. PARGs degrade poly(ADP-ribose), which is synthesized by poly(ADP-ribose) polymerases (PARPs). The balance between PARG and PARP activity determines cellular levels of poly(ADP-ribose) and regulates multiple processes including DNA damage response, lifespan, and neurodegeneration. Since PARGs counteract PARP function, we hypothesized that loss of PARP activity would have the opposite effect on axon regeneration to loss of PARG activity. We found that loss of function of PARP genes *parp-1* and *parp-2* increased axon regeneration. Therefore, PARPs inhibit axon regeneration. Together with our PARG findings, these data suggest that levels of poly(ADP-ribose) are a critical determinant of regenerative potential. Next, we investigated whether we could inhibit PARP activity post-injury to promote regeneration of damaged axons. Multiple PARP inhibitors are currently in clinical trials for indications including cancer and stroke. We tested whether the same PARP inhibitors could enhance axon regeneration. Wild type animals treated with chemical PARP inhibitors after injury showed significantly enhanced axon regeneration compared to controls. Thus, PARP activity regulates the acute response of neurons to axon injury, and PARP inhibition after injury is sufficient to improve regeneration. Together, our findings identify a novel pathway involving control of poly(ADP-ribose) levels that regulates axon regeneration.

Disclosures: **A.B. Byrne:** None. **R. McWhirter:** None. **D.M. Miller:** None. **M. Hammarlund:** None.

Nanosymposium

368. New Progresses in Nerve Regeneration and Transplantation

Location: S102

Time: Monday, October 19, 2015, 1:00 PM - 3:15 PM

Presentation Number: 368.03

Topic: A.07. Transplantation and Regeneration

Title: Toward *in vivo* retinal stem cell activation: Inhibition of BMP and sFRP2 proteins in the adult mouse eye induces ciliary body-specific proliferation and expands the retinal stem cell population

Authors: *K. N. GRISE, L. BALENCI, C. WONDERS, B. L. K. COLES, D. VAN DER KOOY;
Mol. Genet., Univ. of Toronto, Toronto, ON, Canada

Abstract: Adult retinal stem cells (RSCs) are rare cells that reside in the pigmented ciliary epithelium (CE) of the mammalian eye. Once dissociated from the CE, RSCs readily proliferate to form clonal, free floating spheres after 7 days, with the capacity to self-renew and differentiate into all of the cell types of the neural retina and retinal pigmented epithelium. Despite having the capacity to proliferate *in vitro*, RSCs do not proliferate or generate new retinal cells in adult mammals *in vivo*. Previously, we identified BMP and sFRP2 proteins as potential mediators of RSC quiescence with *in vitro* experiments. We found that conditioned media (CM) from the adult lens and cornea suppressed RSC sphere formation, while inhibiting BMP and sFRP2 signaling in the CM restored sphere growth. Here, we investigate whether eye-specific BMP and sFRP2 inhibition *in vivo* disinhibit RSC quiescence in mice. We injected noggin or anti-SFRP2 antibody intravitreally into the right eye once every 24hrs, for 72 hrs, at 2 doses (1.5ug/mL or 2.5ug/mL). The left eye was injected with PBS as a control and one group received no injections to serve as naïve controls. During the injection period, all groups received EdU in their drinking water. Mice were euthanized at either 24hrs or 4 weeks after the last injection and EdU+ cells were quantified in the ciliary body (CB) and neural retina (NR). Noggin or α-sFRP2 treatment did not affect the number of EdU+ cells in NR 24hrs or 4 weeks post-injection. 24hrs post-injection, there were more EdU+ cells in the CB of the 2.5ug/mL α-sFRP2 treated eyes than in the controls and at the 1.5ug/mL dose. Both the 1.5ug/mL and 2.5ug/mL noggin treated eyes had increased EdU+ cells in the CB compared to the controls. 4 weeks post-injection, α-sFRP2 treated eyes had more EdU+ cells than both controls in the CB. Noggin treated eyes also had more EdU+ cells in the CB than naïve controls, but did not reach significance compared to PBS controls. This indicates that α-sFRP2 and noggin may have different efficacies or mechanisms to induce proliferation, or may be acting on different cells. To investigate this further, we performed a clonal sphere assay 7 days after injection of noggin or α-sFRP2. We found that α-sFRP2 increased the total number of primary RSC spheres to 220% of controls, whereas the total sphere number from noggin treated eyes increased to 147%, but was not significantly different from the PBS controls. However, there was a significant change in sphere size distribution in both conditions. These results establish that inhibition of BMP and sFRP2 signaling can cause CB-specific proliferation within the adult mouse eye. Further, inhibiting sFRP2 appears to expand the retinal stem cell pool.

Disclosures: K.N. Grise: None. **L. Balenci:** None. **C. Wonders:** None. **B.L.K. Coles:** None. **D. van der Kooy:** None.

Nanosymposium

368. New Progresses in Nerve Regeneration and Transplantation

Location: S102

Time: Monday, October 19, 2015, 1:00 PM - 3:15 PM

Presentation Number: 368.04

Topic: A.07. Transplantation and Regeneration

Support: Medical Research Council

European Research Council

Christopher and Dana Reeve Foundation

Title: The loss of intrinsic regeneration ability in neurons maturing *in vitro* and the role of Rab11 in this decline

Authors: *H. KOSEKI[1], R. EVA[2], B. Y. H. LAM[3], M. DONEGÀ[2], M. K. L. MA[3], G. S. H. YEO[3], J. W. FAWCETT[2];
[1]John Van Geest Ctr. For Brain Repair, University of Cambridge, Cambridge, United Kingdom; [2]John Van Geest Ctr. For Brain Repair, Dept. of Clin. Neurosciences, University of Cambridge, Cambridge, United Kingdom; [3]MRC Metabolic Dis. Unit, IMS-MRL, Addenbrooke's Hospital, Cambridge, United Kingdom

Abstract: CNS neurons regenerate less than PNS neurons and lose intrinsic regenerative ability with maturation. However our knowledge of the actual intrinsic changes in the axon growth machinery in these maturing CNS neurons is limited. We have developed an in-vitro tissue culture model of embryonic rat cortical neurons that recapitulates this regeneration decline with maturity and is suitable for live-imaging of axon transportation and cytoskeletal molecules after laser axotomy. In this model, neurons show many markers of maturation including dendritic spine and synapse formation, electrophysiological changes and changes in gene expression which we have assayed by RNA sequencing. Neurons progressively lose their ability to regenerate their axons after axotomy, and by 24 days *in vitro* axon regeneration is very uncommon. The axon response after axotomy is to create an active retraction bulb, followed in younger axons often 5 hours or more later by generation of a regenerating process either from the retraction bulb or from a point proximal. We then aimed to elucidate molecular mechanisms leading to this loss, especially from the perspective of axon transportation. We focused on the endosomal small GTPase Rab11, which regulates recycling endosomes involved in axonal transportation of growth receptors such as integrins and trkB, which are important in sustaining the growth cone. We found that Rab11 becomes somatodendritic as neurons mature, consistent with previous in-vivo observations, and similar to integrins and trks. Overexpression of wild type Rab11a in maturing neurons was able to induce altered trafficking, sending some Rab11a positive vesicles into the axon. Upon axotomy, accumulation of these vesicles was seen at the tip, and Rab11 overexpression resulted in an increase in regeneration, suggesting that the

distribution change of Rab11 is important in the maturational decline in axon regeneration ability. We are currently looking into strategies to send Rab11 more efficiently into the axon. Many transportation molecules are strictly governed upon maturation, and focusing on these changes may open new possibilities for promoting axon regeneration.

Disclosures: **H. Koseki:** None. **R. Eva:** None. **B.Y.H. Lam:** None. **M. Donegà:** None. **M.K.L. Ma:** None. **G.S.H. Yeo:** None. **J.W. Fawcett:** F. Consulting Fees (e.g., advisory boards); Acorda Therapeutics, Vertex Pharmaceuticals.

Nanosymposium

368. New Progresses in Nerve Regeneration and Transplantation

Location: S102

Time: Monday, October 19, 2015, 1:00 PM - 3:15 PM

Presentation Number: 368.05

Topic: A.07. Transplantation and Regeneration

Support: NEI

Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

NIH P30 HD018655

HIN P30EY012196

Title: Restoration of visual function by enhancing conductance in regenerated axons

Authors: ***F. BEI**[1], H. H. C. LEE[1], X. LIU[1], C. WANG[1], E. FRANK[2], C. CHEN[1], M. FAGIOLINI[1], Z. HE[1];
[1]Boston Children's Hosp., Harvard Med. Sch., Boston, MA; [2]Physiol., Tufts Univ., Boston, MA

Abstract: Even in the intact nervous system, axonal connections do not automatically translate to functionally relevant neuronal circuits for a given behavior. In the injured central nervous system (CNS), despite recent successes in developing methods to promote long distance axon regrowth, it remains unknown whether regenerated axons induced by these manipulations are able to form functional synapses and support behaviors. Here we analyzed these steps following regeneration of injured retinocollicular axons induced by an established method of activating intrinsic regenerative ability in retinal ganglion cells (RGCs). We show that co-deletion of PTEN and SOCS3 in injured RGCs promotes severed retinocollicular axons to regrow into the superior colliculus (SC). Importantly, regenerated axons form functional synapses with SC neurons as assessed by optogenetics-assisted electrophysiological recordings both *in vitro* and *in vivo*.

However, regenerated axons exhibit a poor ability to conduct electrophysiological signal from the eye to SC, likely due to the lack of myelination. And, no significant increases of visual acuities were detected in the treated mice when they were tested for optomotor performance. We are currently examining the possible mechanisms underlying the failure of myelination in the regenerated axons, and also screening for strategies that enhance the conductance of the regenerated axons and that eventually restore visual function at the behavioral level.

Disclosures: **F. Bei:** None. **H.H.C. Lee:** None. **X. Liu:** None. **C. Wang:** None. **E. Frank:** None. **C. Chen:** None. **M. Fagiolini:** None. **Z. He:** None.

Nanosymposium

368. New Progresses in Nerve Regeneration and Transplantation

Location: S102

Time: Monday, October 19, 2015, 1:00 PM - 3:15 PM

Presentation Number: 368.06

Topic: A.07. Transplantation and Regeneration

Support: Congressionally Directed Medical Research Program for the Department of Defense, MR130444

Competitive Medical Research Fund at the University of Pittsburgh

Louis Fox Center for Vision Restoration, University of Pittsburgh, PA

NIH CORE Grant P30 EY008098

Eye and Ear Foundation of Pittsburgh, PA

Unrestricted Grant from Research to Prevent Blindness, New York, NY

Lions Club of Western Pennsylvania

Title: Using extracellular matrix technology to promote retinal ganglion cell survival and axon regeneration

Authors: *Y. VAN DER MERWE[1,2,3,4], I. P. CONNER[1,3,4], A. E. FAUST[2,3], X. GU[2], A. NAQVI[2,3], T. REN[2,3], A. KANDAKATLA[2,3], V. REDDY[2,3], B. WANG[1,3], K. LUCY[3], F. MEHDI[2,3], L. R. LEWIS[2,3], H. SONG[2,3], K. C. CHAN[1,2,3], G. WOLLSTEIN[3], K. M. WASHINGTON[5], W. R. WAGNER[1,2,6], S. F. BADYLAK[1,2,6], M. STEKETEE[2,3,4,7];
[1]Dept. of Bioengineering, [2]McGowan Inst. for Regenerative Med., [3]Dept. of Ophthalmology,

[4]Louis Fox Ctr. for Vision Restoration, [5]Dept. of Plastic Surgery, [6]Dept. of Surgery, [7]Ctr. for Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Trauma to the retina or to the optic nerve often leads to retinal ganglion cell (RGC) death and irreversible vision loss. Like all central nervous system (CNS) neurons, RGCs usually fail to regenerate injured axons successfully due to multiple factors that lead to secondary tissue damage and scarring. We currently lack a therapeutic platform that can alter the default healing response to decrease scarring and to increase functional tissue repair. Regenerative medicine approaches using extracellular matrix (ECM) technology can reduce scarring and increase functional tissue repair in various tissues and organs, including the peripheral nervous system. ECM derived from younger, homologous tissue sources is often more successful in generating a positive outcome. Here we show after optic nerve crush in rat, tissue-specific ECM hydrogels differentially modulate RGC growth as well as macrophage and microglial toward an M2-like anti-inflammatory phenotype. M2-like microglia and macrophage phenotypes were linked to increased RGC survival and axon regeneration *in vitro* and *in vivo*. Fetal CNS-derived ECM increased RGC survival and axon regeneration the most, whereas urinary bladder ECM increased the M2-like phenotypes the most in microglia and macrophages, suggesting chimeric ECM hydrogels may offer the greatest benefit. These studies show injectable, tissue-specific ECM hydrogels can differentially modulate the innate immune system in a manner that alters the default healing response. ECM hydrogels hold promise for ameliorating RGC death and axon degeneration after ocular trauma in a highly translatable platform.

Disclosures: **Y. Van Der Merwe:** None. **I.P. Conner:** None. **A.E. Faust:** None. **X. Gu:** None. **A. Naqvi:** None. **T. Ren:** None. **A. Kandakatla:** None. **V. Reddy:** None. **B. Wang:** None. **K. Lucy:** None. **F. Mehdi:** None. **L.R. Lewis:** None. **H. Song:** None. **K.C. Chan:** None. **G. Wollstein:** None. **K.M. Washington:** None. **W.R. Wagner:** None. **S.F. Badylak:** None. **M. Steketee:** None.

Nanosymposium

368. New Progresses in Nerve Regeneration and Transplantation

Location: S102

Time: Monday, October 19, 2015, 1:00 PM - 3:15 PM

Presentation Number: 368.07

Topic: A.07. Transplantation and Regeneration

Support: EU 7FP Grant 278612

Title: Neuregulin1/ErbB expression regulation in the injured rat peripheral nerve during degeneration and regeneration

Authors: *G. GAMBAROTTA[1], G. RONCHI[2], K. HAASTERT-TALINI[4], B. E. FORNASARI[2], A. CROSIO[3], I. PERROTEAU[2], S. GEUNA[2];
[1]Dept. of Clin. and Biol. Sci., Univ. of Torino, Orbassano, Italy; [2]Dept. of Clin. and Biol. Sci., Univ. of Torino, Orbassano (Torino), Italy; [3]Traumatology Department, Reconstructive Microsurgery Unit, Univ. of Torino, Torino, Italy; [4]Inst. of Neuroanatomy, Hannover Med. Sch. and Ctr. for Systems Neurosci. (ZSN), Hannover, Germany

Abstract: Following injury to peripheral nerves, Schwann cells dedifferentiate, proliferate, migrate and, when axon regeneration occurs, redifferentiate into a myelinating phenotype. Schwann cells promote regeneration through the creation of a permissive environment for axon regrowth and the production of neurotrophic factors. Neuregulin1 (NRG1) is a polymorphic factor involved in the myelination and remyelination processes. Through three injury models, the expression of different NRG1 isoforms and of their ErbB receptors was investigated in the distal portion of the rat median nerve under degenerating conditions (unrepaired cut nerve) or under regenerating conditions after a mild (nerve crush) and more severe (end-to-end repair of cut nerve) injury. Following peripheral nerve injury, distinct and consecutive phases occur: nerve degeneration, axonal regrowth, nerve regeneration and maturation. A detailed mRNA and protein expression analysis of the NRG1/ErbB system was carried out, focusing the attention not only on soluble and transmembrane NRG1 isoforms, but also on alpha and beta as well as type a, b, and c isoforms. Expression specificity during the distinct and consecutive phases occurring after nerve injury and regeneration or the progress in nerve degeneration was observed. Nerve ultrastructure changes were evaluated by electron microscopy and related to the results of mRNA and protein expression analyses. At the mRNA level, soluble NRG1 isoforms alpha and beta, as well as type a and b, are strongly up-regulated early, during nerve degeneration and the early phases of axonal regrowth, but their expression does not seem to be differentially regulated under regeneration and degeneration conditions. ErbB receptors are strongly regulated in the different phases, but at the protein level ErbBs are similarly regulated in the different injury models. On the contrary, we observed that transmembrane NRG1 isoforms are differentially regulated, at the protein level, under degeneration and regeneration conditions, thus suggesting that their expression could be a good marker to follow and monitor the regeneration process. This accurate regulation suggests that each member of the NRG1/ErbB system plays a specific role following nerve injury, that could be clinically exploited to promote nerve regeneration. This project has received funding from the European Union's Seventh Programme for research, technological development and demonstration.

Disclosures: G. Gambarotta: None. **G. Ronchi:** None. **K. Haastert-Talini:** None. **B.E. Fornasari:** None. **A. Crosio:** None. **I. Perroteau:** None. **S. Geuna:** None.

Nanosymposium

368. New Progresses in Nerve Regeneration and Transplantation

Location: S102

Time: Monday, October 19, 2015, 1:00 PM - 3:15 PM

Presentation Number: 368.08

Topic: A.07. Transplantation and Regeneration

Support: Knights Templar Eye Foundation Career Starter Grant

NIH Grant EY18005-06

Title: Targeted ablation and regeneration of amacrine cells and horizontal cells in the zebrafish retina

Authors: *E. A. MCMAINS, J. M. GROSS;
Univ. of Texas At Austin, Austin, TX

Abstract: Regeneration of inhibitory retinal interneurons has been observed in teleost fish following non-targeted retinal injury. However, regeneration of retinal interneurons following targeted ablation of specific cell types has not been characterized. Two important questions arise from a targeted ablation experiment: (1) Does cell type specific ablation induce regenerative responses biased toward the production of cells of the same cell type? (2) What is the effect of ablating specific cell populations on the growth and survival of neighboring cell types? Here, we used metronidazole-induced, nitroreductase-mediated ablation of horizontal cells and amacrine cells in transgenic zebrafish in combination with immunolabeling and confocal imaging to characterize regeneration of inhibitory interneurons in the retina after their targeted ablation. We found that pro-drug activation of nitroreductase expression in transgenic zebrafish specifically ablates retinal amacrine cells and horizontal cells. All retinal amacrine cells and horizontal cells in the central retina are eliminated via apoptosis following one day of treatment. BrdU pulse chase experiments revealed cell proliferation in the central retina of drug-treated zebrafish at four days post injury. Regenerating cells began expressing markers of early differentiation as early as one week post injury. These findings are the first demonstration of specific ablation and regeneration of inhibitory interneurons in the zebrafish retina and establish a useful tool for understanding how specific cell types regenerate following injury.

Disclosures: E.A. McMains: None. **J.M. Gross:** None.

Nanosymposium

368. New Progresses in Nerve Regeneration and Transplantation

Location: S102

Time: Monday, October 19, 2015, 1:00 PM - 3:15 PM

Presentation Number: 368.09

Topic: A.07. Transplantation and Regeneration

Title: Regeneration of the adult axolotl brain rebuilds neuronal diversity within different tissue architecture

Authors: *R. AMAMOTO[1], E. TAKAHASHI[2], G. DAI[3], A. K. GRANT[4], P. ARLOTTA[1]; [1]Harvard Univ., Cambridge, MA; [2]Boston Children's Hosp., Boston, MA; [3]Massachusetts Gen. Hosp., Charlestown, MA; [4]Harvard Med. Sch., Boston, MA

Abstract: The axolotl can regenerate multiple organs, including the spinal cord and the brain. It remains, however, unclear whether complex neuronal diversity and intricate tissue architecture can be regenerated; yet, this is critical for recovery of function in the central nervous system. Here, we have built a molecular map of neurons in the axolotl pallium and used it to investigate whether neuronal diversity and pallial organization can be precisely regenerated after mechanical injury. Using *in vivo* brain imaging and molecular analysis, we find that axolotls are able to rebuild the pallium through specific regenerative steps. These include a proliferative response by progenitors, which also stimulates neurogenesis in intact regions distal to the injury. We demonstrate that regeneration rebuilds the original diversity of neurons in both pre- and post-metamorphosis axolotls. However, regeneration fails to reestablish the ordered tissue architecture present before injury, and neurons acquire new topographical relationships within the regenerated tissue.

Disclosures: R. Amamoto: None. **E. Takahashi:** None. **G. Dai:** None. **A.K. Grant:** None. **P. Arlotta:** None.

Nanosymposium

369. Presynaptic Structure and Neurotransmitter Release III

Location: S405

Time: Monday, October 19, 2015, 1:00 PM - 3:30 PM

Presentation Number: 369.01

Topic: B.06. Neurotransmitter Release

Support: NINDS U01 NS090527

NSF Graduate Research Fellowship DGE 1106400

Title: Optical quantal analysis of diversity in glutamatergic synaptic transmission and plasticity at the *Drosophila* neuromuscular junction

Authors: *Z. L. NEWMAN, S. L. LEVY, E. Y. ISACOFF;
Mol. and Cell Biol., Univ. of California, Berkeley, Berkeley, CA

Abstract: The *Drosophila* larval neuromuscular junction (NMJ) has proven to be a powerful model glutamatergic synapse. Efforts to elucidate the molecular mechanisms that govern neurotransmitter release at this synapse are complicated by the presence of two distinct glutamatergic motor neuron axons--Type Ib and Type Is--that cannot be easily separated in electrophysiological studies. *In vivo* imaging of synaptic transmission in intact larvae reveal that Ib axons are highly active between muscle contractions and that both axons increase their activity during contractions, consistent with a mixed tonic-phasic behavior in Ib and phasic behavior in Is axons. Optical quantal analysis enabled us to measure transmission properties simultaneously at dozens of synapses in the terminal branches of these two axon types as they innervate a common muscle cell. We find that synapses of Type Ib and Type Is axons have highly divergent basal release properties. Under low stimulation frequency nerve stimulation, Type Ib axons have many synapses that are silent and the active synapses are still 2-3 fold lower in basal release probability compared to active Type Is synapses. The two axons differ in their short-term plasticity in a manner consistent with these differences in basal properties: at moderate frequencies, simultaneous facilitation is seen at Type Ib synapses and depression at Type Is synapses. The differences in synaptic transmission led us to ask whether the molecular mechanisms that control transmitter release also differ between these axons. We find that the differences in synaptic function between Type Ib and Type Is axons cannot be explained by differences in the active zone protein Bruchpilot (Brp, ELKS/CAST homologue in flies). We are currently investigating the relative behavior of these two axons in other forms of activity-dependent plasticity to further clarify the molecular mechanisms of functional diversity at the NMJ.

Disclosures: Z.L. Newman: None. **S.L. Levy:** None. **E.Y. Isacoff:** None.

Nanosymposium

369. Presynaptic Structure and Neurotransmitter Release III

Location: S405

Time: Monday, October 19, 2015, 1:00 PM - 3:30 PM

Presentation Number: 369.02

Topic: B.06. Neurotransmitter Release

Support: NIH NS083031

NIH DK092408

NIH EY017732

Title: A fluorescent ratiometric genetically-encoded pH-indicator reveals activity-induced acid efflux from *Drosophila* motor nerve terminals mediated by plasma membrane and vesicular acid transporters

Authors: *A. J. ROSSANO[1], A. KATO[2,3], K. I. MINARD[4], M. F. ROMERO[3], G. T. MACLEOD[4];
[1]Univ. of Texas HSC At San Antonio, San Antonio, TX; [2]Grad. Sch. of Biosci. and Biotech., Tokyo Inst. of Technol., Yokohama, Japan; [3]Physiol. and Biomed. Engin., Mayo Clin. Col. of Med., Rochester, MN; [4]Dept. of Biol. Sci., Florida Atlantic Univ., Jupiter, FL

Abstract: Repetitive nerve activity leads to rapid cytosolic acid loads in presynaptic terminals which are generated over seconds and cleared within a minute. Such acid transients likely influence mechanisms which underlie neurotransmitter release as many processes necessary for neurotransmitter release are pH-sensitive. To further understand the relationship between nerve activity and pH regulation we investigated the acid extrusion mechanisms that affect cytosolic pH homeostasis in a glutamatergic nerve terminal. A fluorescent ratiometric genetically-encoded pH-indicator ("pHerry") was constructed by joining SuperEcliptic-pHluorin, a pH-sensitive (pK_a ~ 7.1) GFP, to mCherry, a pH-insensitive (pK_a ~ 4.5) RFP, with a flexible linker sequence. Expression of pHerry in the cytosol of *Drosophila* motor nerve terminals shows acid efflux following acid loading by nerve activity is greater than that predicted by measurements of resting acid efflux. Analysis of activity-induced acid transients in terminals deficient in either endocytosis or exocytosis of synaptic vesicles elucidated an activity-induced acid efflux mechanism which required evoked exocytosis of vesicles and persisted until retrieval of the synaptic vesicle membrane from the plasma membrane. Pharmacological and genetic dissection *in situ* indicate this acid efflux is mediated by both conventional plasma membrane acid transporters and vesicular acid transporters which remain active when deposited on the plasma membrane by exocytosis.

Disclosures: **A.J. Rossano:** None. **A. Kato:** None. **K.I. Minard:** None. **M.F. Romero:** None. **G.T. Macleod:** None.

Nanosymposium

369. Presynaptic Structure and Neurotransmitter Release III

Location: S405

Time: Monday, October 19, 2015, 1:00 PM - 3:30 PM

Presentation Number: 369.03

Topic: B.06. Neurotransmitter Release

Support: F31 NS084826

Title: Locating synaptic calcium channels

Authors: ***S. A. MERRILL**[1,2], A. CHERRY[1,2], S. WATANABE[1,2], E. JORGENSEN[1,2];
[1]Biol., Univ. of Utah, Salt Lake City, UT; [2]Howard Hughes Med. Inst., Salt Lake City, UT

Abstract: Neurotransmission occurs when calcium triggers exocytosis of synaptic vesicles primed at release sites. The number, position and activity of nearby calcium channels determine the perdurance of free calcium at a release site. To understand the synapse we must identify the location of calcium channels in relation to synaptic vesicles, fusion proteins, and subcellular structures such as the dense projection. In the simplest model, calcium enters through a single source at the center of the synapse. However, calcium entry through multiple sources within a synapse has been studied only indirectly. In *C. elegans* unc-68 (RyR), egl-19 (L-type), and unc-2 (N-type) channels are each encoded by a single gene and contribute the calcium for synaptic vesicle exocytosis at neuromuscular junctions. We are determining the colocalization of calcium channels with other synaptic proteins at nanometer resolution. CRISPr and miniMos create single-copy transgenes that attach to each channel an enzymatic tag that covalently binds organic fluorophores suitable for imaging by biplane 3D super-resolution fluorescence microscopy. Transgenic animals are crossed with mutations that test the contributions of the vesicle priming proteins unc-13, unc-10 (RIM), and rimb-1 (RIM-binding protein) in localizing each synaptic calcium channel and its adjoining vesicles.

Disclosures: S.A. Merrill: None. **A. Cherry:** None. **S. Watanabe:** None. **E. Jorgensen:** None.

Nanosymposium

369. Presynaptic Structure and Neurotransmitter Release III

Location: S405

Time: Monday, October 19, 2015, 1:00 PM - 3:30 PM

Presentation Number: 369.04

Topic: B.06. Neurotransmitter Release

Support: NIH Grant 5R01NS078179

NSF GRFP

Title: Fife, a *Drosophila* Piccolo ortholog, regulates synaptic structure and function

Authors: ***J. J. BRUCKNER**[1], X. RAO[1], H. ZHAN[1], S. J. GRATZ[2], F. E. UKKEN[2], K. M. O'CONNOR-GILES[1,2];

[1]Lab. of Cell and Mol. Biol., Univ. of Wisconsin, Madison, WI; [2]Genet., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Defects in the organization and function of synapses underlie diverse neurological disorders including autism, depression, and memory loss. Many synaptic functions are carried out at the active zone by a small number of highly conserved scaffolding molecules termed the cytomatrix of the active zone (CAZ). In *Drosophila*, the CAZ includes the CAST/ELKS homolog Bruchpilot, Dunc-13, a single RIM protein, and the Piccolo homolog Fife. By addressing Piccolo function in a simpler model system, we hope to shed light on the diverse functions ascribed to Piccolo and the related protein Bassoon in mammalian systems. Previous work in our laboratory demonstrated a role for Fife in regulating behavior, synaptic ultrastructure, and neurotransmission. We will present our mechanistic investigation of Fife's role in regulating synaptic vesicle mobility and coupling presynaptic Ca^{2+} channels to synaptic vesicle release sites.

Disclosures: J.J. Bruckner: None. **X. Rao:** None. **H. Zhan:** None. **S.J. Gratz:** None. **F.E. Ukken:** None. **K.M. O'Connor-Giles:** None.

Nanosymposium

369. Presynaptic Structure and Neurotransmitter Release III

Location: S405

Time: Monday, October 19, 2015, 1:00 PM - 3:30 PM

Presentation Number: 369.05

Topic: B.06. Neurotransmitter Release

Support: SNF Grant 310030B_156934/1

Title: Synaptotagmin1 to -2 isoform switch during the development of a large hindbrain synapse

Authors: *O. KOCHUBEY, N. BABAI, R. SCHNEGGENBURGER;
Brain Mind Institute, EPFL, Lausanne, Switzerland

Abstract: Synaptotagmins (Syts) are a family of double C2 domain proteins, and in particular the Syt1 and Syt2 proteins function as the fast Ca sensors for transmitter release at synapses. Syt1 is the main fast Ca sensor at excitatory and inhibitory synapses of cultured mouse forebrain neurons, whereas Syt2 is the homologous fast Ca sensor at hindbrain synapses like the calyx of Held and at the neuromuscular junction. This fits with the general expression pattern of these two genes in adult mice (Syt1, forebrain; Syt2, hindbrain and spinal cord). Nevertheless, it has not previously been investigated whether Syt isoforms may switch during the formation and

refinement of an identified synapse. We investigated conventional Syt2 KO mice (Pang et al., 2006 JN) and found that fiber stimulation evoked EPSCs were not significantly changed at P2 - P3. At P5 - P6, significant amounts of fast release remained in Syt2 KO mice, as assessed by measuring EPSCs, and in paired recordings and EPSC deconvolution analysis. Fast transmitter release was only fully removed in Syt2 KO mice at P13 - P15, a time at which Syt2 KO calyces showed very slow release (time constant ~ 300 ms). These findings, supported by immunohistochemistry against Syt2, strongly suggest that nascent calyx of Held synapses use a Ca sensor different from Syt2 to drive fast release. Obvious candidates are Syt1 and Syt9, because both isoforms show a higher expression early postnatally in presynaptic calyx of Held-generating neurons (Xiao et al., 2010 MCN). However, the residual fast release observed at P5 - P6 in Syt2 KO mice persisted in Syt9/Syt2 DKO mice, rendering Syt9 an unlikely candidate. To verify the possible role of Syt1, we used a novel Syt1lox mouse (EUCOMM / EMMA). In Syt1lox x Krox20Cre conditional KO mice, EPSCs were strongly reduced and de-synchronized at P2. Similarly, conditional removal of Syt1 by virus-mediated Cre-expression in Syt1lox x Syt2 KO mice led to a significant decrease of the residual fast release, as compared to Syt2 KO mice. This data thus shows that Syt1 represents an early fast sensor at the nascent calyx of Held synapses, whereas Syt2 has no functional role early postnatally, and is only expressed from ~ P2 - P4 onwards. Thus, the growing calyx of Held nerve terminals undergo a developmental Syt1 - Syt2 isoform switch. The functional expression of Syt1 early postnatally might not be limited to the calyx of Held synapse, and could thus also explain why conventional Syt2 KO mice survive until ~ 2 weeks of age, despite the clear role of Syt2 as an ultra-fast Ca sensor for vesicle fusion.

Disclosures: **O. Kochubey:** None. **N. Babai:** None. **R. Schneggenburger:** None.

Nanosymposium

369. Presynaptic Structure and Neurotransmitter Release III

Location: S405

Time: Monday, October 19, 2015, 1:00 PM - 3:30 PM

Presentation Number: 369.06

Topic: B.06. Neurotransmitter Release

Support: 973 Program 2013CB835100

NSFC grant (30825012)

Title: Kinetic dissection of recycling vesicle pool at the Calyx of Held synapse

Authors: ***J. SUN**, X. QIU, Q. ZHU;
Chinese Acad. of Sci., Beijing, China

Abstract: Vesicle recycling is pivotal for maintaining reliable synaptic signaling. However, this crucial process remains poorly understood, likely owing to technical difficulties. It remains debated as to the basic properties of vesicle recycling, such as the size of recycling pool(RP) relative to the total vesicles reside in nerve terminal, the kinetics of vesicle recycling, and how the usage of RP ensures the capacity of synaptic transmission. Here we developed an approach to quantify the kinetics of vesicle recycling with exquisite signal and temporal resolution at the Calyx of Held synapse. In combination of this approach with the focused ion beam/scanning electron microscopy(FIB/SEM) and FM-dye photoconversion based transmission electron microscopy(TEM), we found that ~80% of vesicles(~270K out of ~330K) in nerve terminal participate in recycling, which is independent of presynaptic stimulation frequency. Under a sustained stimulation, vesicle recycling essentially has two kinetic components and the recycled vesicles start to be reused in tens of seconds when ~45% preserved vesicles in RP were depleted. The heterogeneity of vesicles in recycling revealed the existence of a replenishable pool of vesicles prior to the priming stage and we estimated the size of this sub-pool of RP, termed as readily priming pool (RPP), based on a realistic kinetic model. Thus, our study quantified the kinetics of vesicle recycling and found that RP contain ~80% of total vesicles in calyx-type nerve terminal and can be kinetically dissected as readily releasable pool(RRP, ~2% of RP), readily priming pool(RPP, ~58% of RP) and pre-mature pool(PMP, ~40% of RP). The teaming of the sequentially connected subpopulations of vesicles ensures the rate limited but sustainable synaptic transmission.

Disclosures: **J. Sun:** None. **X. Qiu:** None. **Q. Zhu:** None.

Nanosymposium

369. Presynaptic Structure and Neurotransmitter Release III

Location: S405

Time: Monday, October 19, 2015, 1:00 PM - 3:30 PM

Presentation Number: 369.07

Topic: B.06. Neurotransmitter Release

Support: NIH Grant EY10542

Research to Prevent Blindness

Chinese Scholarship Council

Title: Measurements of the fusion pore formed during synaptic vesicle exocytosis in rod and cone photoreceptors

Authors: *X. WEN[1], W. B. THORESON[2];
[1]Pharmacol. and Exptl. Neurosci., [2]Ophthalmology and Visual Sci., Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Neurotransmitters can be released by kiss-and-run or full-collapse fusion of synaptic vesicles. It is unclear how much kiss-and-run contributes to synaptic release from various neurons. Endocytosis in vertebrate photoreceptors exhibits fast retrieval consistent with kiss-and-run fusion. We studied release using dyes of different sizes to measure fusion pore size during release from rods and cones. We loaded synaptic vesicles into tiger salamander photoreceptors using 3-, 10-, and 70-kD dextran-conjugated Texas Red with diameters of 2.3, 4.6 and 12 nm, respectively. We visualized release of individual vesicles using total internal reflection fluorescence microscope (TIRFM) in isolated photoreceptors and stimulated release by puffing 50 mM KCl onto terminals. We also measured whole terminal release by confocal microscopy in vertical slices of retina and stimulated release by bath application of 50 mM KCl. In TIRFM, vesicle fluorescence increases as vesicles approach the membrane and thus enter the evanescent field of illumination. Vesicle release events were defined by a 60% fluorescence decline in 80 ms with a total decrease of >90%. Remaining events were defined as vesicle retreat from the membrane because their fluorescence declines mirrored fluorescence increases caused by vesicle approach to the membrane. ~70% of vesicles loaded with 3- or 10-kD dye released their contents after approaching the membrane, but only ~20% of vesicles loaded with 70-kD dye released their dye after approach. This suggests that 71% ([70%-20%]/70%) of observed release events involved fusion pores with diameter between 2.3-12 nm and 29% involved full-collapse fusion with pores >12 nm. Bath application of 50 mM KCl for 15 min to retinal slices loaded with 3-, 10-, or 70-kD dyes stimulated declines of 2.4%, 5.4%, and 1.7% in whole terminal fluorescence, respectively. 3 kD dye may enter other structures besides synaptic vesicles. Consistent with this, we observed more labeling of immobile fluorescent structures by TIRFM in terminals loaded with this dye. Differences in release between 10- and 70-kD dyes suggest that 69% ([5.4%-1.7%]/5.4%) of release involves fusion pores between 4.6-12 nm, similar to conclusions from TIRFM results. These results suggest that most release from photoreceptors involves fusion pores with diameter <12 nm and that full-collapse fusion contributes to a small fraction of release events.

Disclosures: X. Wen: None. **W.B. Thoreson:** None.

Nanosymposium

369. Presynaptic Structure and Neurotransmitter Release III

Location: S405

Time: Monday, October 19, 2015, 1:00 PM - 3:30 PM

Presentation Number: 369.08

Topic: B.06. Neurotransmitter Release

Support: MH071739

GM058234

Title: Single vesicle characterization of inter-synaptic trafficking of recycling vesicles

Authors: *N. CHENOUARD, R. W. TSIEN;
Neurosci., NYU Med. Ctr., New York, NY

Abstract: By contrast with a textbook view of synaptic vesicles (SVs), which depicts SVs as confined to individual synapses, studies from multiple groups have revealed an extensive inter-synaptic exchange of SVs along the axon. Whereas previous work performed analysis of populations of vesicles, we have focused on SV traffic at the single vesicle level to identify core mechanisms of transport and regulation. We performed time-lapse microscopy of quantum dots (QDs) as optical markers of single SVs in rat hippocampal cultures. QD labeling at low density allowed us to track unambiguously the motion of individual SVs over several minutes, with high temporal (~0.1 s) and spatial (~30 nm) resolution. We performed an exhaustive characterization of single SV motion by means of new computational methods we developed for the analysis of SV trajectories (Chenouard and Tsien, ISBI 2015, in press). This approach allows us to draw sharp distinctions between adjacent episodes of diffusive and directed motion. We found that, as expected, SVs underwent constrained diffusion within synaptic boutons. Motion along axons was comprised of brief episodes of directed motion over short distances (0.5 - 1.5 μm), presumably due to active transport, punctuated by intervening periods of diffusion. Detailed biophysical characterization of the directed motion of SVs, combined with pharmacological interventions, has provided insight into the different contributions of microtubule- and actin-based transport mechanisms to the inter-synaptic traffic. We observed clear effects of manipulating kinase (e.g. PKA) and phosphatase (e.g. PP1 and PP2A) activity on the incidence of SV active transport events. The well-known engagement of these enzymes by neuronal activity suggests possible regulatory links between presynaptic activity and active transport of SVs.

Disclosures: N. Chenouard: None. **R.W. Tsien:** None.

Nanosymposium

369. Presynaptic Structure and Neurotransmitter Release III

Location: S405

Time: Monday, October 19, 2015, 1:00 PM - 3:30 PM

Presentation Number: 369.09

Topic: B.06. Neurotransmitter Release

Support: Howard Hughes Medical Institute

NIH NS034307

EMBO ASTF 443-2012

ERC 249939 SYNVGLUT

Neurocure EXC 257

SFB 665

SFB 958

Title: Clathrin is required for regeneration but not endocytosis of synaptic vesicles

Authors: *S. WATANABE[1], T. TRIMBUCH[3], M. CAMACHO-PÉREZ[3], B. ROST[3], C. ROSENMUND[3], E. M. JORGENSEN[2];
[1]Dept. of Biol., [2]Biol., Univ. of Utah, Salt Lake City, UT; [3]Neurocure, Charite Universitatsmedizen, Berlin, Germany

Abstract: Clathrin is thought to be required for synaptic vesicles endocytosis at the plasma membrane. However, clathrin-mediated endocytosis is slow, requiring ~15-20 s for vesicle retrieval. We developed a 'flash-and-freeze' fixation method that couples optogenetic stimulation with rapid high-pressure freezing to capture endocytosis at millisecond temporal resolution. We found that in mouse hippocampal synapses, vesicle membrane is recovered within 100 ms following a single stimulus. Large endocytic vesicles retrieved via this ultrafast endocytic pathway lack clathrin coats, suggesting that clathrin is not required for this process. To determine the fate of the large vesicles, we traced exogenously applied ferritin molecules over 20 s following a single stimulus or after 10 stimuli (20 Hz). We found that large endocytic vesicles were delivered to synaptic endosomes about 1 second after stimulation. Clathrin-coated buds formed on synaptic endosomes 1-3 s post stimulation. Synaptic vesicles containing ferritin molecules then accumulated in the terminal after 5-6 s. Some of these vesicles returned to the active zone within 10 s, suggesting that these vesicles are *bona fide* synaptic vesicles. To test whether clathrin is required to resolve endosomes into synaptic vesicles, we decreased clathrin levels by a knock-down of the clathrin heavy chain. In these cells, ultrafast endocytosis is intact, suggesting that clathrin is not required for the membrane retrieval. However, ferritin molecules in clathrin knock-down cells are retained in endosomes suggesting that the resolution of synaptic endosomes requires clathrin. The acute inhibition of clathrin function by Pitstop 2 also blocked regeneration of synaptic vesicles from synaptic endosomes. Together, these results suggest that clathrin is required for biogenesis but not endocytosis of synaptic vesicles.

Disclosures: **S. Watanabe:** None. **T. Trimbuch:** None. **M. Camacho-Pérez:** None. **B. Rost:** None. **C. Rosenmund:** None. **E.M. Jorgensen:** None.

Nanosymposium

369. Presynaptic Structure and Neurotransmitter Release III

Location: S405

Time: Monday, October 19, 2015, 1:00 PM - 3:30 PM

Presentation Number: 369.10

Topic: B.06. Neurotransmitter Release

Support: NIH Grant MH061876

NSF GRFP DGE-1256259

UW-Madison Neuroscience Training Program Grant T32-GM007507

UW-Madison Molecular Pharmacology Training Grant 5T32-GM008688

Howard Hughes Medical Institute

Title: Engineering the presynaptic metal sensor to tune the kinetics of synaptic transmission and network behavior

Authors: *D. A. RUHL[1], C. S. EVANS[2], E. R. CHAPMAN[2];
[1]Neurosci., Univ. of Wisconsin - Madison, Madison, WI; [2]UW-Madison, Madison, WI

Abstract: Neurotransmitter release at central synapses is triggered by synaptotagmin (syt)-1, which interacts with anionic phospholipids and SNARE proteins in response to Ca2+. Here we test the idea that the intrinsic kinetics of sensor/membrane interactions partially determine the time course of synaptic transmission, and further that those synaptic interactions regulate network-level behavior. To tune the kinetics of neurotransmitter release, we grafted structural elements from synaptotagmin-7 (the slowest syt isoform) onto synaptotagmin-1 (the fastest syt isoform). This resulted in a chimera with intermediate kinetic properties in biochemical assays. Further, the chimera (unlike syt-1) was highly sensitive to Sr2+. We exploited this Sr2+ sensitivity to demonstrate that membrane penetration by syt-1 is a key step in synaptic vesicle exocytosis, as engineering syt to penetrate membranes in the presence of Sr2+ also conferred upon it the ability to support Sr2+-triggered synchronous neurotransmission in hippocampal neurons. In Ca2+, the chimera slowed the kinetics of synaptic transmission (longer rise and decay times), revealing that presynaptic sensor/membrane interactions are a major factor regulating the shape of the excitatory postsynaptic current waveform. Finally, to examine the

effect of tuning synaptic kinetics on network behavior, we used an *in vitro* model of population-level oscillations: persistent reverberation. Networks expressing the chimeric synaptotagmin were equally likely to oscillate, and did so for an equal duration, as those expressing wildtype synaptotagmin-1. However, the peak frequency of those reverberations was significantly slower in neurons expressing the chimera. The frequency characteristics of certain oscillations in recurrent neural networks are thus partially governed by neurotransmitter release kinetics - which are in turn governed by the intrinsic kinetics of the presynaptic Ca2+ sensor. Current work aiming to tune the frequency of oscillations in intact neural circuits will be discussed.

Disclosures: D.A. Ruhl: None. **C.S. Evans:** None. **E.R. Chapman:** None.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.01

Topic: C.05. Aging

Support: CIHR

NSERC

FRQS

Weston Brain Institute

Michael J. Fox Foundation for Parkinson's Research

Alzheimer's Society

Brain Canada

Title: Structural trajectories of healthy aging in cortical thickness and subcortical morphometry

Authors: *G. A. DEVENYI[1], R. PATEL[1], J. GERMANN[1], M. M. CHAKRAVARTY[1,2,3]; [1]Cerebral Imaging Ctr., Douglas Univ. Mental Hlth. Institute, McGill, Montreal, QC, Canada; [2]Dept. of Psychiatry, [3]Dept. of Biomed. Engin., McGill Univ., Montreal, QC, Canada

Abstract: Background: Understanding spatio-temporal neuroanatomical trajectories through the course of the adult lifespan is critical to our understanding of healthy aging. Neuroanatomical studies using magnetic resonance imaging (MRI) have previously demonstrated complex

trajectories in smaller age ranges. The goal of this work was to examine the volumetric and morphological trajectories of multiple structures, in a healthy cohort over a comprehensive adult age range. Methods: T1-weighted 1.5T MRIs from the OASIS project (N=436, ages 18-94) were preprocessed with minc-bpipe-library then processed with CIVET for cortical thickness (CT), BEaST for brain volume, and MAGeTBrain for subcortical shape (surface displacement) and volume. Effects of age and age^2 were examined using fixed-model multiple regression, accounting for sex and brain volume with RMINC and corrected for multiple comparisons with FDR. Results: We observed extensive reductions in CT with a linear age term at 5% FDR. Bilateral supplementary motor areas and superior and middle frontal gyrus showed strong statistical correlation of a positive age^2 term, showing steeply declining CT from age 18-60 before levelling in old age or having a slight recovery (Fig a). The left and right piriform cortex in contrast show stable CT until 60 before steeply thinning into old age. The striatum, thalamus and globus pallidus show positive quadratic dependence bilaterally while also showing negative quadratic dependence in more limited areas medially at a 5% FDR. Bilateral striatal volume showed strongly significant ($p<0.01$) correlations with an age^2 term (Fig b). Conclusions: We found extensive reductions in CT and volume across the adult lifespan. Additionally, we found several regions which show complex age dependence including areas with steep reductions in early to mid adulthood which then remain steady throughout old age, as well as regions of accelerated decline with old age. Subcortical volumes were found to be more insensitive(less vulnerable to) to age while still showing substantial changes in shape.

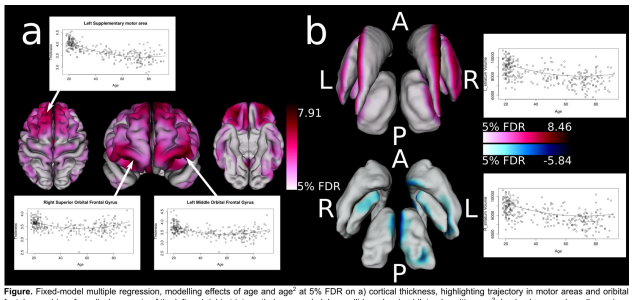


Figure. Fixed-model multiple regression, modelling effects of age and age^2 at 5% FDR on a) cortical thickness, highlighting trajectory in motor areas and oribital fontal gyrus b) surface displacements of the left and right striatum, thalamus and globus pallidus, showing bilateral positive age^2 depdendence and smaller regions of medial negative dependence on age^2, overall left and right striatal volume also show strong ($p<0.01$) dependence on age^2

Disclosures: **G.A. Devenyi:** None. **R. Patel:** None. **J. Germann:** None. **M.M. Chakravarty:** None.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.02

Topic: C.05. Aging

Support: The National Institute on Aging (AG045571)

The Davee Foundation

Northwestern University Alzheimer's Disease Center (AG013854)

Title: Acetylcholinesterase-positive cortical pyramidal neurons: Emergence in adult human life and down-regulation in cognitively average elderly and elderly with superior memory capacity

Authors: M. JANECZEK[1], M. SAMIMI-GHARAI[1], S. WEINTRAUB[1], E. ROGALSKI[1], E. BIGIO[1], *M.-M. MESULAM[2], C. GEULA[1];
[1]Northwestern Univ., [2]Norrthwestern Univ., Cognitive Neurol. and Alzheimer's Dis. Ctr., Chicago, IL

Abstract: We have described an extensive network of cortical pyramidal neurons in the human brain that display an acetylcholinesterase (AChE)-rich pattern by adulthood, but not during childhood. The emergence of these neurons in young adulthood, a time associated with intellectual maturation, and their greater prominence in humans than in other species, led us to hypothesize that this neuronal system may be involved in the development and maintenance of higher cognitive processing in man. In the present set of experiments, we investigated the number and staining intensity of AChE-positive cortical pyramidal neurons in children/teens (0-19 years, n=4), normal young adults (20-64 years, n=8), cognitively average elderly (65-95 years, n=15), and cognitively superior elderly (SuperAgers) defined as individuals above 80 years with performance on tests of memory equal to or better than 50-65 year-olds (n=4). A sensitive histochemical procedure was used to visualize AChE-positive cortical pyramidal neurons. Density of these neurons was determined in the supplementary motor cortex (Brodmann area 6), prefrontal cortex (area 9), middle temporal gyrus (area 21), inferior parietal lobule (area 39-40) and the anterior cingulate cortex (area 24) using modified stereologic techniques in three representative sections through each cortical area. Staining intensity of AChE reaction product was determined using optical density measures. The numerical density and staining intensity of AChE-positive pyramidal neurons in young adult brains was higher when compared with brains of children/teens (34.5% and 32.6% respectively). In young adult and normal elderly, area 6 had the highest density and staining intensity of AChE-positive pyramidal neurons. A consistent decrease in the density of these neurons was observed in the normal aged (5.1-20.8%; $p>0.05$) and a further decrease in SuperAgers (19.8-66.7%; statistically significant in areas 6, 9 and 40; $p<0.01$-0.05). The staining intensity of AChE reaction product displayed a similar decrease in the normal aged (9.15-28.6%; statistically significant in areas 6, 40 and 24; $p<0.01$-0.05) and a further decline in the SuperAged (10.0-41.1%; statistically significant in areas 9 and 21; $p<0.01$-0.05). These findings suggest significant plasticity of cortical pyramidal neurons during the aging process. Decreased cortical AChE, and the potential resultant increased availability of acetylcholine, a neurotransmitter involved in the cognitive processing of memory and attention,

may help maintain cognitive function in normal elderly and contribute to enhanced cognitive performance in SuperAgers.

Disclosures: **M. Janeczek:** A. Employment/Salary (full or part-time); Northwestern University. **M. Samimi-Gharai:** A. Employment/Salary (full or part-time); Northwestern University. **S. Weintraub:** A. Employment/Salary (full or part-time); Northwestern University. **E. Rogalski:** A. Employment/Salary (full or part-time); Northwestern University. **E. Bigio:** A. Employment/Salary (full or part-time); Northwestern University. **M. Mesulam:** A. Employment/Salary (full or part-time); Northwestern University. **C. Geula:** A. Employment/Salary (full or part-time); Northwestern University.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.03

Topic: C.05. Aging

Title: Hematopoietic cell rejuvenation delays age-related cognitive decline

Authors: ***M. DAS**[1], S. CHEN[2], H. GOODRIDGE[2], C. N. SVENDSEN[3];
[1]Regenerative Med. Inst., Cedars Sinai Med. Ctr., West Hollywood, CA; [3]The Regenerative Med. Inst., [2]Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Aging is the number one risk factor for neurodegenerative diseases and age-associated conditions are projected to represent over half the global disease burden by the year 2030. Thus, it is imperative to identify therapeutic strategies for age-associated deterioration in order to promote healthy aging in the elderly population. A series of aging studies using heterochronic parabiosis, in which an old and young mouse are surgically conjoined temporarily allowing them to share a circulatory system, demonstrated that tissue in aged mice is rejuvenated by young blood. The brains of old mice receiving young blood showed increased neurogenesis, cognitive function and synaptic connections. While some blood-borne factors have been identified that could contribute to these effects, cell-based mechanisms have yet to be identified. By transplanting young bone marrow into old mice we have developed a novel model to test whether rejuvenation of hematopoietic cells can delay aging in the nervous system. We found significant improvements in overall activity and lifespan in old mice receiving young bone marrow compared to age-matched controls. Further, old mice receiving young bone marrow showed drastic improvement in the Y-maze compared to old controls, suggesting a role for hematopoietic cells in modulating cognitive decline in old age. Old mice with young bone

marrow also showed increased hippocampal volume and cortical thickness compared to old controls, both regions of the brain that normally atrophy in aging. Additionally, activated macrophages and inflammatory cytokines are reduced in number in the hippocampus and the presence of senescent cells is significantly reduced in old mice receiving bone marrow compared to old controls. This work indicates that young hematopoetic cells can directly contribute to the rejuvenation of the aging brain.

Disclosures: **M. Das:** None. **S. Chen:** None. **H. Goodridge:** None. **C.N. Svendsen:** None.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: SAF2010-20925

SAF2013-43900-R

CIBERNED CB/06/05/0042

BrightFocus Foundation A2014417S

Generalitat de Catalunya Excellence Research Group 2014 SGR 0984

BES-2011-044405

Title: CRTC1 nuclear translocation is critical for hippocampal-dependent memory

Authors: ***C. A. SAURA**, A. J. PARRA-DAMAS, M. CHEN, S. ACOSTA, L. ENRÍQUEZ-BARRETO;
Inst. Neurociències, Departament de Bioquimica i Biologia Mol., Univ. Autònoma de Barcelona, Bellaterra (Barcelona), Spain

Abstract: Deficits in memory encoding and retrieval associated with decreased activity and connectivity of the hippocampus are common in Alzheimer´s disease (AD) patients and people at risk for developing the disease. Spatial and associative memory impairments are early clinical features of dementia patients but the regulatory mechanisms of gene expression underlying these deficits remain largely unknown. In this study, we examined the effect of hippocampal-dependent memory on modulating the transcriptional regulator cAMP-responsive element

binding protein (CREB)-regulated transcription coactivator-1 (CRTC1). Using spatial memory and contextual fear conditioning tasks, we found that spatial and associative learning induce rapid translocation of CRTC1 from dendrites and cytosol to the nucleus of neurons in the adult mouse hippocampus. CRTC1 nuclear translocation is associated with CRTC1 dephosphorylation at Ser151, a residue critical for transcriptional activation, whereas CREB phosphorylation (Ser133) is independent of associative learning. Interestingly, reduced nuclear translocation and activation of CRTC1 is associated with long-term memory deficits in AD mutant APPSw,Ind transgenic mice at early pathological and cognitive decline stages. Indeed, a synaptic transcriptional program dependent on CRTC1 is deregulated in the hippocampus of APPSw,Ind after memory training. Taking together, these results suggest a critical role of CRTC1 nuclear translocation and transcriptional function in memory encoding, and provide evidence that its deregulation underlies memory deficits.

Disclosures: **C.A. Saura:** None. **A.J. Parra-Damas:** None. **M. Chen:** None. **S. Acosta:** None. **L. Enríquez-Barreto:** None.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01NS075487

Alzheimer's Association BFG-14-320887

Title: The Alzheimer’s disease risk gene BIN1 regulates neuronal excitability

Authors: ***E. D. ROBERSON**[1], J. N. COCHRAN[2], T. J. RUSH[2], B. A. WARMUS[2], A. V. FRANKLIN[2], L. L. MCMAHON[2];
[1]Neurol & Neurobio, [2]UAB, Birmingham, AL

Abstract: BIN1 is one of the leading genetic risk factors for Alzheimer’s disease, but its function in the brain is poorly understood. BIN1 has multiple domains, including an SH3 domain that may enable interactions with tau. We and others have identified a role for tau in regulating neuronal excitability, so we investigated whether BIN1 may have similar effects. We used a conditional BIN1 knockout line, in which BIN1 expression was reduced in forebrain excitatory neurons, as complete deletion of BIN1 is lethal in the early postnatal period. Neuronal BIN1

knockout had no obvious effects on behavior or basic measures of synaptic transmission in young mice. However, in whole-cell patch-clamp recordings from CA1 hippocampal neurons, action potential firing rates were reduced, indicating a reduction in neuronal excitability. *In vivo*, neuronal BIN1 knockout reduced susceptibility to pharmacologically-induced seizures in multiple paradigms, consistent with the hypothesis that BIN1 knockout reduces neuronal excitability. Because prior studies of BIN1 function in the heart implicated a role in regulating voltage-gated calcium channel surface localization, we probed BIN1-interacting proteins in the brain by co-immunoprecipitation and identified a tripartite interaction between tau, BIN1, and voltage-gated calcium channel subunits. Localization of BIN1 to this complex may provide a biochemical basis for its role in facilitating action potential firing. Our data suggest that the effect of BIN1 polymorphisms on Alzheimer's disease risk could be due to previously unidentified effects on neuronal excitability. Further study of the mechanisms underlying these effects is critical.

Disclosures: **E.D. Roberson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); E.D.R. owns intellectual property related to tau. **J.N. Cochran:** None. **T.J. Rush:** None. **B.A. Warmus:** None. **A.V. Franklin:** None. **L.L. McMahon:** None.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH P01AG030128

NIH R21 AG044682-01A1

Title: APOE as a therapeutic target for reducing oligomeric Aβ levels

Authors: ***M. LADU**[1], C. SMITH[1], N. C. COLLINS[1], S. GHURA[1], K. P. KOSTER[1], K. YOUMANS[1,2], L. M. TAI[1];
[1]Anat. and Cell Biol., Univ. of Illinois, Chicago, Chicago, IL; [2]Pharmacol. and Neurol., Boston Univ. Sch. of Med., Boston, MA

Abstract: APOE4, the greatest genetic risk factor for AD, increases risk up to 15-fold compared to APOE3, while increased levels of the amyloid-β42 (Aβ42) peptide cause familial forms of

AD. However, the direct or indirect mechanisms through which Aβ42 induces cognitive impairment remain unclear. Further, the Aβ peptide can form multiple conformations *in vivo*, complicating identification and characterization of effective therapeutic strategies. However, recent evidence supports the role of soluble, oligomeric species of Aβ (oAβ) as the proximal neurotoxin in AD, as oAβ is neurotoxic *in vitro* and *in vivo*, and induces a robust neuroinflammatory response. Therefore, successful therapeutic strategies for treating or preventing AD will likely target oAβ, rather than other fibrillar forms of Aβ or amyloid plaques. Evidence suggests that Aβ and apoE interact both structurally and functionally. Under native conditions, levels of soluble apoE4/Aβ complex are lower and less stable than apoE3/Aβ complex, and soluble oAβ levels are higher with apoE4 compared to apoE3. In addition, previous data demonstrates apoE4 is less lipidated than apoE3. Together, these results lead to the hypothesis that: ↑ lipidation of apoE4 → ↑ apoE4/Aβ → ↓ oAβ. Thus, one potential mechanism for modulating oAβ levels is to increase the lipidation of apoE4. Indeed, using EFAD mice (5xFAD mice expressing human APOE), we recently demonstrated that RXR agonists, which increase the expression of lipid transporters ATP-binding cassette transporter A1 (ABCA1) and G1 (ABCG1), increase the lipidation of apoE4, increase apoE4/Aβ complex levels, and, critically, decrease oAβ levels. The observed decrease levels in oAβ levels correlated with an increase in synaptic protein levels (PSD95). Importantly, levels of insoluble Aβ, indicative of Aβ plaques, were unchanged with treatment, suggesting that targeting oAβ is a more relevant target. In line with these data, current therapeutic strategies directly targeting apoE4 lipidation, and multi-target compounds addressing several mechanisms of APOE4-induced AD pathology, improve synaptic viablilty and cognitive deficits via reduced oAβ levels. Therefore, apoE may provide a viable target for modulating oAβ levels.

Disclosures: **M. LaDu:** None. **C. Smith:** None. **N.C. Collins:** None. **S. Ghura:** None. **K.P. Koster:** None. **K. Youmans:** None. **L.M. Tai:** None.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Risk of aggravation of neuronal dysfunction by passive immunotherapy with anti-Aβ antibodies

Authors: *M. A. BUSCHE[1,2], A. KESKIN[1], C. GRIENBERGER[3], U. NEUMANN[4], M. STAUFENBIEL[4], H. FÖRSTL[2], A. KONNERTH[1];
[1]Inst. of Neuroscience, Tech. Univ. Munich, Munich, Germany; [2]Dept. of Psychiatry and Psychotherapy, Technical University Munich, Germany; [3]Janelia Farm Res. Campus, Ashburn, VA; [4]Novartis Pharma AG, Basel, Switzerland

Abstract: Amyloid-β (Aβ) has an essential role in the pathogenesis of Alzheimer´s disease (AD). Large phase III clinical trials of passive immunotherapy aiming at the removal of Aβ from the brain have ended with no clinical benefit, however the reasons for this failure are largely unknown. Here, we employed *in vivo* two-photon calcium imaging with single cell-resolution to analyze the function of layer 2/3 cortical neurons in two different transgenic mouse models of AD, the PDAPP and the Tg2576 models. In both mouse models, we found a massive increase in the fractions of abnormally hyperactive neurons (19.5 % in PDAPP and 31.1 % in Tg2576 mice as compared to 2.9 % in wild-type mice). This increase in the fractions of hyperactive neurons was in line with previous results obtained in the APP23xPS45 mouse model (Busche et al., Science, 2008; Busche et al., PNAS, 2012). Next, we monitored the activity status of the cortical neurons in PDAPP and Tg2576 mice that were passively immunized with monoclonal antibodies against Aβ (PDAPP mice were immunized with 3d6 and Tg2576 mice were immunized with β1 mouse monoclonal antibody). We found in both AD models that the fractions of hyperactive neurons increased substantially (17.9 % in controls vs. 52.4 % in 3d6-treated PDAPP mice and 31.1 % in controls vs. 59.5 % in β1-treated Tg2576 mice). Furthermore, in a fraction of treated animals we found an abnormal synchronicity of hyperactive neurons. In summary, our results demonstrate negative functional consequences of passive immunotherapy with anti-Aβ directed monoclonal antibodies, which may be a cellular mechanism for the lack of positive cognitive effects of such antibodies in recent clinical trials. Moreover, the results emphasize the need to incorporate functional *in vivo* assays in the development and evaluation of therapies for AD.

Disclosures: M.A. Busche: None. **A. Keskin:** None. **C. Grienberger:** None. **U. Neumann:** None. **M. Staufenbiel:** None. **H. Förstl:** None. **A. Konnerth:** None.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DFG

Title: APP synaptic function involves trans-dimerization and Fe65/Fe65L1 signaling

Authors: ***S. KINS**[1], P. STRECKER[1], S. EGGERT[1], S. SCHILLING[1], M. KORTE[2], M. RUST[1], S. GUÉNETTE[3];
[1]Univ. of Kaiserslautern, Kaiserslautern, Germany; [2]Tech. Univ. of Braunschweig, Braunschweig, Germany; [3]Genet. and Aging Res. Unit, MassGeneral Inst. for Neurodegenerative Dis., Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA

Abstract: Accumulating evidence suggests that the Amyloid Precursor Protein (APP) has an essential synaptic function. Thus far, mostly the contribution of APP proteolytic products to synaptic function has been studied. Yet, APP family members may also serve as cell surface-signaling molecules through interaction with intracellular adaptor proteins. Here we show by using a mixed co-culture assay of HEK293 cells and primary neurons, that APP can promote presynaptic differentiation of contacting axons. Interestingly, inhibition of APP shedding increases this synaptogenic function, suggesting that trans-interaction of APP is involved in synapse formation. In line with the assumption that APP may serve as a trans-synaptic signaling molecule, we show that mice lacking the Fe65 and Fe65L1 APP adaptor protein exhibit severe deficits in formation of the neuromuscular junction, and deficits in pre-and postsynaptic function of the central synapse associated with deficits in PPF, PTP, LTP and learning. These phenotypes resemble some key characteristics of genetically modified APP/APLP2 knockout mice, indicating that Fe65/Fe65L1 and APP/APLP2 function in the same synaptic pathway. This conclusion is further supported by an observed genetic interaction between APLP2 and Fe65 or Fe65L1 at the NMJ. Collectively, our data suggest that Fe65/Fe65L1 are essential adaptor proteins that transmit a full length APP dependent signal at the synapse.

Disclosures: **S. Kins:** None. **P. Strecker:** None. **S. Eggert:** None. **S. Schilling:** None. **M. Korte:** None. **M. Rust:** None. **S. Guénette:** None.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Linda Crnic Institute Graduate Fellowship

Linda Crnic Institute Down Syndrome Grant

Title: Determining the mechanism of beta amyloid-induced NMDA receptor dysfunction

Authors: *B. L. SINNEN[1,2], M. J. KENNEDY[1,2];
[1]Pharmacol., Univ. of Colorado, Aurora, CO; [2]Linda Crnic Inst., Aurora, CO

Abstract: Alzheimer's disease is a neurodegenerative disease characterized by the accumulation and aggregation of excess extracellular β-Amyloid1-42 (Aβ) peptide, resulting in loss of synapses and eventually neuronal death. Multiple lines of evidence suggest that the synaptotoxic effects of Aβ are at least in part mediated by NMDA receptors, ionotropic glutamate receptors critical for several forms of synaptic plasticity involved in learning and memory. Precisely how Aβ affects NMDA receptor function to trigger synapse loss remains unclear. Specifically, whether neural activity influences synapse loss and why some synapses are spared from Aβ toxicity remain fundamental, but largely unanswered questions. We developed a novel optical assay that allows us to interrogate NMDA receptor function at individual synapses before and at various times following Aβ treatment. We found that sub-micromolar concentrations of Aβ reduce NMDA receptor function at a subset, but not all synapses. Aβ-triggered NMDA receptor impairment depended on their activation as pharmacologically blocking NMDA receptors during Aβ exposure prevented impairment. While NMDA receptor function was preferentially impaired at more active synapses, Aβ does not show any preference for binding to more active synapses. Thus, we have confirmed that NMDA receptor activity does not affect Aβ binding, but influences Aβ-induced NMDA receptor dysfunction.

Disclosures: B.L. Sinnen: None. **M.J. Kennedy:** None.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Center for Alzheimer's Disease and Related Disorders

Title: Soluble amyloid-β42 activates α7nAChR *in vivo* and alters glutamatergic neurotransmission in AβPP/PS1 mice

Authors: *E. R. HASCUP[1], S. O. BRODERICK[2], K. N. HASCUP[2];
[1]Neurology, Ctr. for Alzheimer's Dis. and Related Disorders, & Pharmacol., [2]Neurology, Ctr. for Alzheimer's Dis. and Related Disorders, SIU Sch. of Med., Springfield, IL

Abstract: Amyloid-β $(Aβ)_{42}$ accumulation occurs years prior to cognitive and functional decline observed in Alzheimer's disease (AD). Evidence supports the binding of $Aβ_{42}$ to alpha 7 nicotinic acetylcholine receptors (α7nAChR) located on presynaptic glutamatergic neurons. We sought to determine if soluble $Aβ_{42}$ elicits sub-region specific hippocampal glutamate release and how glutamatergic dynamics change throughout the life span of the $Aβ_{42}$ overexpressing AβPP/PS1 model of AD. First, human $Aβ_{42}$ (0.01 - 10.0 μM) in 0.9% saline (pH 7.4) was locally applied in the dentate gyrus (DG), CA3 and CA1 of isoflurane anesthetized 6-9 mos male C57BL/6J mice. Glutamate release and uptake were studied using an enzyme-based microelectrode array coupled with *in vivo* electrochemistry. Local application of 0.1 μM $Aβ_{42}$ (n=8) elicited robust, reproducible glutamate release that was significantly increased vs saline (~0.5 ± 0.1 μM; n=9) in the DG (3.7 ± 1.1 μM; $p<0.001$), CA1 (3.3 ± 0.7 μM; $p<0.01$), but not the CA3 (1.7 ± 0.4 μM). Co-application of 0.1 μM $Aβ_{42}$ with the α7nAChR antagonist, α-bungarotoxin (10.0 μM; n=5), completely blocked glutamate release in the DG (0.5 ± 0.1 μM; $p<0.01$), CA3 (0.6 ± 0.1 μM) and CA1 (0.5 ± 0.1 μM; $p<0.01$). Second, we examined 2-4, 6-8 and 12-15 mos AβPP/PS1 and age-matched C57BL/6J mice to understand how progressive accumulation of $Aβ_{42}$ alters glutamatergic neurotransmission. All mice underwent Morris water maze (MWM) testing to assess spatial learning and memory followed a week later by basal and KCl-evoked (70 mM, isotonic, pH 7.4) glutamate release measurements in the DG, CA3 and CA1 under isoflurane anesthesia. During the MWM probe, AβPP/PS1 mice (n=9-13) crossed over the previous platform location fewer times than age-matched C57BL/6J (n=9-13) mice indicating impaired memory by 2-4 mos of age ($p<0.05$). In the DG, AβPP/PS1 released more glutamate than C57BL/6J mice at 2-4 (7.6 ± 1.5, 3.8 ± 1.1 μM; $p<0.05$) and 12-15 (6.0 ± 1.2, 2.3 ± 0.4 μM; $p<0.05$) mos of age which positively correlated ($r=0.4115$; $p<0.05$) with platform crosses over all ages of AβPP/PS1 studied. KCl-evoked glutamate release was also elevated in the CA1 of AβPP/PS1 vs C57BL/6J mice at 2-4 mos (9.1 ± 1.1 μM, 2.9 ± 0.3; $p<0.001$) and 12-15 mos (5.5 ± 1.0 μM, 2.9 ± 0.6; $p<0.05$) that negatively correlated ($r=-0.6432$; $p<0.05$) with platform crosses in the 2-4 mos AβPP/PS1 mice. Taken together, this data supports $Aβ_{42}$ elicits glutamate release through the α7nAChR that might account for the elevated glutamate release observed in AβPP/PS1 mice. Additional studies will examine the 20-24 mos age group to understand changes in glutamate dynamics throughout the life span of this AD model.

Disclosures: E.R. Hascup: None. **S.O. Broderick:** None. **K.N. Hascup:** None.

Nanosymposium

370. Structural and Signaling Changes in Aging and Alzheimer's Disease

Location: N426A

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 370.11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant AG037337

NIA Grant AG047059

NINDS Grant NS083175

ADDF Grant 20100501

Title: A first-in-class oligomer binding displacement approach to Alzheimer's disease modification

Authors: *S. M. CATALANO, N. IZZO, C. REHAK, R. YURKO, K. MOZZONI, C. SILKY, G. LOOK, G. RISHTON, H. SAFFERSTEIN;
Cognition Therapeut. Inc., Pittsburgh, PA

Abstract: Cognition Therapeutics Inc. (CogRx) has discovered CT1812, a novel oligomer receptor antagonist that is the only drug candidate demonstrated to displace binding of Abeta oligomers to receptors on brain cells. By stopping the initiating event in the Abeta oligomer cascade, this first-in-class drug candidate completely blocks downstream synaptotoxicity and restores memory to normal in aged transgenic mouse models of Alzheimer's disease (Izzo et al., 2014a, b). CT1812 blocks Abeta oligomer-induced membrane trafficking deficits (EC50=350nM) and synapse loss (EC50=126nM) *in vitro* by displacing oligomer binding (Kd shift from 512 to 1420nM +/- drug) to neuronal receptors mediated by sigma-2/PGRMC1 receptors. CT1812 also dose-dependently displaces binding from human Alzheimer's patient brain tissue section, suggesting that this drug will be effective at removing bound oligomers from Alzheimer's patient's brain. No other candidate therapeutics have demonstrated these effects. CT18122 has high affinity and selectivity for sigma-2/PGRMC1 receptors (Ki=8.5nM, >100-fold separation from other receptors) and acts as an antagonist at this receptor. In two separate studies, CT1812 improves cognitive deficits in Y maze and Morris water maze following 9-10 weeks of once daily administration at 10 mg/kg in transgenic Thy1-hAPPLond/Swe+ male mice aged 3.4-4.5 months at study start (N=12-14/group) without affecting wt mouse behavior or causing adverse behavioral or histopathological events in any animal. CT1812 is an orally administered lipophilic molecule that is rapidly absorbed and highly brain penetrant, with a brain/plasma ratio = 6, plasma t1/2 = 7-12 hours, excellent safety pharmacology and a wide therapeutic index. CT1812 thus represents one of the first disease-modifying therapeutics that will test the oligomer hypothesis of Alzheimer's disease. We propose to assess the safety, tolerability and pharmacokinetics of oral doses of CT1812 in first in man Phase 1 clinical studies.

Disclosures: **S.M. Catalano:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **N. Izzo:** A. Employment/Salary (full or part-time); Cognition Therapeutics

Inc. **C. Rehak:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **R. Yurko:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **K. Mozzoni:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **C. Silky:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **G. Look:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **G. Rishton:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **H. Safferstein:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc..

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.01

Topic: C.03. Parkinson’s Disease

Support: NIH/NINDS R01 #NS085070

Michael J. Fox Foundation for Parkinson's Research

Foundation for Mitochondrial Medicine

Mayo Clinic Foundation

Center for Individualized Medicine, Mayo Clinic

Marriott Family Foundation

Gerstner Family Foundation

Title: Pathophysiological relevance of PINK1-dependent ubiquitin phosphorylation

Authors: *W. SPRINGER[1,4,2], F. C. FIESEL[2,4], M. ANDO[2], R. HUDEC[2], A. R. HILL[2], M. CASTANEDES-CASEY[1], T. R. CAULFIELD[1], E. L. MOUSSAUD-LAMODIÈRE[1], J. N. STANKOWSKI[1], P. O. BAUER[1], O. LORENZO-BETANCOR[2], I. FERRER[5,6], J. M. ARBELO[7], J. SIUDA[8], L. CHEN[9,10], V. L. DAWSON[9,11,10,14,15], T. M. DAWSON[9,12,13,14,15], Z. K. WSZOLEK[3], O. A. ROSS[2,4], D. W. DICKSON[2,4];
[1]Neurosci. Res., [2]Dept. of Neurosci., [3]Neurol., Mayo Clin., Jacksonville, FL; [4]Neurobio. of Dis., Mayo Grad. Sch., Jacksonville, FL; [5]Inst. de Neuropatologia, Hosp. Universitari de Bellvitge, Hospitalet del Llobregat, Spain; [6]CIBERNED, Ctr. de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Inst. de Salud Carlos III, Hospitalet del Llobregat, Spain;

[7]Parkinson's and Movement Disorders Unit, Dept. of Neurol., Hosp. Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain; [8]Dept. of Neurology, Sch. of Med. in Katowice, Med. Univ. of Silesia, Katowice, Poland; [9]Neuroregeneration and Stem Cell Programs, Inst. for Cell Engin., [10]Dept. of Neurol., [11]Dept. of Physiol., [12]Solomon H. Snyder Dept. of Neurosci., [13]Dept. of Neurology,, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [14]Adrienne Helis Malvin Med. Res. Fndn., New Orleans, LA; [15]Diana Helis Henry Med. Res. Fndn., New Orleans, LA

Abstract: Mutations in PINK1 and PARKIN cause recessive, early onset Parkinson's disease (PD). Together, they orchestrate a protective mitophagic response that ensures safe disposal of damaged mitochondria. The kinase PINK1 phosphorylates, in addition to the E3 ubiquitin (Ub) ligase Parkin also the small modifier protein Ub at a conserved residue (S65). First structural and functional consequences for phosphorylated Ub (pS65-Ub) have been shown *in vitro*, but the (patho-)physiological significance remains unclear. We have generated novel antibodies and validated pS65-Ub signals *in vitro* and in cells under endogenous conditions including primary neurons. pS65-Ub is dependent on PINK1 kinase activity as confirmed in patients' fibroblasts, iNeurons and post-mortem brain harboring pathogenic mutations. pS65-Ub is barely detectable under normal conditions, but is rapidly induced upon mitochondrial stress in cells and accumulates during aging and disease as specific cytoplasmic granules in human brains. Additional studies are now warranted to elucidate pS65-Ub functions and fully explore its potential for biomarker or therapeutic development for PD.

Disclosures: W. Springer: None. **F.C. Fiesel:** None. **M. Ando:** None. **R. Hudec:** None. **A.R. Hill:** None. **M. Castanedes-Casey:** None. **T.R. Caulfield:** None. **E.L. Moussaud-Lamodière:** None. **J.N. Stankowski:** None. **P.O. Bauer:** None. **O. Lorenzo-Betancor:** None. **I. Ferrer:** None. **J.M. Arbelo:** None. **J. Siuda:** None. **L. Chen:** None. **V.L. Dawson:** None. **T.M. Dawson:** None. **Z.K. Wszolek:** None. **O.A. Ross:** None. **D.W. Dickson:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.02

Topic: C.03. Parkinson's Disease

Support: Intramural research programs of National Institute on Aging (AG000944 and AG000928 to H.C.)

The Michael J Fox Foundation grant to L.P.

Title: LRRK2 based striatal dysfunction as a Parkinson's disease pathogenic mechanism

Authors: *L. PARISIADOU[1,2], J. YU[2], C. SGOBIO[2,3], C. XIE[2], G. LIU[1,2], L. SUN[2], X. GU[2], X. LIN[2], N. A. CROWLEY[3], D. LOVINGER[3], H. CAI[2];
[1]Lurie Res. Building,, Feinberg Sch. of Med., Chicago, IL; [2]LNG, Natl. Inst. on Aging, Bethesda, MD; [3]LIN, NIAAA, Bethesda, MD

Abstract: Mutations in the LRRK2 gene represent one of the stronger genetic risk factors for the development of Parkinson's disease (PD), and the pathological features of LRRK2-related parkinsonism are usually indistinguishable from the sporadic cases. Therefore, it is proposed that a greater understanding of LRRK2 physiological role and associated pathology could help uncover the cellular events underlying the pathogenesis of PD. The high expression of LRRK2 in the striatum as opposed to its low expression in the dopaminergic neurons that ultimately die in PD, indicates that it might have a role in the striatal projection neurons (SPNs) under both normal and pathological conditions. Towards this direction, we have recently shown in mouse models that the loss of Lrrk2 and the PD-related R1441C mutation causes prominent morphological and functional alterations in the SPNs. A significant decrease in the number of dendritic spines in the striatum of Lrrk2-/- mice compared with Lrrk2+/+ littermate controls was shown, while the remaining ones displayed decreased spine head and increased length. In addition, the Lrrk2-/- and the Lrrk2 R1441C/R1441C mice displayed altered response to D1-agonist mediated motor activity. Those LRRK2-dependent alterations of SPNs involved increased PKA activity via a mechanism involving the subcellular PKA holoenzyme redistribution in the SPNs. Specifically, LRRK2 interacted with the regulatory subunit βII of PKA (PKARIIβ) and Lrrk2-deficiency resulted to increased translocation of the PKA into the dendritic spines. Specificity in several fundamental neuronal functions is achieved at least in part from compartmentalization of PKA enzymes in neurons and it is now clear that postsynaptic PKA are confined to various subcellular compartments by anchoring molecules such as A-Kinase Anchoring Proteins (AKAPs). Based on that, we propose that LRRK2-dependent altered PKA localization may account for the aberrant PKA signaling observed in Lrrk2-/- and the Lrrk2 R1441C/R1441C neurons. These findings indicate a new LRRK2-based dopamine related pathological mechanism that regulates striatal dysfunction in PD, since striatal neurons utilize the PKA pathway to relay dopamine stimulation to intracellular signaling transduction.

Disclosures: L. Parisiadou: None. **J. Yu:** None. **C. Sgobio:** None. **C. Xie:** None. **G. Liu:** None. **L. Sun:** None. **X. Gu:** None. **X. Lin:** None. **N.A. Crowley:** None. **D. Lovinger:** None. **H. Cai:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.03

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation, Identification of LRRK2 phosphatases

Michael J. Fox Foundation, LRRK2 phosphatases confirmation

King Baudouin Foundation

Title: Identification of phosphatases regulating LRRK2 phosphorylation by RNAi screening

Authors: *J.-M. TAYMANS[1], E. LOBBESTAEL[2], M. BÖLLIGER[3], V. BAEKELANDT[2], J. NICHOLS[3];
[1]Jean-Pierre Aubert Res. Center, Inserm/Ul2 UMR, Lille, France; [2]Neurosci., KU Leuven, Leuven, Belgium; [3]The Parkinson's Inst., Sunnyvale, CA

Abstract: The Parkinson's disease protein leucine rich repeat kinase 2 (LRRK2) is a highly phosphorylated protein. Phosphosite mapping studies have distinguished 2 notable clusters of phosphorylation sites, one in or near the ROC-GTPase domain and another in the ankyrin repeat (ANK) and leucine rich repeat (LRR) interdomain region. Evidence of a physiological role for LRRK2 phosphorylation has accumulated in recent years for those phosphosites of the ANK-LRR interdomain region, i.e. the S910/S935/S955/S973 sites. These phosphosites are dephosphorylated in several pathogenic mutants such as R1441C/G, Y1699C, I2020T. The shift of the phosphorylation equilibrium towards dephosphorylation of LRRK2 observed in disease indicates that phosphatases play an important role in LRRK2 cellular regulation. We have previously reported protein phosphatase 1 (PP1) as a physiological phosphatase of LRRK2. Here, we aimed to identify PP1 partners and additional physiological phosphatases of LRRK2 via RNAi screen using siRNAs directed against 298 proteins of the phosphatome in U2OS cells expressing LRRK2. 39 hits from this initial screen were included in follow up secondary screens using lentiviral vector mediated knockdown and overexpression constructs in HEK293 or HEK293T cells expressing LRRK2. With further validation experiments ongoing, these experiments confirm the importance of PP1 and reveal novel phosphatases responsible for regulating LRRK2 phosphorylation levels. The elucidation of factors modulating LRRK2 phosphorylation is likely to point to new possibilities of targeting LRRK2 activity or of developing LRRK2 based biomarkers of disease progression.

Disclosures: J. Taymans: None. **E. Lobbestael:** None. **M. Bölliger:** None. **V. Baekelandt:** None. **J. Nichols:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.04

Topic: C.03. Parkinson's Disease

Support: Spanish Ministry of Economy and Competitiveness (MINECO)

Junta de Andalucia, Spain

Michael J. Fox Foundation, USA

BBVA Foundation, Spain

Title: Pathogenic mutations in LRRK2 cause alterations in centrosome cohesion and cell cycle progression

Authors: *J. MADERO-PÉREZ[1], E. FDEZ[1], A. C. NAIRN[2], A. AIASTUI[3], A. LÓPEZ DE MUNAÍN[3], S. HILFIKER[1];
[1]Inst. of Parasitology and Biomedicine López-Neyra, Granada, Spain; [2]Dept. of Psychiatry, Yale Univ. Sch. of Med., New Haven, CT; [3]Neurosci. Area, Biodonostia Inst., San Sebastián, Spain

Abstract: Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common cause of familial and sporadic Parkinson´s disease (PD). The effects of pathogenic mutations in LRRK2 have generally been studied in differentiated, non-dividing neuronal cells. However, recent studies indicate that pathogenic LRRK2 may play a role in dividing cells as well, as indicated by alterations in adult neurogenesis or the increased cancer risk in LRRK2 PD patients. Here, we report that distinct pathogenic LRRK2 mutants cause alterations in centrosomal cohesion, associated with alterations in nuclear lamina and cell cycle progression. Centrosomal cohesion deficits are associated with partial displacement of the intercentrosomal linker protein rootletin, and can be partially or fully rescued when expressing rootletin, dominant-negative Nek2a or active PP1α, indicating a LRRK2-mediated deregulation of the balance of the Nek2a/PP1 pathway controlling centrosome cohesion via intercentrosomal linkers. Alterations in centrosome cohesion are reverted upon pharmacological LRRK2 kinase inhibition, indicating that they are LRRK2 kinase activity-dependent. In addition, centrosomal cohesion deficits are modulated by distinct Rab proteins implicated in LRRK2-mediated pathogenesis. Centrosomal alterations are also observed in human dermal fibroblasts from G2019S LRRK2 mutant PD patients compared to healthy controls. Together, our data indicate a novel, unexpected role for LRRK2 in dividing cells.

Disclosures: **J. Madero-Pérez:** None. **E. Fdez:** None. **A. C. Nairn:** None. **A. Aiastui:** None. **A. López de Munaín:** None. **S. Hilfiker:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.05

Topic: C.03. Parkinson's Disease

Support: Spanish Ministry of Economy and Competitiveness (MINECO)

Junta de Andalucia, Spain

BBVA Foundation, Spain

Michael J. Fox Foundation, USA

Title: Distinct Rab proteins modulate the LRRK2-mediated deficits in endolysosomal membrane trafficking

Authors: *P. RIVERO-RÍOS, P. GÓMEZ-SUAGA, S. HILFIKER;
IPBLN-CSIC, Armilla (Granada), Spain

Abstract: Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene cause late-onset autosomal dominant Parkinson´s disease (PD), and sequence variations at the LRRK2 locus are associated with increased risk for sporadic PD. LRRK2 contains both GTPase and kinase domains, and mutations within either catalytic domains have been described to cause familial PD, suggesting that these catalytic activities are crucial mediators of pathogenesis. LRRK2 has been implicated in a set of intracellular vesicular trafficking pathways, and our recent data indicate that several pathogenic LRRK2 mutants in the kinase and GTPase domain interfere with endocytic membrane trafficking in a manner dependent on LRRK2 kinase activity and Rab7. Here, we investigated the role of other Rab proteins in modulating the LRRK2-induced deficits in endocytosis by studying the classical degradative trafficking pathway of the epidermal growth factor receptor (EGFR). We find that several other Rab proteins shown to interact with LRRK2 can revert the LRRK2-mediated deficits in EGFR trafficking. These data correlate with alterations in the size, position and acidity of endolysosomes, and together allow us to postulate a mechanism by which pathogenic LRRK2 may impact upon endolysosomal functioning in a manner dependent on distinct Rab proteins localized to distinct intracellular organelles. These

studies should provide novel insights into regulation of endomembrane trafficking by pathogenic LRRK2.

Disclosures: P. Rivero-Ríos: None. **P. Gómez-Suaga:** None. **S. Hilfiker:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.06

Topic: C.03. Parkinson's Disease

Support: Spanish Ministry of Economy and Competitiveness (MINECO)

Junta de Andalucia, Spain

BBVA Foundation, Spain

Michael J. Fox Foundation, USA

Title: Dissecting the determinants required for the association of LRRK2 with microtubules towards establishing assays for identifying novel LRRK2-modifying compounds

Authors: *M. BLANCA RAMÍREZ[1], E. FDEZ[1], A. GONNELLI[2], L. BUBACCO[2], E. GREGGIO[2], S. HILFIKER[1];
[1]IPBLN CSIC, Granada, Spain; [2]Dept. of Biol., Univ. of Padova, Padova, Italy

Abstract: Mutations in LRRK2 (leucine-rich repeat kinase 2) are associated with both familial and sporadic Parkinson´s disease (PD). LRRK2 is a large protein composed of a kinase and a GTPase domain flanked by protein interaction motifs. Various autosomal dominant mutations in the catalytic domains cause familial PD, suggesting that altered catalytic functions may be crucial for LRRK2-related pathogenesis. Various studies indicate that LRRK2 interacts with microtubules, even though how the two catalytic activities modulate this behaviour remains unclear. Here, we find that most pathogenic mutations analyzed (N1437H, R1441G/C, Y1699C, I2020T) display an increased filamentous localization as compared to wildtype LRRK2. Such localization can be partially disrupted by nocodazole, and fully disrupted upon cold-induced microtubule depolymerization. In addition, filaments colocalize with acetylated tubulin, and modulating the acetylation status of microtubules causes alterations in filament formation consistent with the idea that pathogenic LRRK2 preferentially interacts with stable microtubules. Artificial mutations in certain autophosphorylation sites in the context of pathogenic mutant

LRRK2 cause a pronounced decrease in filament formation. This correlates with a decrease in GTP binding. Similarly, artificial mutations in the GTPase domain of mutant LRRK2 which cause decreased GTP binding abolish filament formation. LRRK2 kinase inhibitors which fully block kinase activity cause filament formation of wildtype LRRK2, and additional filament formation in the context of pathogenic mutant LRRK2. In contrast, kinase inhibitors do not cause extensive filament formation of pathogenic LRRK2 mutants with additional mutations, which make them GTP binding-deficient. Together, these data indicate that GTP binding is required for the filament formation phenotype observed in the context of pathogenic LRRK2, and suggest that this assay can be used to search for novel LRRK2 GTP binding modulators which impact upon kinase activity in the context of innovative PD therapeutics.

Disclosures: M. Blanca Ramírez: None. **E. Fdez:** None. **A. Gonnelli:** None. **L. Bubacco:** None. **E. Greggio:** None. **S. Hilfiker:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.07

Topic: C.03. Parkinson’s Disease

Support: NIH P50 NS038377-16

Adrienne Helis Malvin Parkinson's Disease Program M-1

Title: Parkinson’s disease-linked G2019S LRRK2 mutation alters mRNA translation in human dopamine neurons and LRRK2 transgenic mice

Authors: *J. W. KIM[1], I. MARTIN[1], Y. XIONG[1], S. M. EACKER[1], N. T. INGOLIA[2], T. M. DAWSON[1], V. L. DAWSON[1];
[1]Neuroregeneration and Stem Cell Programs, Inst. for Cell Engin., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Dept. of Mol. and Cell Biol., Univ. of California, Berkeley, CA

Abstract: Translation is a fundamental cellular process and its regulation is a crucial part of protein homeostasis. Translation is tightly linked to vital cell physiology, such as cell cycle, metabolism, stress and even cell death. Neurons are particularly susceptible to translational abnormalities and aberrant translational regulation can lead to various neurological disorders including neurodegenerative diseases. Previous studies have also suggested a clear link between translation and Parkinson’s disease (PD), however the detailed mechanisms are still under

investigation. Leucine-rich repeat kinase 2 (LRRK2) is a large multi-domain protein with GTPase and kinase domains, and mutations in LRRK2 have been identified as the most common risk factor for familial PD. G2019S mutation of LRRK2 increases its kinase activity, a process known to be central to neuronal toxicity. Previous research in our laboratory has identified ribosomal protein s15 as a key LRRK2 substrate for its neurotoxicity, and we also showed that global protein synthesis is increased in G2019S LRRK2 mutants. To deepen our understanding of the effects of G2019S LRRK2 on translational regulation, we implemented ribosome profiling technique to survey genome-wide translational expression in neurons. Ribosome profiling experiments were performed on LRRK2 knockout and transgenic mice as well as human dopamine neurons differentiated from G2019S LRRK2 patient-derived induced pluripotent stem cells (iPSCs). Notably, we found that G2019S LRRK2 causes a global shift in translation. Furthermore, we revealed that the translational shift is mediated by the complexity of 5'UTR secondary structures of the mRNAs. Luciferase reporter assays validated our findings from the ribosome profiling experiments. Consistent with our previous studies, reporter assays also revealed that phosphorylation of s15 mediates the translational effects of G2019S LRRK2. Based on these findings, we suggest that altered translation caused by defective translational regulation is a central pathological mechanism in G2019S LRRK2 PD.

Disclosures: **J.W. Kim:** None. **I. Martin:** None. **Y. Xiong:** None. **S.M. Eacker:** None. **N.T. Ingolia:** None. **T.M. Dawson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Valted, LLC. **V.L. Dawson:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.08

Topic: C.03. Parkinson's Disease

Support: NIH Grant R03NS088913-02

Title: Parkinson's disease gene Leucine-rich repeat kinase 2 (LRRK2) regulates autophagosome formation and interacts with the retromer-associated Wiskott-Aldrich syndrome protein and SCAR homologue (WASH) complex

Authors: ***K. VENDEROVA**[1], R. LINHART[1], D. KAING[2], R. FEDRIZZI[2], J. ROSALES[2], R. EISMATI[2], Y.-J. HO[2];

[1]Dept. of Biopharmaceutical Sci., Keck Grad. Inst., Claremont, CA; [2]Physiol. and Pharmacol., Univ. of the Pacific, Stockton, CA

Abstract: Leucine-rich repeat kinase 2 (LRRK2) is the most common causative gene of Parkinson's disease (PD). However the mechanism by which LRRK2 leads to the pathogenesis is not clear. To address this question, we employed our *Drosophila* lines generated previously (Venderova K et al, Hum Mol Genet 2009) that express the I2020T pathogenic mutant variant of LRRK2 selectively in dopaminergic neurons. These flies present with a robust loss of dopaminergic neurons and locomotor deficits. Our targeted screen *in vivo* shows that these locomotor deficits are completely rescued by overexpression of Atg17/FIP200 - one of the key genes required for autophagosome formation. Atg17/FIP200 is necessary for activation of Rab1. In support of our findings, overexpressing wild-type or constitutively active form of Rab1 also rescued the LRRK2 phenotype, while co-expressing mutant LRRK2 with the dominant negative Rab1 was lethal. We next tested whether LRRK2 is required for autophagy that is either induced by Atg1, or by starvation. Indeed, flies expressing only one copy of the lrrk gene had a much shorter survival under starvation conditions. Overexpressing Atg1 in the eye causes a phenotype. This phenotype is markedly suppressed in lrrk knock-down flies, and enhanced in flies overexpressing LRRK2. We have recently demonstrated that overexpression of another Parkinson's disease gene, Vacuolar protein sorting 35 (VPS35), completely rescues several LRRK2 phenotypes *in vivo* (Linhart R et al, Mol Neurodeg 2014). VPS35 is a component of the retromer complex essential for endosomal sorting and trafficking of specific cargo proteins to the Golgi or to the plasma membrane. Similar to LRRK2, overexpressing Vps35 greatly exacerbated the Atg1 eye phenotype. Conversely, knocking-down Vps35 rescued the eye phenotype. Strikingly however, overexpressing LRRK2 significantly suppressed the Vps35 phenotype. These data suggest that both LRRK2 and retromer are required for Atg1-induced autophagy. Retromer can associate with the WASH complex. We therefore next tested whether LRRK2 toxicity may be due to its effect on the WASH complex. Indeed, overexpressing WASH1 completely rescued the LRRK2 phenotype. Furthermore, reducing gene expression of FAM21 or WASH1 (components of the WASH complex) by 50% caused a significant impairment of locomotor activity, highlighting the importance of the WASH complex for the function of dopaminergic neurons. Finally, we demonstrate that the WASH complex is required for the Atg1-induced autophagy. Altogether, our data suggest that the LRRK2(I2020T) impairs autophagosome formation, and that LRRK2 interacts with the retromer and the WASH complex to regulate autophagy.

Disclosures: K. Venderova: None. **R. Linhart:** None. **D. Kaing:** None. **R. Fedrizzi:** None. **J. Rosales:** None. **R. Eismati:** None. **Y. Ho:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.09

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS0646963

Title: Defining the α-synuclein interactome *in situ*

Authors: *X. CAO[1], K. J. VARGAS[2], S. S. CHANDRA[2];
[1]Yale Univ., New Haven, CT; [2]Neurol., CNNR Program, New Haven, CT

Abstract: The pathological hallmark of Parkinson's disease is the formation of Lewy bodies, which are insoluble protein aggregates that primarily consist of α-synuclein. Many drugs are currently being developed to lower α-synuclein levels to counter Lewy bodies, but their impact on neuronal functions of α-synuclein is unknown. Hence, it is of great interest to define the normal function of α-synuclein through determining its protein interactome, setting the stage for studies to examine how these drugs impact α-synuclein function. To elucidate the transient interacting partners of α-synuclein, biotinylation was utilized in neurons to label proteins proximal to α-synuclein at presynaptic termini. The biotinylation process entails expressing α-synuclein protein fused with a biotin ligase, which covalently attaches biotin to nearby proteins. The strong interaction between streptavidin and biotin was exploited to isolate biotinylated proteins for identification via mass-spectrometry. Functional experiments were also done to analyze these new α-synuclein interacting proteins in the context of synaptic vesicle cycling. Furthermore, the interactome of α-synuclein mutants (A30P and A35T) that predispose patients to Parkinson's disease was also examined to determine differences compared to the interactome of WT α-synuclein.

Disclosures: X. Cao: None. **K.J. Vargas:** None. **S.S. Chandra:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.10

Topic: C.03. Parkinson's Disease

Support: Parkinson's Disease Foundation Stanley Fahn Research Fellowship (KS)

NIH/NINDS K08 NS069625 (VU)

Title: Systemic inhibition of Polo-like Kinases modulates alpha-synuclein *in vivo* in mouse cortex

Authors: *K. SPINELLI, V. R. OSTERBERG, L. J. WESTON, V. K. UNNI;
Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Phosphorylated forms of α-synuclein are enriched in Lewy Bodies in Parkinson's Disease, with Serine-129 phosphorylation (S129-P) often used as a marker of diseased brain tissue. However, recent data in rat and yeast model systems link S129-P to degradation of toxic α-synuclein species, thus conferring cellular and whole-animal protection. Of the kinases that contribute to S129 phosphorylation, Polo-like Kinases (PLKs), in particular PLK2, are thought to be the major contributing enzymes in mammalian brain. To study the role of endogenous kinases in α-synuclein phosphorylation, degradation, and aggregation, we have systemically administered a pan-PLK inhibitor to transgenic mice that express Green Fluorescent Protein (GFP)-tagged human α-synuclein (Syn-GFP). We have previously characterized an immobile, aggregated pool of Syn-GFP that is S129-P-positive and Proteinase K-resistant, selectively found at presynaptic terminals, in these mice. After a single dose of drug, we found a rapid, transient reduction in S129-P-Syn-GFP levels at cortical presynaptic terminals by immunohistochemistry and western blot analysis. Total Syn-GFP protein levels were also modulated, with a delayed time course compared to S129-P levels, indicating that inhibiting PLK could affect synaptic α-synuclein trafficking and/or degradation. Employing *in vivo* cranial window-based multiphoton imaging, we can measure aggregation of Syn-GFP at individual cortical presynaptic terminals using Fluorescence Recovery After Photobleaching (FRAP). By measuring *in vivo* FRAP dynamics in the same mouse brain before and after drug treatment, we can directly correlate changes in aggregation with phosphorylation state of α-synuclein from previously-characterized biochemical data. We have also found a drastic reduction in S129-P-Syn-GFP levels in mice that express Syn-GFP on a PLK2-knock out background. Future experiments will examine how genetic deletion of PLK2 affects Syn-GFP protein dynamics and aggregation. Grant Support: Parkinson's Disease Foundation Stanley Fahn Research Fellowship (KS), NIH/NINDS K08 NS069625 (VU).

Disclosures: K. Spinelli: None. **V.R. Osterberg:** None. **L.J. Weston:** None. **V.K. Unni:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.11

Topic: C.03. Parkinson's Disease

Title: Impact of O-GlcNAc protein modification on alpha-synuclein degradation

Authors: *T.-Y. WU, M. MATTSON;
Lab. of Neurosci., Natl. Inst. On Aging, Baltimore, MD

Abstract: Accumulation of alpha-synuclein (SNCA) aggregates is believed to play a key role in the dysfunction and death of neurons that occurs in Parkinson's disease (PD). When gene duplication- or single nucleotide polymorphism-driven overexpression or mutation of SNCA occurs, SNCA aggregates and damages dopaminergic neurons. Therefore, reducing SNCA accumulation and aggregation is an approach for preventing and treating PD and related synucleinopathies. Recent findings suggest that the glucose dependent post-translational modification, O-linked beta-N-acetylglucosamine (O-GlcNAc), may alter the stability and toxicity of pathogenic proteins. For example, in models relevant to Alzheimer's disease, hypo-O-GlcNAc modification increases the stability and polymerization of Tau. To elucidate the role of O-GlcNAc modification in synucleinopathies, we first established a wild-type SNCA overexpressing line of 293T cells. By immunoprecipitation we found O-GlcNAc modification on SNCA was up-regulated by high glucose or an O-GlcNAcase (OGA) inhibitor (PUGNAC), and was down-regulated by an O-GlcNAc transferase (OGT) inhibitor (ST045849). In primary rat neurons, OGA inhibitor treatment significantly lowered the level of SNCA, suggesting a role for O-GlcNAc modification in regulating the production and/or degradation of SNCA. To further explore the function of O-GlcNAc in regulating the level of SNCA, we employed the Tet-off system for evaluating SNCA turnover rate in PC-12 cells. After adding doxycycline to silence SNCA expression, OGA inhibitor-treated cells degraded SNCA faster than the control or OGT inhibitor-treated cells. Moreover, faster SNCA degradation also occurred in OGA shRNA knockdown Tet-off SNCA-expressing PC-12 cells. To determine the major pathway involved in O-GlcNAc-mediated SNCA degradation, we co-treated Tet-off SNCA-expressing PC-12 cells with the proteasome inhibitor (MG-132) or the autophagy inhibitor (3-MA), together with the OGA inhibitor. Inhibition of proteasome degradation significantly decreased the turnover of SNCA, whereas inhibition of autophagy did not. Our findings reveal that O-GlcNAc modification can promote proteasome-mediated degradation of SNCA, which sheds lights on future intervention strategies for decreasing SNCA accumulation by manipulating O-GlcNAc modification in PD patients.

Disclosures: **T. Wu:** A. Employment/Salary (full or part-time); National Institute on Aging. **M. Mattson:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.12

Topic: C.03. Parkinson's Disease

Support: Alzheimer's Drug Discovery Foundation (ADDF)

The Cullen Family Trust for Health Care

The Michael J. Fox Foundation

The Mitchell Center for Neurodegenerative Diseases

The Moody Project for Translational Traumatic Brain Injury Research

Title: Potential role of exosomal tau and alpha-synuclein oligomers in cell toxicity and spreading pathology in PD and DLB

Authors: *D. L. CASTILLO[1], M. J. GUERRERO-MUÑOZ[2], U. SENGUPTA[2], S. SHAFIEI[2], J. GERSON[2], B. E. HAWKINS[3], R. KAYED[2];
[2]Neurol., [3]Anesthesiol., [1]UTMB, Galveston, TX

Abstract: The coexistence of tau and alpha-synuclein (α-syn) deposits is a defining feature of a group of neurodegenerative diseases including Parkinson's disease (PD) and Dementia with Lewy body (DLB). Conformational changes in native, unfolded proteins tau and α-syn lead to abnormal proteinaceous deposits called neurofibrillary tangles (NFTs) and Lewy bodies (LBs), respectively. Although NFTs and LBs are considered the classical hallmarks of these diseases, recent data suggest that oligomeric assemblies rather than large aggregates are the real toxic species and may engage in propagating neurodegenerative "seeds" within the tissue. However, the mechanism by which oligomers trigger neurodegeneration remains elusive. We previously showed that oligomers of tau and α-syn exist in the same aggregates, forming hybrid oligomers in PD and LBD cases, providing evidence of co-occurrence of α-syn and tau into their most toxic forms, and influencing each other's aggregation via an interface in synucleinopathies. Growing interest in misfolded tau and α-syn has been further emphasized by recent studies showing that tau as well as a-syn can be secreted from neurons via membrane vesicle called exosomes. Moreover, observations in cell culture suggest that tau as well as α-syn can be internalized by neighboring cells, perhaps contributing to the spreading of the disease. Herein, we investigate the interaction of α-syn and tau oligomers in human PD and LBD cases. Cell fractions obtained from

PD and LBD brains, revealed that α-syn and tau oligomers are found mainly in cytoplasm and membranous fractions. Immunohistochemical analysis demonstrated that tau and α-syn oligomers colocalize in exosomes within neuronal cytoplasm. This novel finding suggests that interaction of α-syn and tau oligomers in exosomes play a role in disease pathogenesis and propagation.

Disclosures: D.L. Castillo: None. **M.J. Guerrero-Muñoz:** None. **U. Sengupta:** None. **S. Shafiei:** None. **J. Gerson:** None. **B.E. Hawkins:** None. **R. Kayed:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.13

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation CES, FPM

Title: Alpha synuclein aggregation causes toxicity by decreasing functional forms of the protein

Authors: *M. J. BENSKEY, N. C. KUHN, F. P. MANFREDSSON;
Michigan State Univ., Grand Rapids, MI

Abstract: Abnormal alpha-synuclein (α-syn) expression and/or aggregation has been widely implicated as a potential etiological root for parkinson disease (PD). For example, mutations or multiplications of the α-syn gene result in familial PD, while aggregated α-syn is a primary component of Lewy bodies, the pathological hallmark of sporadic PD. Further, recombinant adeno-associated virus (rAAV) mediated overexpression of human α-syn in the rat substantia nigra pars compacta (SNpc) produces a predictable pattern of α-syn aggregation and cell loss, and is a commonly used model of PD pathology. The correlation between aggregated α-syn and the development of PD pathology has led to the theory that α-syn-mediated pathology arises due to a toxic gain-of-function, and many current therapeutic strategies center on eliminating α-syn from midbrain dopamine neurons of the SNpc. However, we have shown that short hairpin RNA-mediated removal of endogenous α-syn from neurons of the SNpc results in cell loss *in vivo*. Importantly, this cell loss is rescued by supplementation of α-syn. These results indicate that α-syn is essential for neuronal survival, and has led us to develop the novel hypothesis that α-syn and associated aggregates are not directly toxic; rather α-syn aggregation produces toxicity by reducing levels of functional monomeric α-syn through sequestration into intracellular aggregates. To test this hypothesis, we aimed to induce aggregation in neurons of the SNpc by

overexpressing human α-syn in the rat SNpc, while also maintaining functional levels of monomeric α-syn through the concomitant expression of a non-aggregatable α-syn (NAS) isoform. Thus in the current study, rAAV was used to deliver human α-syn either alone or in combination with the NAS isoform to the rat SNpc. One month post-surgery, animals that received rAAV-human α-syn displayed a significant increase in forepaw akinesia, indicative of degeneration of the injected SNpc. In contrast animals which received the NAS isoform in combination with human α-syn showed no difference in forepaw akinesia as compared to control animals. Ongoing assays will probe the integrity of the nigrostriatal system in all groups by quantifying the number of SNpc neurons using unbiased stereological cell counts, as well as levels of dopamine and metabolites in the striatum. We predict that the maintenance of soluble α-syn using the NAS isoform will preserve α-syn function; preventing the neurodegeneration that is produced by α-syn aggregation, indicating that loss of α-syn function is a critical event in PD pathology.

Disclosures: M.J. Benskey: None. **N.C. Kuhn:** None. **F.P. Manfredsson:** None.

Nanosymposium

371. Alpha-Synuclein, LRRK2, and Other Molecular Mechanisms in Parkinson's Disease

Location: N230

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 371.14

Topic: C.03. Parkinson’s Disease

Title: Autophagic-lysosomal dysfunction promotes exosomal release of pathological proteins in Parkinson’s and Alzheimer’s disease

Authors: *W.-H. YU[1], N. HERNANDEZ[2];
[1]Taub Inst. / Pathology, Columbia Univ., New York City, NY; [2]Taub Inst., Columbia Univ., New York, NY

Abstract: Autophagic-lysosomal dysfunction has been linked to neurodegenerative diseases like Alzheimer’s and Parkinson’s disease with strong evidence indicating that in aging and disease, this major protein/lipid quality control pathway is inefficient. There is increasing association with genetic mutations that may contribute to lysosomal stress, including reduction in glucocerebrosidase (GC) function in Parkinson’s and related disorders. The net effect is reduced lysosomal activity that may contribute to the accumulation of redundant proteins, lipids and dysfunctional organelles. While most proteins are retained internally and sequestered as aggregates, recent work has shown that proteins like α-synuclein and tau can spread from one cell to another, or from one region to another. The transmission of pathology may be an

opportunity for neurons to enhance self-preservation mechanisms extruding potentially toxic proteins into the extracellular milieu. We have evidence that chemically-induced lysosomal stress can increase the extracellular release in the form of exosomes and may contain proteotoxic elements. Exosomes are intracellular vesicles released from most cells that are readily taken into recipient cells and may represent a medium for pathological transfer of proteins. Further, it is likely that exosomal release is significantly increased versus free protein release when there is lysosomal stress. Cumulatively, this project link lysosomal stress and exosomal release and potential transfer to recipient cells.

Disclosures: W. Yu: None. **N. Hernandez:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.01

Topic: D.04. Vision

Support: NIH Grant EY11747

R01EY016454

Title: Human and monkey detection performance in natural images compared with V1 population responses

Authors: *Y. BAI[1,2], Y. CHEN[1,2], W. GEISLER[1,2], E. SEIDEMANN[1,2];
[1]Dept. of Psychology, Univ. of Texas-Austin, Austin, TX; [2]Ctr. for Perceptual Systems, Austin, TX

Abstract: Detection is a fundamental task that is critical to visual behavior. Our aim here was to measure and model behavioral and neurophysiological performance for detecting targets under naturalistic conditions. We first measured behavioral detection performance in three humans and two macaque monkeys. The target was a localized oriented stimulus that was presented for 250 milliseconds to reflect the typical fixation duration in visual search. Detection thresholds were measured on uniform backgrounds and for several contrasts of natural image backgrounds. We found that (i) threshold contrast power is a linear function of background contrast power for both humans and macaques, and (ii) the relative threshold functions for humans and macaques are in good agreement, although (iii) the macaques are less sensitive overall. We have also begun exploring the quantitative relationship between V1 population responses and the measured

detection performance. We used voltage-sensitive dye imaging (VSDI) to measure the neural population activity in V1 for the same stimuli, while the monkeys held fixation. The spatial scale of VSDI measurements was sufficient to resolve orientation columns over the whole region activated by the target. We used a baseline condition with the target only (on uniform backgrounds) to define a "matched template", which defines a set of weights for spatially pooling the VSDI responses. For each condition, we measured the matched-template response to each background and target + background trial to obtain neurometric functions. Our preliminary results suggest that there is a strong correlation between orientation column responses and behavioral thresholds. In conclusion, the macaque is a good model of human detection behavior in natural images, and population responses at the columnar scale in V1 appear to be predictive of behavioral detection performances in natural images.

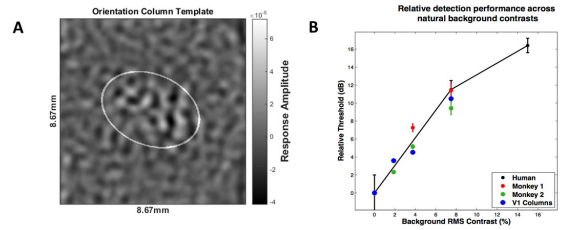


Figure A: Orientation column template. Example orientation column response from a high contrast Gabor target added on a uniform background using voltage sensitive dye imaging (VSDI). The ellipse indicates the area of the template, which is defined by the target-evoked region. Each pixel value represents the VSDI response amplitudes for orientation columns.

Figure B: Relative detection performance as a function of background contrast. Plotted are thresholds (in dB) for detecting a known target in unknown natural backgrounds, relative to detecting the same target in a uniform (blank) background, as a function of the contrast of the natural backgrounds. Data points labelled Human and Monkey 1 & 2 are detection thresholds measured in a psychophysical experiment. Data points labelled V1 Columns represent detection thresholds derived by applying a simple neural decoder (matched template) to VSDI responses measured at the scale of orientation columns in monkey V1.

Disclosures: **Y. Bai:** None. **Y. Chen:** None. **W. Geisler:** None. **E. Seidemann:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.02

Topic: D.04. Vision

Support: DFG NI 708

Title: Stimulus driven decline in neuronal variability, a general phenomenon, not a consequence of efficient encoding

Authors: *A. E. LAZAR, W. SINGER, D. NIKOLIC;
Ernst Strüngmann Inst., Frankfurt, Germany

Abstract: The onset of a visual stimulus causes a reduction in neuronal variability in a number of visual areas including V1 (Churchland 2010). Mechanistically, this implies that interactions in cortical circuits become more stable when driven. We investigated the extent to which the decline in response variability following stimulus onset depends on the content of the visual stimulus. We recorded V1 population responses simultaneously with chronically-implanted, movable electrodes from awake rhesus macaques during a passive viewing task. The stimuli were black and white shapes, natural scenes and scrambled controls of the original images. We measured the variability of single unit responses across multiple presentations of the same stimulus by calculating the Fano factor (the spike-count variance divided by the spike-count mean). In agreement with previous research, our results showed that all of the considered visual stimuli, including the controls, reduced the inter-trial variability of neuronal responses. Interestingly, however, this reduction in neuronal variability was not correlated with a measure of response discriminability (d'), which quantifies the difference between responses to different stimuli. Importantly, in a higher visual area, a hypothetical decision unit should be able to extract relevant information about a stimulus based on the input received from V1 neurons. We trained a Bayesian classifier to separate different stimuli based on short segments (50 ms) of population activity. Classification performance was high for shapes and natural scenes but low for the control images. In an apparent contradiction, all visual stimuli decreased neuronal firing variability at the level of V1, however only the shapes and natural scenes generated stimulus specific evoked responses. One interesting interpretation of this result is that scrambled images contain less reducible information compared to shapes and natural scenes. As such, any neuronal transformation meant to increase the efficiency of the stimulus representation may act as a filter which disproportionately favors stimuli with spatial structure. Our results imply that caution should be exercised when interpreting variability reduction as a signature of stimulus information content. Churchland, M.M., et al. (2010). Nat. Neurosci. 13, 369-378.

Disclosures: **A.E. Lazar:** None. **W. Singer:** None. **D. Nikolic:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.03

Topic: D.04. Vision

Support: NIH Grant EY04440

NIH Grant EY022428

Howard Hughes Medical Institute

Title: The neural basis of fine orientation discrimination in macaque monkeys

Authors: *R. L. GORIS[1,2], C. M. ZIEMBA[1], G. M. STINE[1], E. P. SIMONCELLI[1,2], J. A. MOVSHON[1];
[1]Ctr. for neural science, New York Univ., New York, NY; [2]HHMI, New York, NY

Abstract: Visual experience relies in large part on our ability to appreciate subtle differences in the orientation of visual features. In primates, selectivity for orientation emerges in primary visual cortex (V1) and is also common in downstream cortical areas such as V2. We investigated the relation between single cell activity in macaque V1 and V2 and simultaneously measured psychophysical judgments of stimulus orientation. We trained two macaque monkeys to discriminate the orientation of drifting gratings presented for 500 ms in the near periphery. To enable a direct comparison of neuronal and behavioral sensitivity, we tailored the stimulus (grating size, scale, and speed) and task (the orientations to be discriminated) to the tuning properties of the neuron under study. Both animals performed the task well, with thresholds that varied between 1 and 5 deg for a wide range of stimulus conditions (mean threshold: 3.3 deg and 2.8 deg, respectively). Ideal observer analysis of neuronal responses revealed that single V1 and V2 neurons carried almost as much information about stimulus orientation as the animals' behavioral reports. On average, psychophysical sensitivity exceeded neuronal sensitivity by 65% in V1 and 45% in V2. We also estimated "choice probability": the degree to which fluctuations in neural activity predict fluctuations in behavioral judgments across repeated presentations of the same stimulus. Although both monkeys had similar behavioral sensitivity, choice probability differed between animals. For one monkey, there was no systematic choice-related activity evident in the responses of V1 or V2 neurons. For the other, there was a weak but systematic choice probability. However, the sign of this relationship was, unexpectedly, negative: when an orientation-selective neuron fired more spikes, the animal was less likely to make a decision in favor of the orientation preferred by the neuron. Our results suggest that single cell sensitivity in V1 imposes an upper bound on behavioral sensitivity for fine orientation discrimination, and that the component of neuronal variability that gives rise to choice-related activity in sensory neurons is divorced from the component that limits behavioral sensitivity.

Disclosures: R.L. Goris: None. **C.M. Ziemba:** None. **G.M. Stine:** None. **E.P. Simoncelli:** None. **J.A. Movshon:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.04

Topic: D.04. Vision

Support: Gatsby Charitable Foundation

Simons Foundation SCGB323228

Action on Hearing Loss 549:UEI:JL

Title: Changes in inhibition explain variability in cortical activity and its role in sensory representations

Authors: *C. STRINGER[1], M. PACHITARIU[1], K. J. HILDEBRANDT[2], P. BARTHO[3], K. D. HARRIS[1], J. F. LINDEN[1], P. LATHAM[1], N. LESICA[1], M. SAHANI[1];
[1]Univ. Col. London, London, United Kingdom; [2]Univ. of Oldenburg, Oldenburg, Germany; [3]Hungarian Acad. of Sci., Budapest, Hungary

Abstract: The firing rate of a neuron in the mammalian cortex fluctuates in coordination with the activity of its neighbors. The nature of this relationship varies across behavioral states, and affects the reliability of the neuron's sensory representation. We found that the rich range of statistical structures in multi-neuron recordings could be reproduced by different operating regimes of a single deterministic network model of spiking neurons. We fit the parameters of the spiking network model to the statistics of spontaneous and driven activity from 46 different electrophysiology datasets of 20-100 neurons recorded in the sensory cortices of rats and gerbils, using novel computational techniques. First, we used graphics processing units to simulate networks of 512 spiking neurons at 10000x real-time speed. Second, we used Bayesian optimization to find parameters which best reproduced a collection of summary statistics for each dataset: autocorrelation function, mean and variance of spike counts, and stimulus response. The model successfully fit both the diversity of autocorrelation timescales and the magnitude of the correlations present in the neuronal activity. To investigate the consequences for coding, we drove the simulated networks with external inputs. We consistently observed that noise correlations within each network were smaller for stimuli evoking high firing rate responses than for stimuli evoking lower firing rate responses. This prediction was verified in recordings from both awake and anesthetized auditory cortex. Further, evoked responses were least correlated in simulated networks with the largest inhibitory-to-excitatory firing rate ratios. The high inhibitory activity abolished population fluctuations and enhanced coding properties. We confirmed this prediction in two ways. First, looking at multiple sound-evoked recordings from auditory cortex, we found that high levels of fast-spiking inhibition did indeed correlate with reduced noise correlation. Next, we continuously activated auditory cortex PV-positive neurons virally transfected with stable step-function opsin (SSFO), and found that stimulus-independent coordinated population variability decreased while signal-driven activity increased. Our modelling work suggests that networks with a common architecture can generate widely

different multi-neuron patterns depending on their precise parameters. These results provide a computational tool for relating the statistical structure of multi-neuron recordings to neural network connectivity and mechanisms.

Disclosures: C. Stringer: None. **M. Pachitariu:** None. **K.J. Hildebrandt:** None. **P. Bartho:** None. **K.D. Harris:** None. **J.F. Linden:** None. **P. Latham:** None. **N. Lesica:** None. **M. Sahani:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.05

Topic: D.04. Vision

Support: NIH Grant 1R01-EY018847-01A1/05

Title: Correlated variability in population activity: noise or signature of internal computations?

Authors: *G. DENFIELD[1], A. ECKER[2], A. TOLIAS[1];
[1]NEUROSCIENCE, BAYLOR COLLEGE OF MEDICINE, Houston, TX; [2]Max Planck Inst. for Biol. Cybernetics, Tubingen, Germany

Abstract: Neuronal responses to repeated presentations of identical visual stimuli are variable. The source of this variability is unknown, but it is commonly treated as noise and seen as an obstacle to understanding neuronal activity. We argue that this variability is not noise but reflects, and is due to, computations internal to the brain. Internal signals such as cortical state or attention interact with sensory information processing in early sensory areas. However, little research has examined the effect of fluctuations in these signals on neuronal responses, leaving a number of uncontrolled parameters that may contribute to neuronal variability. One such variable is attention, which increases neuronal response gain in a spatial and feature selective manner. Both the strength of this modulation and the focus of attention are likely to vary from trial to trial, and we hypothesize that these fluctuations are a major source of neuronal response variability and covariability. We first examine a simple model of a gain-modulating signal acting on a population of neurons and show that fluctuations in attention can increase individual and shared variability and generate a variety of correlation structures that are relevant to population coding, including limited range and differential correlations. To test our model's predictions experimentally, we devised a cued-spatial attention, change-detection task to induce varying degrees of fluctuation in the subject's attentional signal by changing whether the subject must

attend to one stimulus location while ignoring another, or attempt to attend to multiple locations simultaneously. We use multi-electrode recordings with laminar probes in primary visual cortex of macaques performing this task. We demonstrate that attention gain-modulates responses of V1 neurons in a manner that is consistent with results from higher-order areas. Consistent with our model's predictions, our preliminary results indicate neuronal covariability is elevated in conditions in which attention fluctuates and that neurons are nearly independent when attention is focused. Overall, our results suggest that attentional fluctuations are an important contributor to neuronal variability and open the door to the use of statistical methods for inferring the state of these signals on a trial-by-trial basis.

Disclosures: G. Denfield: None. **A. Ecker:** None. **A. Tolias:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.06

Topic: D.04. Vision

Support: Simons Collaboration on the Global Brain

NSF-DMS-1313225

Title: Modeling the neural mechanics of attention-mediated suppression of noise correlations

Authors: *T. KANASHIRO[1], G. K. OCKER[2,3], M. R. COHEN[2,3], B. DOIRON[4,3];
[1]Ctr. for the Neural Basis of Cognition, Carnegie Mellon Univ., Pittsburgh, PA; [2]Neurosci., [3]Ctr. for the Neural Basis of Cognition, [4]Mathematics, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Many studies describe the cognitive effects and associated neural correlates of attention, but a mechanistic understanding of how they arise is still lacking. It is well established than in primate visual cortex attention increases trial-averaged neural firing rates and stimulus response gains. Recent population recordings from V4 show that attention also decreases the trial-to-trial covariability (noise correlation) of similarly tuned excitatory neurons. Our aim is to incorporate these observations into a single model of cortical activity under attentional modulation. A simple linear response theory of attention suggests a multiplicative relationship between covariance and gain on the micro-scale. We confirm this hypothesis through analysis of V4 population data using a statistical model that assumes a low-rank attentional modulation of the pairwise covariance structure of the network. The success of this analysis motivates a

stochastic mean-field rate model where attention is modeled as an increase in neural excitability. Linear response analysis of this model shows that attention shifts the network into a more stable asynchronous state, allowing recurrent inhibition to better cancel correlated input, thereby decreasing noise correlations. Our analysis shows that this mechanism of attentional modulation favors inhibitory over excitatory neurons, for which there are promising experimental observations. Further, we show that in order for the stimulus response gain to increase with attention despite this input correlation quenching, the stimulus must favor excitatory neurons over inhibitory ones, suggesting complementary roles for top-down attentional and bottom-up stimulus signals. A common notion is that attention improves behavior by increasing the signal-to-noise ratio of neural activity. We assess the attentional effect on information by computing the linear Fisher information using the mean-field model expressions for covariance and gain. We find that attention does not change the total information content of the system, but shifts it so that the information of the excitatory population increases. This makes sense in the context of downstream targets receiving projections from pyramidal neurons. Finally, we present preliminary work extending the model to populations of differently tuned neurons, to account for recent population recordings from V4 that show that attention modulates noise correlations differently depending on relative tuning properties. Specifically, attention decreases noise correlations of similarly tuned, and increases those of differently tuned neurons.

Disclosures: **T. Kanashiro:** None. **G.K. Ocker:** None. **M.R. Cohen:** None. **B. Doiron:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.07

Topic: D.04. Vision

Support: NIH EY014924

Stanford NeuroVentures grant

Howard Hughes Medical Institute

Title: Attentional modulation of cortical state dynamics and its contribution to spiking variability in area V4

Authors: *T. A. ENGEL[1,3], N. A. STEINMETZ[4], T. MOORE[2,3], K. BOAHEN[1];
[1]Dept. of Bioengineering, [2]Dept. of Neurobio., Stanford Univ., Stanford, CA; [3]Howard Hughes Med. Inst., Stanford, CA; [4]Univ. Col. London, London, United Kingdom

Abstract: Cortical activity is permeated with endogenously generated fluctuations. Varying strengths of these fluctuations at different frequencies manifest as distinct patterns of ensemble neural activity that are characteristic of different cortical states. Cortical state influences sensory processing, but it remains unknown whether it is actively controlled to serve behavioral goals. To answer this question we analyzed ensemble neural activity recorded with linear electrode arrays across cortical layers in area V4 of two macaque monkeys. We observed that the ensemble neural activity spontaneously transitions between intervals of vigorous spiking ("On" states) and quiescence ("Off" states) on all recorded channels. Transitions between On and Off episodes occurred nearly simultaneously throughout the cortical depth in spontaneous and stimulus-driven activity, during a fixation task and during a cognitively demanding visual attention task and they were not reliably locked to behavioral events. We characterized the dynamics of On-Off transitions using a Hidden Markov Model (HMM) with a binary-valued latent state variable and Poisson spike emissions. The HMM provided an excellent fit to the population spiking activity recorded across the cortical depth and accounted for half of the variance in the spike trains on average. We then used the HMM fit as a statistically principled way to segment spiking data into the On and Off episodes and studied the dynamics of On-Off transitions in different behavioral contexts. We found that the mean duration of On episodes increased when monkeys attended or prepared a saccade to the receptive field location, consistent with a local shift toward desynchronization of ensemble activity. Thus the dynamics of On-Off transitions were modulated locally within the retinotopic map during covert and overt selective attention. We then investigated how these local changes of cortical state dynamics are related to previously found reduction in correlated neural variability with attention. Our results provide direct evidence that cortical state dynamics are among major sources of spiking variability in behaving primates and that cortical state dynamics are controlled locally within a retinotopic map to serve cognitive demands.

Disclosures: T.A. Engel: None. **N.A. Steinmetz:** None. **T. Moore:** None. **K. Boahen:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.08

Topic: D.04. Vision

Support: NIH Grant EY023456

NIH Grant EY018894

NIH Grant EY022928

NIH Grant EY008098

Research to Prevent Blindness

NIH Grant DA023428

Title: Differential effects of attention on correlated variability of inhibitory and excitatory populations in V4

Authors: *A. C. SNYDER, M. J. MORAIS, M. A. SMITH;
Dept. of Ophthalmology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Perceptual systems are continuously bombarded by information from the environment. We make use of selective attention to filter this information - enhance the relevant and suppress the distracting. The neural circuit mechanisms that underlie selective attention, however, remain unclear. Computations in cortex take place in networks of noisy neurons, and modulation of that noise likely plays an important role in attention. Two lines of research support this hypothesis. First, recordings of populations of V4 neurons have demonstrated that shared variability decreases in neurons with receptive fields at the focus of spatial attention. Second, measurements of human EEG show retinotopically specific decreases in the amplitude of 8-15 Hz “alpha”-band oscillations in the EEG corresponding to the focus of spatial attention. The decrease in oscillation amplitude suggests the underlying neurons are less coherent in their activities, but the relationship between EEG signals and the underlying neural activity is not well-understood. In order to directly test the hypothesis that changes in the correlated spiking variability in neuronal populations mediates the relationship between oscillatory EEG signals and attention performance, we simultaneously recorded EEG and neuronal populations in visual area V4 of alert macaque monkeys performing a spatial attention task. We found a surprising “U”-shaped relationship between spiking correlations and EEG oscillations. In order to better understand this observation, we employed an established computational model of populations of inhibitory and excitatory neurons. We found that providing a private oscillatory signal delivered to only the inhibitory subpopulation closely replicated our observations, which is in line with prior suggestions that inhibitory neurons may occupy a privileged role in attention signaling. We tested this prediction of the model by classifying our sample of neurons into putative inhibitory and excitatory subclasses on the basis of waveform shape, and then measured the spike count correlation within and between these classes across different attentional states. We found that correlation decreased with attention among excitatory neurons, in line with previous reports, but among inhibitory neurons correlation actually increased with attention. This suggests that

inhibitory neurons are indeed the recipients of a shared signal during the attentive state, and that this signal leads to a decrease in correlation in the rest of the population. Our results thus provide a network-level account for the role of inhibition in attention.

Disclosures: **A.C. Snyder:** None. **M.J. Morais:** None. **M.A. Smith:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.09

Topic: D.04. Vision

Support: NIH grant EY11379

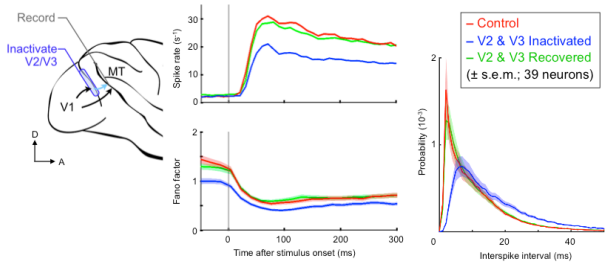
NIH grant EY12196

NSF grant NSF-08-557

Title: Bottom-up and top-down inputs drive the variability of cortical neurons

Authors: ***C. GOMEZ-LABERGE**[1], A. SMOLYANSKAYA[1], J. J. NASSI[1], G. KREIMAN[2], R. T. BORN[1];
[1]Neurobio., Harvard Med. Sch., Boston, MA; [2]Children's Hosp. Boston, Boston, MA

Abstract: Neurons in the cerebral cortex respond inconsistently to a repeated sensory stimulus, so how can they provide the basis for stable sensory experiences? Although the exact causes of neuronal response variability are unknown, the consistency with which it has been observed across a variety of cortical regions has encouraged the general view that each cell produces random spike patterns that noisily represent its response rate. In contrast to this view, we discovered that reversibly inactivating sources of either bottom-up (V2-to-MT) or top-down (V2-to-V1) input to cortical visual areas in the alert primate reduced both the spike train irregularity and the trial-to-trial variability of single neurons. A simple network model of integrate-and-fire neurons in which a fraction of the pre-synaptic inputs are silenced can reproduce this reduction in variability, provided that there exist temporal correlations primarily within, but not between, excitatory and inhibitory input pools. A large component of the variability of cortical neurons can therefore be ascribed to synchronous input produced by signals arriving from multiple sources. Taken together, our results impose strong constraints on theories of neuronal variability by causally linking the presence of bottom-up and top-down input to the spiking statistics of cortical neurons.



Disclosures: **C. Gomez-Laberge:** None. **A. Smolyanskaya:** None. **J.J. Nassi:** None. **G. Kreiman:** None. **R.T. Born:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.10

Topic: D.04. Vision

Support: NIH Grant R01 EY021827-04

Title: Optogenetically induced low-frequency correlations impair perception

Authors: ***A. S. NANDY**, J. J. NASSI, J. H. REYNOLDS;
SNL-R, Salk Inst., La Jolla, CA

Abstract: Deployment of covert attention to a spatial location causes a significant decrease in correlated variability (common fluctuations) among neurons in area V4 whose receptive fields lie at the attended location (Cohen & Maunsell, 2009; Mitchell et al., 2009). This reduction is especially prominent in the low-frequency range (< 10Hz). These studies have estimated that the reduction in common fluctuations accounts for a substantial fraction (80%) of the improvement in sensory processing that occurs when attention is directed toward a stimulus. However, these estimates depend on assumptions about how population signals are read out, and the conclusion that low frequency correlated variability impairs perception, is purely hypothetical. Indeed, under some conditions correlations might be expected to improve encoding of sensory information (Averbeck et al., 2006). Here, we test this proposal directly by inducing low-frequency fluctuations in V4 via optogenetic stimulation, to see if this interferes with the animal's performance in an attention-demanding orientation-change detection task. On a subset of trials we stimulated neurons in area V4 using a recently developed approach to primate optogenetics (Ruiz, Lustig, Nassi et al., 2013). We injected lentivirus carrying the CaMKIIα promoter to

preferentially drive expression of the depolarizing opsin C1V1 (lenti-CaMKIIα-C1V1-ts-EYFP) in excitatory neurons in area V4. We find that low-frequency laser stimulation (4-5Hz) impairs the animal's ability to detect fine orientation changes. Physiologically, this stimulation elevates correlations among pairs of neurons by biasing neuronal responses toward specific stimulation phases, but without changes in mean firing rate. The impairment is frequency specific in that stimulation at higher frequencies (20Hz, 40Hz) does not impair performance, despite comparable modulation of neuronal responses. These results demonstrate that low-frequency correlated variability can impair perception, supporting the hypothesis that attention-dependent reductions in correlated variability contribute to improved perception of attended stimuli.

Disclosures: **A.S. Nandy:** None. **J.J. Nassi:** None. **J.H. Reynolds:** None.

Nanosymposium

372. The Nature and Significance of Neuronal Variation

Location: S401

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 372.11

Topic: D.04. Vision

Support: NIH grant 4R00EY020844 – 03

NIH grant R01 EY022930

NIH grant 5T32NS7391-14

Whitehall foundation grant

Klingenstein-Simons Fellowship

Simons foundation

Sloan Research Fellowship

Title: A normalization model accounts for stimulus and attention-related changes in correlated variability across cortical areas

Authors: *D. A. RUFF, M. R. COHEN;
Dept. of Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Models of divisive normalization can explain the trial-averaged responses of neurons in sensory, association, and motor areas under a wide range of conditions. For example, several

studies have used normalization models to characterize how attention scales the responses of neurons in visual cortex. Attention, like other processes that divisively scale responses, is also associated with changes in the extent to which pairs of neurons share trial-to-trial variability (termed spike count or noise correlations). Currently, normalization models do not address response variability. Normalization models of attention predict that average neuronal responses are proportional to a linear combination of the contrasts of the visual stimuli, and attention changes the weights of the input associated with each stimulus. We hypothesized that contrast is encoded by feedforward inputs to the modeled neuron. If so, normalization models make specific, testable predictions about how correlations between visual neurons and their feedforward inputs should depend both on the visual stimuli presented and on attention. We tested those predictions by simultaneously recording from individual neurons in area MT and several dozen neurons in area V1 while rhesus monkeys shifted attention between two moving stimuli within the MT neuron's receptive field and a third stimulus in the opposite hemifield. We fit a standard normalization model to the trial-averaged responses of the MT neuron in the different stimulus and attention conditions, replacing the contrasts of the visual stimulus with the trial-averaged responses of the V1 neurons whose receptive fields overlapped each stimulus. We then predicted the response of the MT neuron on each trial using the fitted model parameters and the actual responses of the V1 neurons recorded on that trial. The normalization model accounts well for many aspects of the V1-MT correlations we measured, including that 1) attention increases correlations between neurons in V1 and MT (Ruff and Cohen, SfN 2014), and 2) cross-area correlations depend on stimulus properties (such as motion direction) that do not affect within-area correlations. We also used simulations to show that the attention-dependence of V1-MT correlations is much better explained by a mechanism in which attention changes the weights of V1 inputs to MT than by mechanisms that change the gains of neuronal responses in either area. Our study expands current models to show that normalization can capture interactions between neurons in different areas and provides a framework for using correlated variability to probe the neural mechanisms underlying canonical neural computations.

Disclosures: D.A. Ruff: None. **M.R. Cohen:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.01

Topic: D.04. Vision

Title: Population tuning, sampling, and granularity: A computational investigation of the influence of pattern contrast and noise structure on MVPA

Authors: *F. M. RAMIREZ[1,2,3,4], C. ALLEFELD[1,4], J.-D. HAYNES[1,2,3,4];
[1]Bernstein Ctr. for Computat. Neurosci., Berlin, Germany; [2]Berlin Sch. of Mind and Brain, Humboldt Univ. zu Berlin, Berlin, Germany; [3]Dept. of Psychology, Humboldt Univ. zu Berlin, Berlin, Germany; [4]Berlin Ctr. for Advanced Neuroimaging, Charité-Universitätsmedizin, Berlin, Germany

Abstract: The increased sensitivity afforded by multivariate pattern analysis methods (MVPA) has led to their widespread application in neuroscience. Nonetheless, the sources of information enabling the classification of distinct stimulus classes are rarely identified or interpreted in neurobiological terms. One of the broadest distinctions drawn on the basis of fMRI data combined with MVPA is between global and fine-grained effects. While it is frequently assumed that fine-grained patterns can reveal the tuning properties-or representational content-of indirectly sampled neural populations, global effects are considered a distinguishable source of information-say, possibly reflecting arousal or attentional modulations not necessarily diagnostic regarding the features encoded by underlying neural populations. Thus, a key challenge in MVPA is to distinguish the spatial scale of data features enabling the classification of brain patterns associated with two or more experimental conditions, as well as discovering the tuning properties of neural populations from the output of MVPA methods. Here, based on computer simulations emulating the biased sampling of feature-tuned neural populations (cf. Ramírez et al., 2014. J. Neurosci.) we show that (i) coarse granularity-i.e., spatial clustering of neurons with similar tuning properties-and narrow tuning widths of sampled neural populations lead to increased pattern contrast, the latter aspect of the signal proving informative regarding the underlying form of tuning even in the presence of concomitant global signal modulations. (ii) Further, we show that the relationship between signal and noise levels (SNR)-regardless of the underlying tuning properties-can significantly influence confusion matrices constructed on the basis of classification error rates, possibly challenging ensuing inferences regarding pattern similarity based on such matrices. (iii) We confirm that popular multivariate methods-e.g., linear discriminant analysis (LDA) and support vector machines (SVM)-can exploit the covariance structure of the noise, leading to remarkable sensitivity to small effects. However, we also show that if the noise covariance is low across voxels or it changes across runs, n-fold cross-validation-i.e., partitioning the data-can exhibit a significantly lower sensitivity compared with approaches avoiding partitioning. Finally, (iv) we show that the practice of subtracting the mean across voxels prior to classification cannot rule out global effects as the underlying source of decoded information. These results bear on the interpretation of a growing body of studies combining fMRI and MVPA.

Disclosures: **F.M. Ramirez:** None. **C. Allefeld:** None. **J. Haynes:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.02

Topic: D.04. Vision

Support: Australian Research Council Future Fellowship FT120100816

Research supported in part by the NIMH Intramural Research Program

Title: Not all that glitters is gold: predicting behavior from brain representations suggests that only a subset of decodable information is used by the brain

Authors: *T. GROOTSWAGERS[1,2], D. B. T. MCMAHON[3], D. A. LEOPOLD[4], T. A. CARLSON[1,2];
[1]Cognitive Sci., [2]Ctr. for Cognition & its Disorders, Macquarie Univ., Sydney, Australia; [3]Lab. of Sensorimotor Res., [4]Lab. of Neuropsychology, NIH, Bethesda, MD

Abstract: An implicit assumption in many brain decoding studies is that if decodable information exists in a brain region, then this information is being used by the brain for behavior. In the present study, we examined this assumption in the context of a model that uses the fine-grained structure of representations to predict behavior (Carlson et al., 2014). Using this model, we can study the distinction between whether information in a representation is merely decodable, or if the information is formatted in a manner that the brain is "reading out" information from the representation, i.e. its structure can be used to predict behavioral outcomes. The model assumes that the brain is its own decoder, and is based on fitting a decision boundary for category decisions in a representation. Following from standard signal detection theory, the difficulty of category choices is determined by the distance of individual exemplar representations from the boundary. Thus exemplars far from the category boundary will be easier (faster) choices, and exemplars close to the boundary will be more difficult (slower) choices. Our study took advantage of the high resolution of single unit recordings and the apparent homology between human and non-human primate inferior temporal cortex (ITC) (Kriegeskorte et al., 2008). We first decoded categories of objects by training multivariate pattern classifiers on neuronal recordings from the anterior fundus face patch within the macaque superior temporal sulcus (McMahon et al., 2014). The stimulus set included 10,000 images spanning 10 categories; human and monkey faces and bodies, birds, butterflies, plants, man-made objects, scenes, and Fourier patterns. We found robust decoding performances for both broad (e.g. animate vs. inanimate) and fine-grained categories (e.g. human faces vs. monkey faces). We then used the

model to test whether the structure of the representation could predict behavior. Amazon's Mechanical Turk was used to collect human reaction times for the same category decisions using the same stimuli. For categorization tasks involving faces, the representation in monkey ITC predicted human reaction times, indicating a connection between representational structure and perceptual decision making behavior. For other category decisions that were also decodable, the representational structure was not predictive of behavior. This finding challenges the assumption that is if a brain region contains decodable information, the brain must be using it.

Disclosures: T. Grootswagers: None. **D.B.T. McMahon:** None. **D.A. Leopold:** None. **T.A. Carlson:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.03

Topic: D.04. Vision

Support: William R. Hewlett Stanford Graduate Fellowship

National Eye Institute NRSA Grant NEIF32EY019815

National Institutes of Health Grant 1 R01 EY019429

Title: Typicality sharpens category representations in object-selective cortex

Authors: *M. IORDAN[1], M. R. GREENE[1], D. M. BECK[2], L. FEI-FEI[1];
[1]Computer Sci., Stanford Univ., Stanford, CA; [2]Beckman Inst. and Psychology Dept., Univ. of Illinois, Urbana, IL

Abstract: The purpose of categorization is to identify generalizable classes of objects whose members can be treated equivalently. Within a category, however, some exemplars are more representative of that concept than others. Despite long-standing behavioral effects, little is known about how typicality influences the neural representation of real-world objects from the same category. Using fMRI, we showed participants 64 subordinate object categories (exemplars) grouped into 8 basic categories. Typicality for each exemplar was assessed behaviorally and we used several multi-voxel pattern analyses to characterize how typicality affects the pattern of responses elicited in early visual and object-selective areas: V1, V2, V3v, hV4, LOC. We found that in LOC, but not in early areas, typical exemplars elicited activity more similar to the central category tendency and created sharper category boundaries than less typical

exemplars, suggesting that typicality enhances within-category similarity and between-category dissimilarity. Additionally, we uncovered a brain region (cIPL) where category boundaries favor less typical categories. Our results suggest that typicality may constitute a previously unexplored principle of organization for intra-category neural structure and, furthermore, that this representation is not directly reflected in image features describing natural input, but rather built by the visual system at an intermediate processing stage.

Fig. 1. Typical Exemplars are More Correlated to Central Category Tendency

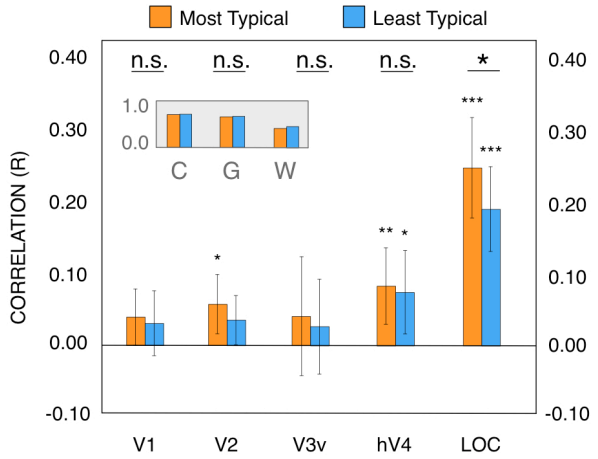
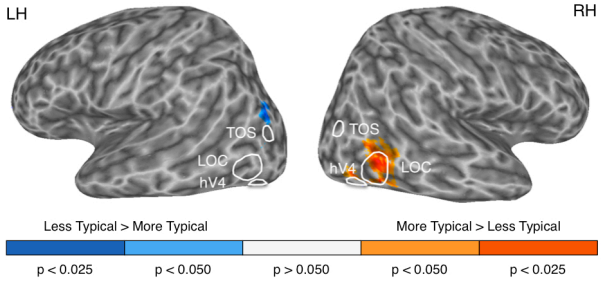


Fig. 2. Searchlight Analysis: Typical Category Boundaries Are Stronger in LOC and Atypical Category Boundaries are Stronger in cIPL



Disclosures: **M. Iordan:** None. **M.R. Greene:** None. **D.M. Beck:** None. **L. Fei-Fei:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.04

Topic: D.04. Vision

Support: NIH Grant EY016187 (Dr. Livingstone)

Burroughs Wellcome Postdoctoral Enrichment Award (Dr. Ponce)

Title: How inferotemporal cortex neurons depend on extrastriate input networks

Authors: *C. R. PONCE[1], S. G. LOMBER[3], M. S. LIVINGSTONE[2];
[1]Dept Neurobiol, [2]Dept. of Neurobio., Harvard Med. Sch., Boston, MA; [3]Dept. of Psychology, Western Univ., London, ON, Canada

Abstract: We compared the importance of V2 and V4 inputs to macaque inferotemporal (IT) cortex, using a novel combination of cortical cooling and chronic recording. Inferotemporal cortex neurons are essential to object recognition. Posterior IT neurons represent a highly interconnected node in the ventral stream network; they receive inputs from areas V2, V3, V4, MT, FST and anterior IT. This anatomical diversity is not prominent in computational models of IT, such as feedforward convolutional neural networks. In these models, IT-like units receive inputs from a linear sequence of receptive fields, implying a single-pathway architecture. One exception is a model (Serre, Oliva and Poggio, 2007, PNAS) where IT neurons receive direct inputs from a V4-like stage and a V2-like stage. The model "lesioned" each pathway to show that 1) each intervention reduced but did not abolish the classification accuracy of IT and 2) the V4-like projection is more important for classification accuracy. Our results support both of these predictions. We implanted electrode arrays in the pIT cortices of two macaque monkeys, and cryogenic cooling loops ("cryoloops") against V2, V3 and V4 cortices. We trained the animals to perform a fixation task and we recorded IT multiunit spike responses while independently activating either the V2(3) cryoloops or the V4 cryoloop. We observed that each intervention reduced the IT spike counts by an average of 34%. Support vector machines trained on the IT data showed a decrease in classification accuracy during both cooling conditions, with the V4 inactivation causing larger classification inaccuracy than the V2(3) inactivation. In contrast, overall firing rate decrease did not reliably distinguish between the two inactivation conditions. Using a multidimensional neural space trajectory analysis, we determined that V4 inactivation is more likely to scramble the activity space representation of individual images, independently of the common reduction in firing rate across the population. The local field potential showed similar patterns. We conclude that multivariate approaches to lesion studies in the ventral pathway are a promising path to untangling the input network to IT, and that future feedforward convolutional models of IT would benefit from including the anatomical diversity of the visual system.

Disclosures: C.R. Ponce: None. **S.G. Lomber:** None. **M.S. Livingstone:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.05

Topic: D.04. Vision

Support: NWO VENI Grant

JSMF Scholar Award

Title: Illusory figures selectively activate deep layers of the primary visual cortex: a 7T-fMRI study

Authors: *P. KOK, L. J. BAINS, T. VAN MOURIK, D. G. NORRIS, F. P. DE LANGE; Donders Inst. for Brain, Cognition, and Behaviour, Radboud Univ., Nijmegen, Netherlands

Abstract: Electrophysiological studies in monkeys and haemodynamic studies in humans have documented increased activity in the primary visual cortex (V1) during the perception of illusory figures (e.g., Kanizsa stimuli). It has been hypothesized that this elevated neural activity in early visual cortex is the result of top-down feedback from higher-order cortical regions. To investigate this, detailed layer-specific measurements of the human visual cortex are required. The neocortex consists of six laminae, through which neural activity flows in a specific manner. Specifically, bottom-up input into a cortical region targets the middle layers, while top-down feedback avoids the middle layers and targets deep and superficial layers instead. Therefore, revealing the laminar profile of the neural response to illusory figures in the primary visual cortex can inform us about the sources of these signals. Here we used functional magnetic resonance imaging (fMRI) at high field (7 Tesla) and high spatial resolution (0.8 mm isotropic voxels) to probe the response to illusory figures in human V1 at different layer depths (Koopmans et al. 2011). We find that, whereas bottom-up stimuli activate all cortical layers, the response to illusory figures is confined to the deep layers. This suggests that the neural response to illusory figures comes about through highly specific top-down feedback from higher-order regions. These results are in line with recent studies of figure perception using invasive laminar recordings in macaques (Self et al. 2013), and they show the potential for non-invasive *in vivo* recordings of neural activity with laminar specificity in humans.

Disclosures: P. Kok: None. **L.J. Bains:** None. **T. Van Mourik:** None. **D.G. Norris:** None. **F.P. De Lange:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.06

Topic: D.04. Vision

Support: Medical Research Council of the UK (program MC-A060-5PR20)

British Academy Postdoctoral Fellowship to MM

a European Research Council Starting Grant (ERC-2010-StG 261352) to NK

Title: Object representations in human inferior temporal cortex: categorical or feature-based?

Authors: *K. M. JOZWIK, N. KRIEGESKORTE, M. MUR;
MRC Cognition and Brain Sci. Unit, Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Introduction: Human inferior temporal (IT) cortex contains a high-level representation of objects at the interface between vision and semantics. Object features, as well as object category membership, have each been shown to contribute to the object representation in IT. However, their explanatory power has not been directly compared for the same set of stimuli. Here, we ask whether the IT object representation is best explained by a categorical or a feature-based model of the stimuli. **Methods**: We asked human observers to generate category (e.g. is a face) and feature (e.g. consists of eye, hair, oval) descriptions for a set of 96 real world object images. We constructed the models as a weighted combination of these category or feature descriptions. The weights were set to optimally predict the IT representation of the same 96 images, previously measured using fMRI in a separate set of human subjects. Weights were estimated using a cross-validated non-negative least-squares fitting procedure. We compared the models to the IT representation using representational similarity analysis. **Results**: Our results show that a categorical and a feature-based model explain the IT representation equally well. However, the models emphasize different aspects of the representation. The categorical model emphasizes the division between humans and animals, and between manmade and natural objects, while the feature-based model emphasizes the division between faces and bodies. A combined categorical-and-feature-based model is best at predicting the IT representation. Combining the descriptions with appropriate weights significantly improves the model predictions. **Conclusion**: Our findings suggest that the categorical and feature-based models explain unique IT representational variance, and that feature-based models can explain variance in addition to categorical models. Our findings are a first step toward bridging the gap between single-neuron stimulus selectivity (category and feature descriptions) and population coding of stimulus information (representational geometry) in IT.

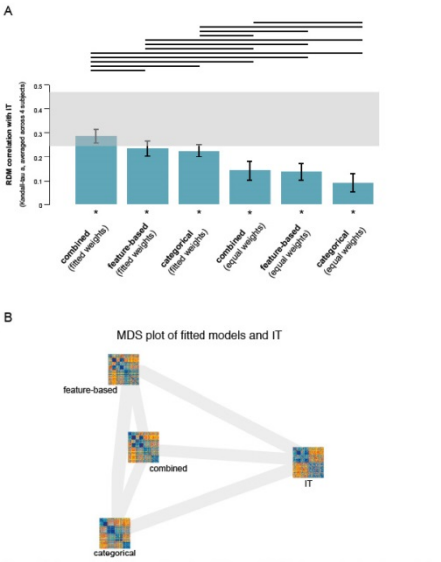


Figure 1 | Categorical and feature-based model fits to IT. A The bar graphs show the correlation between the IT representational dissimilarity matrix (RDM) and each of the model RDMs. Significant correlations between a model RDM and the IT RDM are indicated by an asterisk (stimulus-label randomization test, $p < .05$ corrected). Significant differences between models in how well they can account for the IT representation are indicated by horizontal lines plotted above the bars (stimulus-bootstrap test, $p < 0.05$ corrected). Error bars show the standard error of the mean based on the bootstrap resampling of the stimulus set. The weighted combined model outperforms all other models. **B** The multidimensional scaling plot (criterion: metric stress) visualizes the relationships between the weighted model RDMs and the IT RDM. Distances between RDMs reflect their dissimilarity. The thickness of the lines reflects the inevitable distortions that are introduced by dimensionality reduction. The plot shows that the categorical and feature-based models are clearly separated.

Disclosures: **K.M. Jozwik:** None. **N. Kriegeskorte:** None. **M. Mur:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.07

Topic: D.04. Vision

Support: ATTEND Grandi Progetti 40102257

Title: Disentangling the effects of shape and category on the representation of animate and inanimate objects in human ventral temporal cortex

Authors: *D. PROKLOVA, D. KAISER, M. PEELEN;
Cimec - Ctr. For Mind/Brain Sci., Rovereto, Italy

Abstract: A large number of studies have provided evidence for a category-related organization of object representations in human ventral temporal cortex (VTC), including selective fMRI responses to several object categories (e.g. faces, scenes) and a broader distinction between responses to animate and inanimate objects. It is still unclear, however, what drives these apparently categorical distinctions. Specifically, it remains debated whether category-specific responses reflect true category effects or whether these can be reduced to simpler properties - such as object shape - that are closely associated with particular categories. In the present study we aimed to distinguish between these accounts, testing whether the animate-inanimate organization of VTC can be explained by shape differences between animate and inanimate objects. We developed a stimulus set containing pairs of images of animate and inanimate objects that were closely matched by shape (e.g. snake-rope). Shape similarity between all stimulus pairs was quantified by measuring interference between items in a separate visual search task. The similarity of fMRI response patterns in regions of interests (ROIs) covering the VTC and early visual cortex (EVC) was assessed using multivoxel pattern analysis and representational similarity analysis. This allowed us to compute information carried by these patterns about object shape and object category independently. Results showed that VTC ROIs contained significant information about both shape and category, while EVC ROIs only contained shape information. Searchlight analysis confirmed these results, revealing partially overlapping representations of shape and category in VTC and only shape information in posterior occipital regions. Importantly, highly significant category information was present in VTC even after regressing out shape similarity between stimuli derived from the visual search task. These results indicate that the animate-inanimate distinction in VTC response patterns does not merely reflect shape similarity but reflects, at least partly, a true domain-related organization. We discuss other principles that may underlie the animate-inanimate organization of VTC.

Disclosures: **D. Proklova:** None. **D. Kaiser:** None. **M. Peelen:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.08

Topic: D.04. Vision

Support: NIH grant 1R01EY022355

Title: Neural representation of contextual consistency and position regularity of objects in a pair

Authors: *R. WANG, Y. XU;
Harvard Univ. Vision Lab., Cambridge, MA

Abstract: Objects rarely appear in isolation in real-life. But rather, they often appear together and interact with each other in a predictable and meaningful manner. Indeed, behavioral studies have demonstrated that objects pairs are processed more efficiently when they appear together in a contextually consistent than inconsistent manner or position regular than irregular manner. In the current study, using fMRI multi-voxel pattern analysis, we examined the neural presentation of contextual consistency and position regularity in human observers in retinotopically defined early visual areas as well as object processing regions in lateral and ventral visual cortex (LO and pFs). In Experiment 1, object pairs were shown in either a contextually consistent (i.e., a cake above a cake stand, and a cooking pot above a burner) or an inconsistent manner (i.e., a cake above a burner, and a cooking pot above a cake stand); and in Experiment 2, object pairs were shown in either a positionally regular manner (i.e., a cake above a cake stand) or an irregular manner (i.e., a cake under a cake stand). In both experiments, we obtained fMRI response patterns in our pre-defined regions of interests for the different pair conditions as well as for each object shown alone. We then linearly combined the patterns for the individual objects shown alone and tested the Euclidean distance between the synthesized two-object patterns and the actual two-object patterns. In early visual cortex, such as V1 and V2, the difference between the actual and the synthesized two-object patterns did not differ between the contextually consistent and inconsistent pairs or between the position regular and irregular pairs. However, in pFs, the difference between the actual and the synthesized two-object patterns was greater for the contextually consistent than inconsistent object pairs. Similar results were also observed for position regular and irregular pairs in pFs. These results suggest that stronger nonlinear interactions between the two objects are represented in pFs when they form a meaningful object pair. They further illustrate one way in which learned contextual consistency and position regularity may be represented in the human brain.

Disclosures: R. Wang: None. **Y. Xu:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.09

Topic: D.04. Vision

Support: NIH grant 1R01EY022355

Title: Attentional modulation of object category decoding in human parietal and occipito-temporal regions

Authors: *M. VAZIRI PASHKAM, Y. XU;
Vision Scinces Laboratory, Dept. of Psychology, Harvard Univ., Cambridge, MA

Abstract: Although visual object representations have been discovered in the primate parietal cortex more than a decade ago, the nature of these representations remains largely unknown. In particular, it is not known how these representations are modulated by attention. Using fMRI and multiple voxel pattern analysis, here we investigated object representation in the human parietal cortex under different attentional manipulations. The parietal regions we examined included five topographic areas along the intra-parietal sulcus (IPS) as well as superior and inferior IPS, two regions previously implicated in visual object individuation and identification, respectively. We also examined responses from topographic areas in early visual cortex, and object shape processing regions in lateral occipital (LO) cortex and posterior fusiform gyrus (pFs). During the experiment, observers viewed a sequential presentation of ten colored exemplars from each of eight object categories. They were asked to detect an occasional 1-back repetition either on the object (object task) or the color (color task). Using SVM, we measured decoding accuracy for the object categories in each region of interest (ROI) in both tasks. In Experiment 1, color appeared directly on the objects. In all the ROIs examined, category decoding accuracy did not differ between when observers attended a category-relevant feature (i.e., object task) and when they attended a category-irrelevant feature (i.e., color task). In Experiment 2, we colored a set of transparent dots appearing on top of the objects. These dots occupied the same spatial envelope as the objects. Category decoding accuracy did not differ between the two tasks in early visual areas, but was significantly higher in the object than color task in higher parietal and occipito-temporal regions. Interestingly, this task effect was significantly greater in the parietal than occipito-temporal regions. These results show that attention to an irrelevant object feature does not affect object category decoding in neither the ventral nor dorsal visual processing pathways, consistent with the notion of object-based encoding shown by prior literature. However, attention to an irrelevant feature on an irrelevant object occupying the same spatial envelope decreases decoding in both pathways except in early visual areas. Notably, parietal regions showed greater sensitivity to this attention manipulation than occipito-temporal regions, suggesting greater involvement of the parietal regions in tracking the demand of the task at hand.

Disclosures: M. Vaziri Pashkam: None. **Y. Xu:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.10

Topic: D.04. Vision

Support: Grant 2013070 from the US-Israel Binational Science Foundation to LYD and RTK

NINDS R37NS21135 to RTK

Nielsen Corporation to RTK

R01NS078396 to JP

NSF grant BCS1358907 to JP

Title: The neural basis of sustained visual perception

Authors: E. M. GERBER[1], K. G. BUCHANAN[2], R. A. KUPERMAN[3], K. I. AUGUSTE[5,4], T. GOLAN[1], J. PARVIZI[6], R. T. KNIGHT[7,8], *L. Y. DEOUELL[9];
[1]Edmond and Lily Safra Ctr. for Brain Sci., Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]Helen Wills Neurosci. Inst., UC Berkeley, Berkeley, CA; [3]Pediatric Neurol., [4]Neurolog. Surgery, Children's Hosp. and Res. Center, Oakland, Oakland, CA; [5]Neurolog. Surgery, Univ. of California, San Francisco, San Francisco, CA; [6]Neurol. and Neurolog. Scienc, Stanford Univ., Palo Alto, CA; [7]Helen Wills Neurosci. Inst., [8]Psychology, Univ. of California, Berkeley, Berkeley, CA; [9]The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: A static image stimulus (e.g. a house) can induce a sustained visual percept, presumably driven by neural activity sustained throughout stimulus duration (duration-dependent sustained responses, DDSRs). However, the vast body of research on cortical visual processing is based on brief, fixed-duration stimuli (typically up to 500 ms), and on onset responses, which cannot provide information on DDSRs. Here we apply a novel variable-duration stimulation paradigm using images to directly test for sustained activity in the visual cortex. Electrocorticographic data was recorded from 10 patients implanted with subdural electrodes over occipital, temporal, parietal and frontal regions for clinical indication. Electrodes over early visual cortex exhibited clear high-frequency (> 30 Hz broadband response) DDSRs, sustained above baseline throughout stimulus duration, allowing reliable decoding of stimulus duration (but not category) from neural responses. In contrast, electrodes in category-selective inferior temporal cortex showed weak to no duration-dependence. This is surprising given that activity in category-selective regions is considered to correlate closely with conscious visual experience, and would be predicted to parallel a sustained visual percept. We observed a circumscribed region, coinciding with the more posterior face-selective electrodes along the Fusiform Gyrus, which was strongly both category-selective and duration-dependent (3 face-selective electrodes from 2 patients). Directing attention to the beginning or to the full duration of the stimulus did

not affect the results. Thus, duration-dependence and category-selectivity were anatomically dissociated: the former was dominant in early visual areas and the latter along the more anterior inferior temporal cortex, with a small degree of overlap over the posterior Fusiform Gyrus. The results suggest a new organization within the ventral visual stream, where regions which otherwise appear functionally uniform (e.g. all showing face-selectivity) are dissociated in regard to their role in visual processing over longer stimulation windows. We hypothesize that within category-selective visual cortex, duration-dependent sites on the posterior inferior temporal lobe are associated with the sustained experience of a visual percept, while sites with no duration-dependent activity, located more anteriorly, are associated with more phasic, stimulus-onset-related aspects of visual processing, such as initial stimulus categorization and identification.

Disclosures: **E.M. Gerber:** None. **K.G. Buchanan:** None. **R.A. Kuperman:** None. **K.I. Auguste:** None. **T. Golan:** None. **J. Parvizi:** None. **R.T. Knight:** None. **L.Y. Deouell:** None.

Nanosymposium

373. Visual Processing: Object Representation

Location: S402

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 373.11

Topic: D.04. Vision

Support: NIMH intramural funding

MRC intramural funding

British Academy

Title: Representational dynamics: neural population coding of objects in nonhuman primate inferior temporal cortex

Authors: ***M. C. MUR**[1], A. H. BELL[2,3], N. J. MALECEK[3], E. L. MORIN[3], J. DUNCAN[1], N. KRIEGESKORTE[1];
[1]MRC Cognition and Brain Sci. Unit, Cambridge, United Kingdom; [2]Univ. of Oxford, Oxford, United Kingdom; [3]Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Successful interaction with the world around us requires a meaningful representation of visual objects. Object identity and category are coded by populations of neurons in primate inferior temporal (IT) cortex. However, the dynamic nature of these population representations, in particular how they evolve over the timescale of milliseconds after stimulus onset, is not well understood. Recent MEG studies in humans have begun to address this question, but are limited

by low spatial resolution. Here, we analyze single-unit recordings from monkey IT to identify at which time points after stimulus onset object identity and category can be decoded from neuronal population activity. Single-unit activity was recorded from the inferior bank of the superior temporal sulcus of two adult male rhesus monkeys during passive object viewing (Bell et al., 2011). Stimuli were 100 grayscale object images from five categories: faces, body parts, fruit, objects, and indoor scenes. Images were presented in random order while the monkeys maintained fixation. Here, we extracted patterns of activity across all visually-responsive neurons (approximately 500 neurons per monkey) at each time point after stimulus onset using a sliding-window approach. We used representational similarity analysis to determine onsets and peaks of object-identity and category information. Inference was performed using bootstrap resampling of the neurons ($p < 0.05$ after correction for multiple comparisons). The earliest information in the IT neuronal population starts to arise 50-80 ms after stimulus onset. This information predominantly indicates the emergence of category clusters (faces, fruit, and objects precede scenes and body parts). Category clustering peaks at 130-160 ms after stimulus onset. The emergence of animate/inanimate category information follows a time course similar to that of the basic-level categories. Information about object identity emerges after the onset of category information: individual stimuli within each category become discriminable 10-30 ms after the start of their own category's clustering. Object discriminability also peaks later than category information. These findings suggest that, in the IT population, category information appears before individual objects can be discriminated. This is consistent with earlier monkey electrophysiology studies on invariant object representations in IT, and indicates that human MEG results, which reported the opposite order of events, might be driven by early visual cortex shortly after stimulus onset (consistent with Cichy et al. 2014).

Disclosures: **M.C. Mur:** None. **A.H. Bell:** None. **N.J. Malecek:** None. **E.L. Morin:** None. **J. Duncan:** None. **N. Kriegeskorte:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.01

Topic: D.16. Posture and Gait

Support: NIH HD048741

NIH NRSA F31

Title: Adaptive learning dominates instructive learning in split-belt walking

Authors: *A. LONG[1], A. BASTIAN[2];
[1]Biomed. Engin., [2]Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Many patients have difficulty walking after stroke, even following extensive rehabilitation. In therapy, the norm is to try to change the automatic walking pattern with explicit instruction. We think that it might be more powerful to combine instructive (explicit) learning with adaptive (more implicit) learning. Here, we studied healthy young adults as they learned a new walking pattern via different combinations of these mechanisms. For instructive learning, we provide visual feedback of the subject's foot placement in relation to a target and instruct them to "step on the target". This forces subjects to explicitly focus on a strategy. For adaptive learning, subjects walk on the split-belt treadmill (two independently driven belts) with one belt moving faster than the other. This drives subjects to learn implicitly through an error-driven process. We tested an ADAPT group where subjects learned a 3:1 split-belt treadmill perturbation gradually introduced over 15 minutes with no visual feedback. They implicitly learned where to place the 'fast' foot relative to the 'slow foot' during adaptation, and showed after-effects after learning. We then added an instructive component to the adaptation paradigm in two groups: the CONGRUENT group also received visual feedback about foot placement that mirrored where people normally step during learning; the INCONGRUENT group received visual feedback to help them step on symmetrically fixed targets and prevent changing their step locations during adaptation. After 12 minutes of visual feedback, the INCONGRUENT group received 10 seconds of no visual feedback while maintaining the split belts and then the same visual feedback for the remaining 3 minutes. Results show that creating a common goal between instructive and adaptive learning in the CONGRUENT group did not change after-effects (magnitudes and decay rates) compared to the ADAPT group. Surprisingly, creating a conflict between the two systems in the INCONGRUENT group also did not change the after-effect (magnitude and decay rate). The 10 second catch trial revealed that the subjects immediately jumped to a new walking pattern that was smaller than the fully adapted pattern, suggesting that their brain was still developing an internal model of how to walk with split belts despite the maladaptive instruction. Our results show that instruction neither enhances nor interferes with adaptive learning. It was striking that incongruent feedback allows for some learning of the desired motor pattern, though it is incomplete. These results demonstrate that adaptive learning is a powerful motor learning mechanism and should be incorporated into rehabilitation strategies.

Disclosures: A. Long: None. **A. Bastian:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.02

Topic: D.16. Posture and Gait

Title: Self-recognition of one's own whole-body imbalance evokes the crisis-related cortical and brainstem activity

Authors: *T. ATOMI[1,2], M. NORIUCHI[2], K. OBA[3], Y. ATOMI[4], Y. KIKUCHI[2];
[1]Dept. of Physical Therapy, Fac. of Med. Sci., Teikyo Univ. of Sci., Uenohara, Yamanashi Prefecture, Japan; [2]Dept. of Frontier Hlth. Science, Div. of Human Hlth. Sci., Grad. Sch. of Tokyo Metropolitan Univ., Tokyo, Japan; [3]Div. of Med. Neuroimage Analysis, Dept. of Community Med. Supports, Tohoku Med. Megabank Organization, Tohoku Univ., Sendai, Japan; [4]Dept. of Material Hlth. Science, Fac. and Grad. Sch. of Engin., Tokyo Univ. of Agr. and Technol., Tokyo, Japan

Abstract: [Introduction] Bipedalism is the fundamental evolutionary adaptation that sets hominids - and therefore humans - apart from other primates. The human body consisting of multi-segment is arranged vertically some segments, such that the head, trunk, legs, and feet. Some of the most important brain systems are dedicated to the maintenance of balance and to providing an online representation of where the body is located, via the integration of many different exteroceptive / interoceptive inputs (visual, auditory, vestibular, somatosensory, motor, visceral, and so on). Although the neural mechanism for automatically detecting one's own body instability is an important consideration, there have thus far been few functional neuroimaging studies because of the restrictions placed on participants' movements. [Methods] Thirteen young healthy male participants took part in the experiment. We used functional magnetic resonance imaging to investigate the neural substrate underlying whole body instability, based on the self-recognition paradigm that uses video stimuli consisting of one's own and others' whole bodies depicted in stable and unstable states. After the fMRI scans, the participants were asked to rate their emotional states, and we conducted multiple regression analyses with the eigenvariate values in the spherical region of interest and the subjective ratings. [Results] Analyses revealed significant activity in the regions which would be activated during genuine unstable bodily states: The right parieto-insular vestibular cortex (PIVC), inferior frontal junction / ventral premotor cortex (IFJ/PMv), posterior insula and parabrachial nucleus (PBN), and rosotro-lateral prefrontal cortex (RLPFC). In addition, right IFJ/PMv activity was negatively correlated with emotional subjective ratings "calmness" scores. [Conclusions] The self-specific neural processing of body instability consists mainly of three component processes: 1) a vestibular/interoceptive process, which is related to detection of vestibular anomalies and to sympathetic activity as a form of alarm response (the right PBN and posterior insula), 2) an automatic motor-response preparation process (right IFJ/PMv), in which the necessary motor responses are automatically prepared/simulated in the brain to protect one's own body, and 3) a meta-cognitive process (right RLPFC) for self-recognition from the 3rd person perspective view. In addition, this right dominance may be based on lateralization of homeostatic brain structures

and functions, which has been evolutionarily driven by a preexisting behavioral and autonomic asymmetry that is present in all vertebrates.

Disclosures: **T. Atomi:** None. **M. Noriuchi:** None. **K. Oba:** None. **Y. Atomi:** None. **Y. Kikuchi:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.03

Topic: D.16. Posture and Gait

Title: Effect of attentional focus on stability and muscular activation of the leg while standing

Authors: ***N. RICHER**, N. POLSKAIA, A. ATHANATHIOUS, D. SAUNDERS, Y. LAJOIE; Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Studies reveal postural stability benefits of directing attention away from postural control but it is unclear whether these improvements are indicative of the use of automatic postural processes or a stiffening strategy. The objective was to examine muscular activation of the leg while standing and concurrently performing various attentional focus and cognitive tasks to elucidate which mechanism is employed. Thirteen healthy young adults (21.1 ± 3.01 years, 6 male) stood as still as possible on a force platform with feet together, arms at their sides and gaze directed to a target 3 m ahead. They performed 5 separate conditions: 1) control standing; 2) internal focus (IF) which consisted of concentrating on minimizing movements of the ankles; 3) external focus (EF) which consisted of concentrating on maintaining the position of 3 markers extending laterally from each ankle joint; 4) single-number sequence (SNS) cognitive task, where participants counted and summed the occurrence of a single number in a 3-digit number sequence; 5) double-number sequence (DNS) cognitive task, where participants counted and summed the occurrence of 2 single numbers in a 3-digit number sequence. Five 60-s trials were performed per condition in random order. Muscular activation of the tibialis anterior (TA) and medial gastrocnemius (MG) of the dominant leg was recorded using electromyography. Data collected by the force platform was used to derive area of 95% confidence ellipse (area), standard deviation (SD) of centre of pressure (COP) in anterior-posterior (AP) and medial-lateral (ML) directions, and mean velocity of COP in AP and ML directions. Significance was set at $p < 0.05$. Results demonstrated a significantly smaller area in EF, SNS and DNS as opposed to control and IF, and a smaller area in DNS than EF. Significantly lower SD of COP in AP direction was found in SNS and DNS as opposed to control, IF and EF. SD of COP in the ML

direction was significantly higher in control as opposed to all other conditions and was significantly lower in DNS than IF. Significantly higher mean velocity in the AP and ML direction was found in SNS and DNS as opposed to control, IF and EF. Muscular activation of TA and MG did not differ across conditions. Results reinforce findings that cognitive tasks enhance stability as opposed to IF, EF and control conditions and show limited advantages of EF as opposed to IF. The lack of difference in muscular activity suggests that improvements are not due to the use of a stiffening strategy but to the use of an automatic type of postural control. By distracting participants from conscious postural control, cognitive tasks allow automatic processes to control posture more efficiently.

Disclosures: **N. Richer:** None. **N. Polskaia:** None. **A. Athanathious:** None. **D. Saunders:** None. **Y. Lajoie:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.04

Topic: D.16. Posture and Gait

Support: NSF 1431078

Title: Which regions of the ground surface do humans need to see to control walking over complex terrain?

Authors: ***B. R. FAJEN**[1], S. L. BARTON[1], J. S. MATTHIS[2];
[1]Rensselaer Polytechnic Inst., Troy, NY; [2]Ctr. for Perceptual Systems, Univ. of Texas at Austin, Austin, TX

Abstract: When humans walk over complex terrain, visual information from the upcoming ground surface plays an essential role in the ability to avoid obstacles and step on safe footholds. Previous studies suggest that visual information about potential target footholds for an upcoming step is especially important during the last half of the preceding step (Matthis & Fajen, 2013, 2014; Matthis, Barton, Fajen, 2015). That is, the last half of each step is the critical phase for the visual control of the upcoming step. This strategy is rooted in the biomechanics of walking and facilitates the efficient exploitation of passive mechanical forces inherent to bipedal gait. Biomechanics may also constrain which regions of the upcoming ground surface walkers need to see during the critical control phase. To efficiently exploit their inverted-pendulum-like structure, walkers must initialize each step with a properly tailored pushoff force from the

trailing foot. The pushoff force must be adjusted to the position of the target at the end of the upcoming step relative to the previous target. This suggests that walkers rely on information based on the relative position of pairs of consecutive targets, and leads to the following prediction -- that the two upcoming targets must be simultaneously visible to support accurate stepping. To test this prediction, we instructed subjects to walk along a path of irregularly spaced target footholds (small circular patches of light projected onto the floor) while their movements were tracked by a motion capture system. On some trials, the visibility of a subset of targets was manipulated such that they were only visible for a brief period. The duration of the period of visibility varied such that the two upcoming targets were simultaneously visible in some conditions but not others. We found no significant change in stepping accuracy in conditions in which consecutive targets were simultaneously visible relative to a control condition in which all targets were always visible. However, stepping accuracy degraded in conditions in which the two upcoming targets were not simultaneously visible. To conclude, walkers must be able to see regions of the upcoming terrain that include pairs of consecutive upcoming targets, and both targets must be simultaneously visible to the walker. If vision is restricted such that an upcoming target is not detected until after the previous target falls out of view, stepping accuracy may degrade. The findings reflect an efficient control strategy rooted in the biomechanics of bipedal gait, in which visual information is primarily used to initialize the mechanical state of the body leading to a ballistic movement toward the next target.

Disclosures: **B.R. Fajen:** None. **S.L. Barton:** None. **J.S. Matthis:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.05

Topic: D.16. Posture and Gait

Support: This work was supported by Council for Science, Technology and Innovation (CSTI), Cross-ministerial Strategic Innovation Promotion Program (SIP), “Technologies for creating next-generation agricultur

Title: Flexible recruitment of muscle synergies during treadmill walking dependent on speeds

Authors: *B. KIBUSHI[1], S. HAGIO[1,2], T. MORITANI[1], M. KOUZAKI[1];
[1]Kyoto Univ., Sakyo-Ku, Kyoto, Japan; [2]Res. Fellow of the Japan Society for the Promotion of Sci., Tokyo, Japan

Abstract: For walking, we need to simplify redundant degrees of freedom with musculoskeletal system, it might be solved by control via muscle synergies (Hagio et al., 2015). In case of the regulation of walking speed, the central nervous system (CNS) is required flexible selection from numerous combination of stride frequency and stride length. However, how the CNS recruits muscle synergies for flexible regulation of walking speed has not been revealed. We hypothesized that the flexible recruitment of muscle synergies enables the versatile regulation of walking speed. Our purpose was to investigate how muscle synergies are recruited during treadmill walking by examining the relevance to control of walking speeds. To prove that, 10 healthy man (23.3±0.9 years) walked on a treadmill at 14 various walking speeds (2.0-8.0 km/h and preferred walking speed) over 50 gait cycles. Surface electromyograms were recorded from 24 muscles in lower limb and trunk, and we used non-negative matrix factorization algorithm to extract muscle synergies (Tresch et al., 1999). Three-dimensional position of 29 retro-reflective spherical markers was measured to calculate the kinematic data. The stride length and the stride frequency were identified by foot switches. We extracted 3 to 10 muscle synergies across the subjects and walking speeds, and number of muscle synergies tended to increase with walking speeds. We founded 4 types of typical muscle synergies which were recruited among broad walking speeds. These muscle synergies activated during heel contact phase and forward propulsion phase per each legs. Other muscle synergies were recruited flexibly dependently on walking speeds. The center of mass trajectories during treadmill walking looks like so similar among speeds, in addition, combinations of the stride frequency and the stride length to change walking speeds were various. Therefore, it was suggested that the CNS manipulates properly combination of stride length and stride frequency by modulating the recruitment of muscle synergies flexibly to achieve stable output of walking motion.

Disclosures: **B. Kibushi:** None. **S. Hagio:** None. **T. Moritani:** None. **M. Kouzaki:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.06

Topic: D.16. Posture and Gait

Support: US Army's Telemedicine and Advanced Technology Research Center: 81XWH-09-2-0020

Department of Defense Joint Warfighter: W81XWH-14-C-0105

Title: Changes in gait dynamics when walking on slippery walkways

Authors: *M. WHITMORE, L. HARGROVE, E. PERREAULT;
Northwestern Univ., Chicago, IL

Abstract: The presence of a slippery surface is a dangerous, common cause of falling. Some populations, such as the elderly and lower-limb amputees, are at a higher risk of falling when encountering these surfaces. The incidence of slip and fall injuries increases as people get older. In addition, lower-limb amputees have a limited ability to adjust their gait on these surfaces due to their prosthesis. While there have been many studies on the compensatory strategies for initial transition to slippery surfaces, little is known about the compensatory strategies employed during steady state locomotion on different surfaces. This information is important for understanding able-bodied control and eventually for replicating that control in artificial devices. The objective of this work was to analyze the changes in lower-limb muscle activity during steady state locomotion on slippery surfaces. Based on previous work, it was hypothesized that there would be a global increase in lower-limb muscle activity as the walkway became more slippery, presumably to increase limb stiffness and stability. An experiment was conducted using three walkways, including non-slippery (NS), moderately slippery (MS), and very slippery (VS) surfaces. The moderately slippery condition was meant to simulate a real-life, commonly encountered slippery surface. This condition had subjects walk with socks over highly polished laminate floors. The very slippery condition, meant to simulate ice, had subjects walk with bare feet in shoe covers over a plastic sheet covered in oil. Electromyography (EMG) was recorded from select lower-limb muscles and the magnitude of activity was quantified using root-mean square (RMS) over periods of stance. The resulting analysis revealed more specific proximal to distal lower-limb changes than originally hypothesized. As the walkway became more slippery, activity at the ankle decreased (NS > MS > VS $p<0.05$). The opposite affect was seen at the knee, in which activity increased as the walkway became more slippery (NS < MS < VS $p<0.05$). The hip muscles showed increased activity on the very slippery walkway alone. These results suggest that to walk without slipping requires a reduction in activity at the ankle, possibly to increase joint compliance, and an increase in activity at the knee, possibly to increase joint stiffness. The hip becomes important once the walkway becomes very slippery. By understanding how able-bodied people safely negotiate slippery surfaces, this information can be applied to populations who have greater tendencies to fall when encountering these conditions.

Disclosures: M. Whitmore: None. **L. Hargrove:** None. **E. Perreault:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.07

Topic: D.16. Posture and Gait

Support: NSBRI NASA NCC 9-58

NSBRI MA02701

NSBRI PF04101

NASA NNX11AR02G

NASA Flight Analogs Project, National Institutes of Health, and National Center for Advancing Translational Sciences, 1UL1RR029876-01

Title: Aerobic and resistance exercise effects on mobility and gray matter changes during 70 days of bed rest

Authors: *V. KOPPELMANS[1], L. PLOUTZ-SNYDER[2], Y. E. DE DIOS[3], D. L. SZESCY[4], N. E. GADD[3], S. J. WOOD[5,6], P. A. REUTER-LORENZ[8], I. S. KOFMAN[3], J. J. BLOOMBERG[7], A. P. MULAVARA[7,2], R. D. SEIDLER[9,8,10];
[1]Univ. of Michigan, Sch. of Kinesiology, Ann Arbor, MI; [2]Universities Space Res. Assn., Houston, TX; [3]Wyle Science, Technol. & Engin. Group, Houston, TX; [4]Bastion Technologies, Houston, TX; [5]Psychology, Azusa Pacific Univ., Azusa, CA; [7]Neurosci. Motion Lab., [6]NASA Johnson Space Ctr., Houston, TX; [8]Psychology, [9]Sch. of Kinesiology, [10]Neurosci. Program, Univ. of Michigan, Ann Arbor, MI

Abstract: Long duration spaceflight microgravity results in cephalad fluid shifts and deficits in posture control and locomotion. Effects of microgravity on sensorimotor function have been investigated on Earth using head down tilt bed rest (HDBR). HDBR serves as a spaceflight analogue because it mimics microgravity in body unloading and bodily fluid shifts. Preliminary results from our prior 70 days HDBR studies showed that HDBR is associated with focal gray matter (GM) changes and gait and balance deficits. In consideration of the health and performance of crewmembers we investigated whether exercise reduces the effects of HDBR on GM and motor performance. Numerous studies have shown beneficial effects of exercise on brain health. We therefore hypothesized that an exercise intervention during HDBR could potentially mitigate the effects of HDBR on the central nervous system. Ten subjects were assessed before (12 and 7 days), during (7, 30, and ~70 days) and after (8 and 12 days) 70 days of 6-degrees HDBR at the NASA HDBR facility in UTMB, Galveston, TX, US. Each subject was randomly assigned to a control group or an exercise group. Regular exercise consisted of daily supine aerobic and resistance exercise (e.g. squat, heel raise, leg press, cycling and treadmill running), which started 20 days before the start of HDBR. At each time point T1 MRI scans were obtained using a 3T Siemens scanner. Focal changes over time in GM density were assessed using voxel based morphometry (VBM8) under SPM. Functional mobility was assessed

using an obstacle course. Vestibular contribution to balance was measured using Neurocom Sensory Organization Test 5. Behavioral measures were assessed pre-HDBR, and 0, 8 and 12 days post-HDBR. Linear mixed models were used to test for effects of time, group, and group-by-time interactions. VBM revealed significant group differences in changes in GM measured pre-HDBR and at 70 days in-HDBR in bilateral primary motor cortex regions, and vermis IX of the cerebellum ($p<.001$, uncorrected for multiple comparisons). Functional mobility performance was less affected by HDBR in exercise subjects than in control subjects and post HDBR exercise subjects recovered faster than control subjects. The group performance differences and GM changes were not related. Exercise in HDBR reduces the adverse effect of HDBR on functional mobility. In addition, exercise appears to result in differential brain structural changes in motor regions such as the primary motor cortex and the cerebellum. Whether these structural changes are related to functional changes other than gait or balance warrants further research.

Disclosures: V. Koppelmans: None. **L. Ploutz-Snyder:** None. **Y.E. De Dios:** None. **D.L. Szescy:** None. **N.E. Gadd:** None. **S.J. Wood:** None. **P.A. Reuter-Lorenz:** None. **I.S. Kofman:** None. **J.J. Bloomberg:** None. **A.P. Mulavara:** None. **R.D. Seidler:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.08

Topic: D.16. Posture and Gait

Title: Design and evaluation of self-body awareness underwear that applying a slight tactile and compression stimuli to the skin and provide a good posture and enhanced cardiorespiratory function during and after treadmill exercise, and at rest

Authors: *Y. ATOMI[1], N. HIROSE[2], T. ATOMI[2,3], K. TANAKA[2], M. SHIMIZU[1], Y. KOYAMA[4], H. SUZUKI[5];
[1]Dept of Material Hlth. Science, Fac. and Grad. Sch. of Engin., Tokyo Univ. of Agr. and Technol., Tokyo, Japan; [2]Dept. of Physical Therapy, Teikyo Univ. of Sci., Uenohara, Japan; [3]Dept. of Frontier Hlth. Sci., Grad. Sch. of Tokyo Metropolitan Univ., Tokyo, Japan; [4]RenYou co.ltd, Kyoto, Japan; [5]Toray Industries, Inc., Nantong, China

Abstract: Keeping standing position in daily life and bipedal walking and running with maintaining balance with upper body straight upwards may contribute to evolution of homo sapience/human beings from monkey. Through these anti-gravitational activities we have created human culture in enriched environment. However we cannot maintain upright posture by only

reflex but conscious motion and effort. We can find signs here a necessity to connect body and mind and may contribute to keep human body system with multi-joints resulting in keeping continuous posture swaying. We have previously developed and reported that tactile stimulus to the skin from special underwear is effective to improve walking and running posture. In the present study, we aimed to evaluate functions of a new compression underwear (C-wear) expected to improve cardiorespiratory function and also provide a balance of bipedal posture during physical exercise and recovery, based on the hypothesis to help the function of pumping effect by compression to calf leg and to decrease lateral head-sway of head. Seven young males were participated in the experiment. Upper and bottom mild compression wear (on calf back) were evaluated at rest, during treadmill exercise. Cardiorespiratory function was estimated by ventilatory threshold (VET) (Minato Co., AE-300S), and postural changes were measured during walking and running wearing C-wear or control wear using Vicon. Slight but significantly improving effects of VET during treadmill exercise was observed in C-wear (bottom) clothing. Improved venous return during rhythmic exercise may be enhanced by compression on calf back of both legs. Another effect is a tendency to change standing posture toward more upright position. Clothing c-wear (upper) showed almost the same effect as reported last year (PC-inner). That is, improving balance of posture at rest and walking with less fluctuations of central of gravity (COG). These effects indicate compression information via skin with clothing may normalize posture and gait of almost peoples, which are usually somewhat deformed. Our new developed compression-wear is effective to keep good balanced posture during activities and improve cardiorespiratory functions as well as to keep quiet sitting posture.

Disclosures: **Y. Atomi:** None. **N. Hirose:** None. **T. Atomi:** None. **K. Tanaka:** None. **M. Shimizu:** None. **Y. Koyama:** None. **H. Suzuki:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.09

Topic: D.16. Posture and Gait

Title: Identifying cognitive contributions to fall risk in older adults

Authors: ***W. E. HUDDLESTON**, E. W. CORBIN, B. E. SMITH, N. M. RECKA; Kinesiology: Integrative Hlth. Care & Performance, Univ. of Wisconsin - Milwaukee, Milwaukee, WI

Abstract: Falling is a serious, yet common, problem in older adults. One of every 3 adults over the age of 65 years falls each year, resulting in medical costs of $34 billion in 2013. Our purpose was to investigate the effect of cognitive load on various aspects of gait quality in this population. We hypothesized that high cognitive load conditions lead to visual attention deficits, impairing gait in older adults. Fourteen healthy and cognitively alert older adults (70-91 years, 4 males, >7/9 on GPCOG, independent ambulators) performed three randomly assigned tasks including a modified Timed Up and Go (mTUG; participants stood up from a chair, walked 5.7 meters around a cone, and returned to a seated position); a cognitive task (subtracted 7s from a given number as quickly and as accurately as possible), and these two tasks combined. Visual cues in the environment are critical to the mTUG (i.e., the cone and the chair), allowing us to compare gaze patterns across the two walking tasks. If participants gazed less at the cone and chair during the dual task, we would conclude that high cognitive load negatively affected visual attention. We tracked eye movements (Mobile Eye-XG, ASL) to identify the focus of overt visuospatial attention, and recorded walking characteristics using a pressure-sensing mat (GAITRite). Dependent measures included cognitive performance (number rate and accuracy on subtract 7s task), overt visuospatial attention (fixation time on targets), and gait parameters (total time, speed, step width, stride length, % double limb support, and cadence). As expected, total time to complete the walking task significantly increased with increased cognitive load. Associated gait changes with the longer walk times included significantly decreased stride length, decreased walking speed, increased double stance time, and decreased cadence. However, stance width did not significantly change with increased cognitive load. Gaze time on target (visual attention measure) was not significantly different between tasks, although older adults who had the most difficulty with the cognitive task also had the greatest differences in total walking time and gaze time on target between the two conditions. Our results suggest that deficits in visuospatial attention due to increased cognitive load do not completely explain observed gait changes in older adults when performing the mTUG. However, older adults with the greatest difficulty on the cognitive task demonstrated the greatest impairments in walk times and visuospatial attention. Thus, fall prevention programs should consider assessing and addressing cognitive status to optimize effectiveness.

Disclosures: **W.E. Huddleston:** None. **E.W. Corbin:** None. **B.E. Smith:** None. **N.M. Recka:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.10

Topic: D.16. Posture and Gait

Support: SMB was funded by a grant from the Netherlands Organisation for Scientific Research (NWO #451-12-041).

Title: Differences in cortical control of gait stability in young and older adults

Authors: *S. BRUIJN, N. KLUFT, J. H. VAN DIEËN, A. DAFFERTSHOFER;
Res. Inst. MOVE, Fac. of Human Movement Sci., VU Univ. Amsterdam, Amsterdam, Netherlands

Abstract: Walking on two legs is inherently unstable, especially in the medio-lateral plane. How we humans control this medio-lateral instability and how this control may change with age remains unclear. What is known, however, is that ageing comes with a decline in stability that often leads to falls. We sought to identify cortical contributions to control of gait stability by measuring brain activity using EEG during stabilized and normal walking in healthy young and older subjects. Subjects walked on a treadmill in two conditions, each lasting 10 minutes; normal, and while being laterally stabilized by elastic cords [1]. Kinematics of the trunk were sampled at 100 samples/s by an optoelectronic system, and EEG was recorded at 2048 samples/s using a 64 channel cap. We assessed differences in gait stability in terms of local divergence exponents, and trunk excursion [2]. As expected EEG data were strongly contaminated by movement artifacts that we could remove using independent component analysis [3]. Subsequently activities were source-localized via dynamic imaging of coherent sources and tested for changes in their spectral content. During normal walking, there were no differences in stability between groups. Stabilized gait led to significant decreases of local divergence exponents in both groups, but more so in the younger group, Moreover, stabilized gait reduced trunk excursion only in the younger subjects. In the young subjects, source localization in the beta band yielded significant sources in bilateral pre-motor cortices, which showed more beta-activity during stabilized than normal gait, specifically during toe off of the contralateral leg. Our results suggest that in younger subjects, control of medio-lateral gait stability has cortical contributions, that may be related to controlling push off [4]. The fact that older adults showed less behavioral effects of stabilizing gait may indicate that their gait is intrinsically less stable. The effects of stabilizing gait on cortical activity in older adults remain to be analyzed.
References [1]Dean et al. (2007) IEEE Trans Biomed Eng. 54(11):1919-26. [2]Bruijn et al. (2013 J R Soc Interface 10(83). [3]Gwin et al. (2010) J Neurophysiol. 103(6):3526-34. [4]Kim et al (2015) J Neuroeng Rehab (online)

Disclosures: S. Bruijn: None. **N. Kluft:** None. **J.H. Van Dieën:** None. **A. Daffertshofer:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.11

Topic: D.16. Posture and Gait

Support: NIH AG-006457

NIH T32-NS045553

NIH T32-AT002688

Medical Research Foundation of Oregon

University of Idaho College of Letters, Arts, and Social Sciences: Kurt O. Olsson Early Career Research Fellowship

Title: Lighten Up! Mindfulness-based approach to postural control improves coordination and reduces fall risk in older adults with and without Parkinson's disease

Authors: *R. G. COHEN[1], F. B. HORAK[2], V. S. GURFINKEL[2];
[1]Dept. of Psychology & Communication Sci., Univ. of Idaho, Moscow, ID; [2]Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: BACKGROUND: Mindfulness-based approaches to movement, including Tai Chi, Tango, and Alexander Technique, have shown promise for improving balance and reducing fall risk both in healthy older adults and in people with Parkinson's disease, but the mechanism for that improvement is not yet clear. OBJECTIVE: Our approach, which we call 'Lighten Up,' is based on the Alexander Technique; students learn to reduce muscular interference in everyday activities while maintaining an expansive attitude. We investigated the effects of the Lighten Up instructions on axial rigidity, upright postural alignment, mobility, and postural sway. We also investigated a contrasting set of effort-based postural instructions, which we call 'Pull Up,' and a relaxed control condition. METHOD: Healthy older subjects (age 60+) and subjects with PD (ON medication) practiced the three sets of instructions and then attempted to implement each one during quiet standing, torso rotation, and while initiating gait. We measured kinematics, resistance to axial rotation, and ground reaction forces. RESULTS: Both sets of experimental instructions led to increases in upright postural alignment relative to the control condition. However, the Lighten Up instructions decreased neck compression, while the Pull Up instructions increased neck compression. During torso rotation, the Lighten Up instructions increased the flexibility of axial tone, while the Pull Up instructions made subjects more rigid. The Lighten Up instructions also led to reduced amplitude and velocity of postural sway relative

to both other conditions, suggesting improved steadiness. During step initiation, the Lighten Up instructions led to the smoothest movement of the center of pressure, suggesting improved control. CONCLUSION: Mindful movement approaches such as Alexander Technique may benefit older adults and people with Parkinson's disease by facilitating increased upright postural alignment and mobility while reducing neck compression and postural unsteadiness. Our findings suggest that simple changes in postural instructions can have beneficial effects on motor problems associated with aging. Because the two sets of instructions used here had markedly different effects, we conclude that the effects were not due to attention to the body, per se, or even solely to the increase in standing height. These results imply that how one conceives of postural uprightness has a profound effect on how one stands and moves, and that this influence can be harnessed for rehabilitative and training purposes.

Disclosures: R.G. Cohen: None. **F.B. Horak:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); APDM, Inc.. **V.S. Gurfinkel:** None.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.12

Topic: D.16. Posture and Gait

Support: AHA Predoctoral Fellowship 15PRE21820002

Title: Relationship between walking speed and kinematic trajectory in people with poststroke hemiparesis

Authors: *D. D. RUMBLE, C. P. HURT, D. A. BROWN;
Physical Therapy, Rehabil. Sci. Program, Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: PURPOSE/HYPOTHESIS: Walking disability is a major concern among people with poststroke hemiparesis. One major characteristic of walking disability is slow walking speed. Recent studies have focused on factors underlying slow walking speed, such as strength and balance impairment. However, preliminary results from our laboratory suggest, with weakness and balance accounted for, the hemiparetic gait trajectory may be susceptible to increased step by step variability (SSV) and may play a major role in generating foot placement errors. Where a nonimpaired individual may adapt their gait to accommodate faster speeds, people poststroke may have increased susceptibility to speed-induced missteps resulting in the choice of slower

speeds as a strategy to avoid unstable walking conditions. A problem with past studies was the inability to study large range of speeds that might reveal complex behaviors at very fast speeds. We hypothesize that at progressively faster speeds the SSV will increase for the paretic limb but not for the nonparetic limb nor for nonimpaired individuals. METHODS: We used a specialized robotic interface that provided assistive horizontal force to allow people to walk at faster speeds than previously possible, coupled with a treadmill to explore SSV, using a high speed motion capture system, in both the paretic, nonparetic, and nonimpaired limb. RESULTS: To date, we have recorded observations of 2 people with poststroke hemiparesis and 5 nonimpaired individuals walking at a wide range of speeds. For each participant, thirty strides of the foot trajectory in the anterior-posterior (AP) and vertical direction of both the left and right limbs were collected. People poststroke exhibited greater SSV in the vertical direction, but not the AP direction, for the paretic limb compared to both their non-paretic side and to nonimpaired individuals. Additionally, for the paretic limb, vertical SSV increased considerably for very fast speeds - speeds greater than fast walking speed to their maximum walking speed. DISCUSSION/CONCLUSION: The control of foot trajectory in the vertical direction seems to reduce as gait speed increases for the paretic limb compared to the nonparetic limb and to the nonimpaired limbs. We will further explore the underlying factors contributing to these observations.

Disclosures: **D.D. Rumble:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; American Heart Association. **C.P. Hurt:** None. **D.A. Brown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); HDT.

Nanosymposium

374. Posture and Gait: Health and Disease

Location: N226

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 374.13

Topic: D.16. Posture and Gait

Support: This research is partially supported by the Health and Labour Sciences Research Grants for Comprehensive Research on Persons with Disabilities from Japan Agency for Medical Research and development, AMED.

This research was partially supported by Grants for Advanced Research and Development Programs for Medical Innovation from AMED-CREST, AMED

This research is partially supported by Grants for Development of Medical Devices and Systems for Advanced Medical Services from Japan Agency for Medical Research and development, AMED.

Title: fNIRS-mediated Neurofeedback associated with mental practice with motor imagery enhances gait recovery after stroke: interim analysis of randomized clinical trial

Authors: *M. MIHARA[1], H. FUJIMOTO[1,3], N. HATTORI[3], Y. WATANABE[2], T. KAWANO[3], M. HATAKENAKA[3], H. YAGURA[3], I. MIYAI[3], H. MOCHIZUKI[1];
[1]Dept. of Neurol., [2]Dept. of Radiology, Osaka Univ. Grad. Sch. of Med., Osaka, Japan;
[3]Neurorehabilitation Res. Inst., Morinomiya Hosp., Osaka, Japan

Abstract: Background: Balance impairment in the patients with brain injury severely affects their activities of daily living (ADL), and our previous studies suggested that the dorsomedial portion of motor related cortex including the supplementary motor area (SMA) and its descending projection supposed to play an important role in the intentional postural control in humans and balance recovery after brain damage. We have developed functional near infrared spectroscopy mediated neurofeedback system (fNIRS-NFB) in which subjects try to modulate their own neural activity voluntarily with real-time feedback, and previous study confirmed that the fNIRS-NFB augment the rehabilitation effect for the upper limb paresis after stroke. Objective: We are conducting a randomized clinical trial to investigate whether fNIRS-NFB targeting the SMA activity associated with mental practice with motor imagery would augment the post-stroke balance recovery. To confirm the safety and feasibility of this new technique, we performed interim analysis. Methods: Subacute stroke patients with subcortical lesions (N = 31, 23 males, Age : 60.1± 11.6, 117.0± 20.7 days from onset) with written informed consent have been enrolled into this study. In addition to the usual inpatient rehabilitation up to 180min/day, all the patients participated 6 sessions of mental practice with motor imagery of gait and postural related task concurrent with neurofeedback of the SMA activation (3 times/wk×2 wks). Clinical measures including Berg Balance Scale (BBS), Gait speed, and 3m-Timed Up-and-go test (TUG) are assessed before, just after, and 2 wks after fNIRS-NFB. Subjects are randomly assigned to 2 groups (REAL and SHAM). In REAL group, their own neuronal activity was provided, whereas neuronal activity recorded from other subjects was provided in SHAM group. Neither patients nor physicians did not recognize which group they were assigned (double-blinded). Results: Baseline clinical characteristics were comparable between two groups. There was significant interaction between gait and balance measures including BBS and TUG with significant improvement in the REAL group ($F_{2,29}$=7.26, $p<0.005$ and $F_{2,29}$=3.39, $p<0.05$, respectively). Comparing the before and after fNIRS-NFB, only REAL group showed significant increase of gait task related cortical activation in the SMA. There was no side-effects associated with fNIRS-NFB in both groups. Conclusion: This interim analysis suggested that the fNIRS-NFB

might be feasible and safe intervention for the post-stroke patients to augment gait and balance recovery.

Disclosures: **M. Mihara:** Other; Japan Agency for Medical Research and development, AMED.. **H. Fujimoto:** None. **N. Hattori:** Other; Japan Agency for Medical Research and development, AMED. **Y. Watanabe:** Other; Japan Agency for Medical Research and development, AMED.. **T. Kawano:** None. **M. Hatakenaka:** None. **H. Yagura:** None. **I. Miyai:** Other; Japan Agency for Medical Research and development, AMED. **H. Mochizuki:** Other; Japan Agency for Medical Research and development, AMED..

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.01

Topic: E.05. Stress and the Brain

Support: 1F31MH105211-01

DA09082

MH093981

Title: Repeated exposures to social stress during adolescence sensitizes the brain norepinephrine system of female rats

Authors: ***H. M. GUAJARDO**[1], A. L. CURTIS[2], J. R. ARNER[2], R. J. VALENTINO[2,1]; [1]Neurosci. Grad. Group, Univ. of Pennsylvania, Philadelphia, PA; [2]Dept. Anesthesiol. and Critical Care, Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Traumatic stressful experiences have been associated with diverse psychiatric disorders. Patient histories often show a traumatic stressful experience early in life, i.e. adolescence, from which a spectrum of impairments and brain dysfunctions may reverberate at varying intensities throughout the course of the life. Notably, stress-related psychiatric disorders are more prevalent in females. Because social stress is a common stressor for humans, this study examined the effects of repeated social stress occurring during adolescence for female rats on activity of the locus coeruleus (LC)-norepinephrine (NE) system. The LC-NE system is a major stress-response system of the brain that is activated by acute stress and this activation is thought to mediate arousal and cognitive adaptations to the stressor. Although adaptive, excessive activity of the LC-NE system has been implicated in the hyperarousal symptoms of stress-related

psychiatric disorders. In this study, female adolescent (PND-42) rats were implanted with a multiwire electrode in LC and exposed to the resident-intruder model of social stress for five consecutive days, or a control manipulation that involved exposure to a novel cage. The resident was a lactating female within the first 10 days post-partum and her pups were removed from the resident cage during the resident-intruder trial. Surprisingly, the initial exposure to social stress had little effect on spontaneous or auditory-evoked LC neuronal activity. In contrast, preliminary results suggest that for adult female rats exposure to the identical social stress increases LC discharge rate as expected. Notably, the fifth exposure to social stress robustly increased LC spontaneous activity of adolescent females suggesting that the neurons may become sensitized to repeated exposures. These findings for female adolescents contrast with our recent observations in adolescent males where LC activation was significant after social stress during the initial exposure but not with repeated exposures. Together the results highlight the impact of social stress on the LC-NE stress response system and the role of sex and developmental stage in determining these effects.

Disclosures: H.M. Guajardo: None. **A.L. Curtis:** None. **J.R. Arner:** None. **R.J. Valentino:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.02

Topic: E.05. Stress and the Brain

Title: Low maternal care programs dysregulation of the neurosteroid/GABAergic system in female offspring: An animal model for premenstrual dysphoric disorder

Authors: *A. BORROW[1], S. DONUK[2], N. M. CAMERON[1];
[1]Psychology, [2]Binghamton Univ., Binghamton, NY

Abstract: Natural variations in rodent maternal behavior during early life influence affective behavior in adult offspring. Recipients of Low levels of maternal licking and grooming (LG) during the first week of life are more anxious than animals that have received High LG from their mothers. During proestrus, Low LG female offspring also show a greater peak of progesterone, a neurosteroid that exerts anxiolytic effects through the actions of its metabolite, allopregnanolone (THP), at extrasynaptic GABAAR within the limbic system. We hypothesized that the higher peak of progesterone demonstrated by Low LG offspring in proestrus would result in a higher peak of THP in plasma and the brain relative to High LG offspring, as well as

an estrous cycle-dependent fluctuation in the THP-responsive GABAAR subunits α4 and δ within the dorsal hippocampus. In Experiment 1, plasma levels of progesterone and THP at proestrus and metestrus in Low and High LG offspring, and GABAAR subunit expression and THP levels were characterized within the dorsal hippocampus. In Experiment 2, levels were assessed at proestrus and metestrus following s.c. treatment with either finasteride (a 5α-reductase inhibitor) or vehicle. Results from Experiment 1 indicate that Low LG offspring have lower levels of THP within the dorsal hippocampus, and that, unlike High LG offspring, plasma and hippocampal THP levels are not correlated with GABAAR expression within this region. In Experiment 2, finasteride only affected plasma THP levels in High LG offspring. In addition, only placebo-treated High LG offspring showed an estrous cycle-dependent plasticity in α4 subunit expression. These data suggest an impaired metabolism of progesterone to THP in adult female recipients of Low LG, and a decrease in the ability of THP to alter GABAAR expression within the dorsal hippocampus of these animals. Our results parallel findings from studies of women with premenstrual dysphoric disorder, a condition which has been associated with an impaired metabolism of progesterone to THP, and the absence of a correlation between THP and GABA levels, suggesting a diminished influence of THP on the GABAergic system.

Disclosures: A. Borrow: None. **S. Donuk:** None. **N.M. Cameron:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.03

Topic: E.05. Stress and the Brain

Support: NIH Training Grant T32-GM008688

NSF Grant IOS-1122074

Title: Predator-induced fear alters serotonergic signaling pathways in the adolescent female amygdala; a rodent model to study sex-specific effects of early life stress

Authors: *S. L. KIGAR[1], L. CHANG[2], A. CUARENTA[2], J. R. SEHRING[2], N. T. KARLS[2], M. R. HAYNE[2], V. P. BAKSHI[3], A. P. AUGER[2];
[1]Mol. and Cell. Pharmacol. Program, [2]Psychology, [3]Psychiatry, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Major depressive disorder and anxiety disorders, such as Post-Traumatic Stress Disorder (PTSD), are the leading cause of disability globally and are twice as likely to affect women as compared to men (World Health Organization [WHO], 2012). In particular, adolescent girls have a heightened sensitivity to stress that could increase the probability of these psychiatric conditions (Zahn et al., 2009). Understanding how biological sex confers vulnerability is critically important to the development of more effective treatment strategies, and the benefits associated with inclusion of females in basic research studies has been stressed elsewhere (McCarthy, et al., 2012). Our laboratory has recently developed a novel, neonatal predator odor exposure (POE) paradigm as an ecologically relevant model for ELS (define abbreviation) in an effort to elucidate the role of sex differences in the neurodevelopment of psychiatric disorders. Our study revealed that POE on postnatal days 1-3 (PN1-3) was associated with high levels of anxiety-like behavior in both male and female adolescent rats, as assessed using an elevated plus maze (EPM). One potential mediator of this anxiety response is altered serotonin, or 5-HT, signaling which has been implicated in both anxiety and depression (O'Leary & Cryan, 2010). Using qPCR, we examined the mRNA expression of 5-HT receptor subtypes Htr2a and Htr1a in animals sacrificed 30min after the last exposure on PN3 and in juvenile animals used for behavior testing. Our results suggest there are sex-, region-, and temporally-specific effects of POE on serotonergic signaling pathways, and that females are responding more strongly in the amygdala to the stressor. These data support the idea that males and females will respond differently to environmental stressors, though behavioral outcomes may be similar, and thus may benefit from different treatment and/or intervention strategies. We are continuing to investigate whether the changes observed are programmed through epigenetic mechanisms using an enzyme-based DNA methylation analysis method.

Disclosures: **S.L. Kigar:** None. **L. Chang:** None. **A. Cuarenta:** None. **J.R. Sehring:** None. **N.T. Karls:** None. **M.R. Hayne:** None. **V.P. Bakshi:** None. **A.P. Auger:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.04

Topic: E.05. Stress and the Brain

Support: NIH Grant R01MH051399

NIH Grant P50MH096890

HDRF

Title: Early life stress enhances susceptibility to depression via long-lasting transcriptional alterations

Authors: *C. J. PENA, I. PURUSHOTHAMAN, H. M. CATES, R. C. BAGOT, D. M. WALKER, L. SHEN, E. J. NESTLER;
Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Adverse experiences during childhood enhance the risk of psychiatric disorders and poorer physical health in adulthood. However, knowledge of the neurobiological and transcriptional mechanisms underlying these outcomes is still limited. We have developed a paradigm in mice whereby early life stress (ELS) in a critical window alters susceptibility to depression-like behaviors. Adult male mice that experienced ELS have no detectable behavioral abnormalities under control conditions, but exhibit exaggerated social avoidance and anhedonia after undergoing social defeat in adulthood. This latent increase in stress susceptibility is accompanied by broad changes within the brain's reward circuitry, as revealed by RNA-sequencing in the nucleus accumbens and ventral tegmental area (VTA) and physiological recordings of VTA dopamine neurons. Within the VTA, IPA analysis identified several potentially important upstream regulators of transcriptional dysregulation in animals exposed previously to ELS, including OTX2 (orthodenticle homeobox 2), NR5A1 (SF1), and NR3C1 (glucocorticoid receptor, GR). OTX2 is a transcription factor known for its role in midbrain dopamine neuron development, and more recently for critical period plasticity in the visual system. Our data implicate it as a novel regulator of vulnerability to depression-like behavior; indeed, ELS suppresses mRNA levels of several OTX2 target genes in the adult VTA. Interestingly, Otx2 mRNA is reduced proximal to ELS at postnatal day 21 but not different from standard-reared animals in adulthood, suggesting that OTX2 induces long-lasting organizational or epigenetic changes within the VTA. Viral-mediated over-expression of OTX2 within the adult VTA rescues the enhanced stress susceptibility seen after ELS, without effects on animals reared under standard conditions. Manipulation of OTX2 at different ages may reveal critical windows of stress vulnerability and suggest novel therapeutic interventions.

Disclosures: C.J. Pena: None. **I. Purushothaman:** None. **H.M. Cates:** None. **R.C. Bagot:** None. **D.M. Walker:** None. **L. Shen:** None. **E.J. Nestler:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.05

Topic: E.05. Stress and the Brain

Support: CAPES-PROEX

CNPQ

FAPESP

Title: Multimodal Early-Life Stress paradigm as potential animal model for depressive-like behavior induction in rats

Authors: *L. D. GODOY[1,3], E. H. L. UMEOKA[2], N. GARCIA-CAIRASCO[1,3];
[1]Physiol. Dept., [2]Neurosci. and Behavioral Sci. Dept. - Ribeirão Preto Sch. of Med., Univ. of Sao Paulo, Ribeirao Preto, Brazil; [3]INeC - Neurosci. and Behavioral Inst., Ribeirão Preto, Brazil

Abstract: Recent studies on Major Depression (MD) pathophysiology have strongly associated chronic stress and its consequences, from HPA axis dysregulation to behavior expression. Permanent endocrine and neural changes may occur when stressors are presented early in life, resulting in a relevant increased risk factor for MD development. Evidences suggest the contributive role of early-life stress (ELS) to MD, but with no clear demonstration of long-lasting effects. Wistar Rat pups (P1-P21) were exposed to Unpredictable Multimodal ELS paradigm: daily propylene glycol injection, associated with either 1 h maternal separation, or 1 h restraint-shaker stress or 10 min cold exposure. Animals were sacrificed 30 minutes after cold exposure at P3, P7 and P21 for corticosterone (cort) plasma levels assessment. To determine ELS effects on basal cort levels, animals were sacrificed at P22 under resting condition. Animals that underwent ELS and Controls were evaluated at P82 - P85 in sucrose consumption test (SCT) (animals could choose between 1% sucrose solution and water). Sacrifice was performed at P90. Body, adrenal gland and thymus weights were determined at P21 and P90. There was not habituation to ELS protocol since plasmatic cort levels were significantly increased in ELS Group, when compared to Control at P3 ($p<0.001$), P14 ($p<0.001$) and P21 ($p<0.01$). Interestingly, under resting condition at P22, a trend ($p=0.065$) of increased cort levels in ELS Group compared to Control group was observed. At P21, adrenal glands weight of ELS animals was increased ($p<0.001$), and thymus and body weight were decreased ($p<0.01$ and $p<0.001$, respectively) when compared to Controls. At P90 increased adrenal glands ($p<0.001$) and reduced thymus ($p<0.01$) were still observed in ELS Group when compared to Control Group, no significant differences for body weight were found at P90. Moreover, adult rats that underwent ELS protocol showed significant ($p<0.05$) lower sucrose intake in the SCT when compared to Control group. Our findings demonstrated that during the Multimodal ELS paradigm exposure, the HPA axis is activated, with no habituation to stressors. More importantly there are differences in adrenal and thymus weight at P90, showing long-term changes in HPA axis related organs. Taken together, these findings indicate that this ELS paradigm is effective in inducing changes in the HPA axis-related organs, as well as anhedonia in adulthood. Therefore,

this ELS protocol can be a suitable experimental model for characterization of psychiatric comorbidities associated with stress, especially MD.

Disclosures: L.D. Godoy: None. **E.H.L. Umeoka:** None. **N. Garcia-Cairasco:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.06

Topic: E.05. Stress and the Brain

Support: AFIP

CAPES-PROEX 1035/2014

Title: Post-weaning REM sleep restriction induces anxiety, anhedonia and changes in monoamine levels in the amygdala and hippocampus

Authors: *D. SUCHECKI[1], R. B. MACHADO[2], J. S. ROCHA[2];
[1]Univ. Federal De Sao Paulo, Sao Paulo, Brazil; [2]Psychobiology, Univ. Federal de Sao Paulo, Sao Paulo, Brazil

Abstract: Modern society is characterized by self-imposed sleep curtailment that has been associated with numerous physical and mental health problems. Prolonged sleep deprivation or restriction have been associated with triggering of emotional and mood disorders. Adolescence is marked by changes in brain and behavior, including the sleep pattern and epidemiologic studies report a reduction of sleep hours in juveniles and adolescents. The goal of the present study was to assess the emotional and affective behavior of adolescent male rats as a consequence of post-weaning REM sleep restriction for 3 weeks (from post-natal day 21 to 41 - 18 h of REM sleep deprivation on the multiple platform method, followed by 6 h of free sleep in the home-cage). After the end of sleep restriction protocol, rats were allowed 2 days of sleep recovery, after which, behavioral testing commenced. In Experiment 1, rats were tested in the negative sucrose contrast test (NSCT - hedonic behavior) and the elevated plus maze (EPM - anxiety behavior). One hour after the EPM, rats were decapitated and the brains were harvested and dissected in hypothalamus, dorsal and ventral hippocampus, amygdala and frontal cortex. In Experiment 2, rats were tested in the positive sucrose contrast test (PSCT - anhedonic behavior), open field (anxiety behavior), social investigation (social behavior) and novel object recognition test (memory). REM sleep restriction led to heavier adrenals and induced anxiety- (avoidance of

open arms of the EPM and central area of the open field) and depressive-like behaviors (anhedonia in the PSCT), without changes in social behavior and memory. Increased levels of noradrenaline in the amygdala and ventral hippocampus and of serotonin in the dorsal hippocampus provided the neurobiological underpinning for the behavioral changes observed. In conclusion, prolonged REM sleep restriction in juvenile male rats resulted in increased emotional and impaired affective behaviors associated with neurochemical changes in brain areas involved with the regulation of emotion.

Disclosures: D. Suchecki: None. **R.B. Machado:** None. **J.S. Rocha:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.07

Topic: E.05. Stress and the Brain

Support: NIH grant MH41256 to BSM

NIH grant MH102065 to JDG

Title: Early life stress alters the gene expression response of CA3 neurons to stress in adulthood

Authors: *J. D. GRAY[1], J. F. KOGAN[1], T. G. RUBIN[3], E. F. SCHMIDT[2], N. HEINTZ[2], B. S. MCEWEN[1];
[1]Neuroendocrinology, [2]Lab. of Mol Bio, The Rockefeller Univ., New York, NY; [3]Neurol., Albert Einstein Col. of Med., New York, NY

Abstract: Exposure to early life stress (ELS) has been associated with increased incidence of mental disorders later in life. Rodent models of ELS have revealed lasting changes in the neuroendocrine system, suggesting altered adult stress reactivity. Stress can both increase the severity and potentiate the onset of mental illness. In this study, the interaction of ELS with stress in adulthood on the gene expression response of CA3 neurons of the hippocampus was examined. Transgenic mice expressing an EGFP fused to the L10a ribosomal subunit that is under the control of a cell-type specific promoter (Gprin3) was used to isolate the *in vivo* translating RNA fractions from a genetically homogenous population of CA3 neurons. Mice expressing Gprin3-EGFP-L10a were subjected to bedding and nesting deprivation from P2-P12 (Rice···Baram, 2008) and then given standard housing conditions until 4mos of age, when they were exposed to an acute forced swim stress. Mice were rapidly decapitated and the

hippocampus was dissected for RNA isolation by Translating Ribosomal Affinity Purification (TRAP). TRAP immunoprecipitated and unbound fractions were subjected to RNA-sequencing using an Illumina Hi-Seq 2500 to collect 100bp reads at a sequencing depth of 30M reads/sample. Results were aligned against the mouse genome (mm9) and the numbers of reads for each transcript were normalized against total reads to obtain relative expression levels. Strand software was used to perform statistical analysis of relative expression levels to identify differentially expressed genes. Previous comparisons of TRAP fractions from adult mice between ELS and controls revealed over 9,456 entities (5,229 increased; 4,227 decreased) that are persistently changed after ELS. Acute swim stress has been shown to alter 9,357 entities (4,589 increased; 4,768 decreased) in adult mice not exposed to ELS. In contrast, mice subjected to ELS exhibited changes in 3,679 genes after a swim stress that are distinct from non-ELS mice. Pathway analysis of these novel stress reactivity genes identified metabolic (insulin signaling) and neuroendocrine (androgen signaling) gene networks as having a significant number of transcripts whose levels were changed. As an expansion of our previous study of acute and chronic stress (Gray et al. Mol Psych 2014), these *in vivo* gene expression profiles provide a refined map of stress-induced hippocampal changes that are unique to CA3 neurons and will help unravel the mechanisms underlying the unique plasticity and damage-vulnerability of these cells to ELS.

Disclosures: **J.D. Gray:** None. **J.F. Kogan:** None. **T.G. Rubin:** None. **E.F. Schmidt:** None. **N. Heintz:** None. **B.S. McEwen:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.08

Topic: E.05. Stress and the Brain

Support: NSERC

CIHR

AIHS

Title: Role of serotonin 1A receptor in offspring's susceptibility to maternal stress as measured by behavioural outcomes in adulthood

Authors: *V. KIRYANOVA[1], V. M. SMITH[2], V. NAGESH[1], M. C. ANTLE[2], R. H. DYCK[2]; [2]Psychology, [1]Univ. of Calgary, Calgary, AB, Canada

Abstract: Chronic maternal stress during the early developmental period results in sustained, detrimental consequences for the offspring, as adults. Previous research demonstrates that offspring's genetic factors that affect the function of the serotonergic system (e.g. polymorphism in tryptophan hydroxylase-2, monoamine oxidase A, serotonin transporter genes) interact with early adverse environment, including maternal stress, affecting long-term behaviours; however, the role of serotonin 1A receptor (5-HT1AR) has not been extensively examined in this regard. The present study examines long-term effects of maternal stress on male and female offspring with fully functional (wild type, WT), partially functional (heterozygous, HET), and non-functional (knockout, KO) 5-HT1AR gene. METHODS: Mouse dams (5-HT1AR HET, bread with 5-HT1AR HET males) were randomly assigned to groups: one group was exposed to chronic unpredictable stress (embryonic day 7 to 18), while a separate control group consisted of animals that were not exposed to stress. At two months of age, the male and female offspring (WT, HET, KO) went through a comprehensive behavioral test battery. The behavioural battery included tests of social behaviour, memory, aggression, anxiety, sensorimotor information processing, and exploratory and risk assessment behaviours. RESULTS: We found that, in males, prenatal stress lead to hyperactivity and emotional memory deficits regardless of offspring genotype. However, genotype moderated the effect of prenatal stress on social and aggressive behaviours of male animals. Specifically, while prenatal stress did not affect social behaviour of WT and HET mice, social preference was abolished in KO mice exposed to prenatal stress. Furthermore, prenatal stress also altered aggressive behaviour in HET and KO animals, while having no effect on aggressive behaviour of WT mice. In females, prenatal stress alone had no effect on the offspring. However, unlike in males, prenatal stress abolished social preference in WT, but not HET or KO mice. CONCLUSION: Our findings indicate that 5-HT1A receptor availability can affect outcomes of the offspring following prenatal stress; these effects are highly sex specific.

Disclosures: V. Kiryanova: None. **V.M. Smith:** None. **V. Nagesh:** None. **M.C. Antle:** None. **R.H. Dyck:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.09

Topic: F.02. Animal Cognition and Behavior

Support: PUF Funding to JBB, MRC, RMS and AMM

LIA Funding to JBB and AMM

LABEX CORTEX to JBB and AMM

Title: Ontogeny of ultrasonic vocalization and respiratory responses to an aversive event in rats

Authors: *J. BOULANGER BERTOLUS[1], M. RINCÓN-CORTÉS[2], R. M. SULLIVAN[2], A.-M. MOULY[1];
[1]Lyon Neurosci. Res. Ctr., Lyon Cedex 07, France; [2]Emotional Brain Institute, Nathan Kline Institute, Child & Adolescent Psychiatry, New York Univ. Sch. of Med., New-York, NY

Abstract: When confronted with highly emotional events, either positive or negative, rats have been shown to emit vocalizations in the ultrasonic range (USVs) which can affect their respiratory rate, at least in adult animals. Although vocalizations are emitted at all developmental ages, they evolve throughout the rat's life, both in terms of quantity and quality. Until now, very few studies have been exploring USVs with similar paradigms throughout the ontogenesis and no study has investigated the parallel evolution of USVs, respiration and behavior at different ages of development. Therefore, in this study, we investigated the co-evolution of these three parameters in response to a mild foot-shock at three ages: infant (PN12-14), juvenile (PN22-24) and adult (PN80-90). The foot-shock induced sustained emission of USVs at all ages, with significant differences in USVs frequencies and durations throughout development. For example, while adults and juveniles emit USVs in one narrow frequency band, at 22 and 30kHz respectively, infants emit USVs into two wide frequency bands peaking around 40 and 70kHz respectively. We also characterized the reciprocal influences of the respiratory rate and freezing on USVs emission. Results suggest that USVs extend the expiration duration in adult, and to a lesser extent in juvenile rats, while they do not influence the respiratory rate in infants. Moreover, USVs are mainly emitted during freezing in juveniles and adults. In infants, high-frequency USVs are emitted during movement while low-frequency USVs are emitted during freezing. Finally we investigated whether the emission of USVs was modulated as a function of the predictability of the foot-shock arrival. In the predictable condition the animals were trained in an odor-shock conditioning: an odor is presented to the animal and co-terminates with a foot-shock. In the unpredictable condition, the odor and the shock were separated by 3min. We showed that when the shock was unpredicted, the level of USVs was significantly greater than when the shock was predicted. Interestingly, this difference was only observed in infant rats and preferentially concerned the highest frequency band. These results are discussed with regard to the physiological and behavioral development of the animal.

Disclosures: J. Boulanger Bertolus: None. **M. Rincón-Cortés:** None. **R.M. Sullivan:** None. **A. Mouly:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.10

Topic: E.05. Stress and the Brain

Support: NIH Grant P50 MH079513

Title: Effects of early deprivation on functional brain systems supporting executive function in adolescence

Authors: *K. M. THOMAS[1], R. H. HUNT[1], R. A. COWELL[2], A. S. HODEL[1], S. E. VAN DEN HEUVEL[1], M. R. GUNNAR[1];
[1]Univ. Minnesota, Minneapolis, MN; [2]St Norbert Col., De Pere, WI

Abstract: Children raised in institutional or orphanage care experience mild to severe deprivation as a result of inadequate physical care, and lack of cognitive and socio-emotional stimulation (Rutter, 1981). Cognitive, behavioral, or physical delays have been documented in this population and persist to varying degrees after adoption to family contexts (Johnson, 2001). In particular, attention and executive function difficulties have been identified even after adoption into positive and supportive environments (Hostinar et al., 2012). Age at adoption may moderate the relationship between early deprivation and later cognitive deficits. The current study examined the role of duration of institutional care on behavioral and brain measures of cognitive conflict and motor control in adolescents with a history of orphanage rearing. Eighty-four post-institutionalized (PI) internationally adopted youth (aged 12-14 years) and 24 non-adopted (NA) comparison youth were included. PI youth were classified as either earlier adopted (<1 year at adoption; n=42) or later adopted (1-5 years at adoption; n=42). A cognitive-motor remapping task was administered during fMRI scanning (Casey et al., 2002). On each trial, a single numeral (1, 2 or 3) was presented. Participants were instructed to press with the matching finger as quickly as possible in response to each number. Compatible (easy) trials matched numbers to fingers in an intuitive pairing. Incompatible (difficult) conditions required participants to remap numbers to non-intuitive fingers. Images were acquired on a 3T Siemens Trio scanner (34 slices, 4mm thick). FSL software was used to analyze functional data. PI youth showed greater activity than comparison youth in the anterior cingulate (ACC) and bilateral dorsolateral prefrontal cortex (dlPFC), as well as precuneus and bilateral parietal cortex for incompatible vs. compatible trials, suggesting a lasting impact of early deprivation on later brain function. Prefrontal activity did not differ between earlier and later adopted youth. In contrast, parietal activity was significantly greater for later adopted than for earlier adopted youth,

suggesting that some brain regions are sensitive to the duration of early deprivation. Overall, behavioral data suggest that PI youth, especially those who lived longer in orphanage care, show poorer executive function than non-adopted and earlier adopted peers. fMRI data provide evidence both for global effects of early adversity (affecting all PI youth; Hodel et al, 2015) and for dose dependent effects of deprivation (LA>EA). Further analyses are under way to examine functional connectivity in this sample.

Disclosures: K.M. Thomas: None. **R.H. Hunt:** None. **R.A. Cowell:** None. **A.S. Hodel:** None. **S.E. Van Den Heuvel:** None. **M.R. Gunnar:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.11

Topic: E.05. Stress and the Brain

Support: NIMH P50-MH79513

NIH T32-HD007151

NIH T32-MH73129

NIH P41-RR008079

NIH P41-EB015894

NIH P30-NS076408

Title: Prefrontal white matter organization at adolescence following early life stress

Authors: *A. S. HODEL, R. H. HUNT, K. JEDD, M. R. GUNNAR, K. M. THOMAS; Inst. of Child Develop., Univ. of Minnesota, Minneapolis, MN

Abstract: Post-institutionalized (PI) children experience a temporally discrete period of deprivation (institutional care) followed by an enriched environment (i.e. typically high socioeconomic status, high education levels) of the adoptive family. Although longer duration of adversity predicts larger deficits in prefrontal-dependent behavior, inconsistent associations between duration of institutional care and metrics of neurodevelopment have been reported. 114 PI adolescents and a control group of children growing up in their biological families (*n*=92) between 12-14 years provided neuroimaging data. PI children were adopted between 4-62

months of age and were subdivided into early-adopted (n=57; <1 year) and later-adopted (n=57; >1 year) groups. T1-weighted high-resolution MRI scans were collected and segmented using Freesurfer. Children completed a 12-direction DTI sequence and a subset (n=44 PI; n=54 controls) also completed a 56-direction sequence. FSL's TBSS pipeline was used to estimate fractional anisotropy (FA) within anatomically defined tracts selected from the JHU White Matter Tractography Atlas. Statistical analyses included age and sex as covariates. Preliminary analyses reported in this abstract include only participants with 56-direction DTI data. PI children had smaller cortical white matter volume (beyond differences in head size) than their non-adopted peers (p<.01), with no difference between earlier and later adoptees. Age at adoption was a trend-level predictor of white matter volume, but only among later-adoptees (p<.08), and this effect was eliminated after covarying for head size. PI children had lower FA values in white matter tracts that traverse the frontal lobe including the anterior forceps (p<.04), superior (p<.06) and inferior (p<.01) longitudinal fasiculus, and occipitofrontal fasiculus (p<.01). Effects were driven by differences from non-adopted controls, rather than differences between earlier and later adoptees. Age at adoption was a trend-level predictor of FA in several tracts, but only among later-adoptees. Our results suggest there are persisting effects of early life stress on prefrontal white matter organization at adolescence. Although the largest differences were observed between PI children and non-adopted controls, preliminary analyses suggest that prefrontal white matter integrity may be sensitive to duration of early adversity within later adoptees. Final analyses will include multiple white matter metrics (mean, axial, and radial diffusivity) and seed-target connectivity (frontostriatal projections) to better delineate relationships with duration of institutional care.

Disclosures: **A.S. Hodel:** None. **R.H. Hunt:** None. **K. Jedd:** None. **M.R. Gunnar:** None. **K.M. Thomas:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.12

Topic: E.05. Stress and the Brain

Title: Adolescent- and sex-related differences in stress-induced HPA and oxytocin hormonal responses in rats

Authors: *R. D. ROMEO, C. LIU, J. FLORES-GALDAMEZ, S. MINHAS;
Psychology and Neurosci. and Behavior Program, Barnard Col. of Columbia Univ., New York, NY

Abstract: Studies have indicated that adolescent exposure to stress is a potent environmental factor that contributes to psychological and physiological disorders. However, the mechanisms by which stress mediates these dysfunctions are not well understood. Periadolescent animals display greater stress-induced hypothalamic-pituitary-adrenal (HPA) axis responses than adults, which may contribute to these vulnerabilities. Specifically, adrenocorticotropin hormone (ACTH) and corticosterone (CORT) responses remain elevated for twice as long in prepubertal compared to adult rats. In addition to the HPA axis, the hypothalamo-neurohypophyseal tract (HNT) is also activated in response to stress. In adult males, stress activates this system resulting in secretion of oxytocin (OXY) from neurons in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) into the bloodstream. However, it is currently unknown whether a similar response occurs in prepubertal males or whether females respond to stress with increased OXY secretion. Given the influence of these hormones on a variety of emotional behaviors and physiological systems, the following study investigated both the stress-induced HPA and HNT hormonal responses in prepubertal (30d) and adult (70d) male and female rats exposed to 30 min of restraint stress. We also examined the number of OXY containing cells in the PVN and SON of prepubertal (30d), mid-pubertal (45d), adult (70d) males and females. Though we found the well-established protracted ACTH and CORT response in prepubertal animals, as well as greater HPA reactivity in females, only the adult males and females showed a significant stress-induced OXY hormonal response. Despite these age-dependent differences in OXY responsiveness, we found no differences in the number of OXY containing neurons in the PVN or SON. Moreover, we counted a limited number of cells co-localizing both OXY and FOS, a marker cellular activation, following stress in both prepubertal and adult males. This lack of double labeling indicates that either the age-related difference in OXY reactivity is not mediated by differential activation of OXY cells or that FOS is a poor marker of stress-induced neuronal activation in these neurosecretory cells. Taken together, these data indicate that different neuroendocrine systems can show opposite patterns of stress reactivity during adolescent development and that these responses can be further modified by sex. Given the impact of these hormones on a variety of tissues and organ systems, it will be imperative to further explore these changes in hormonal stress reactivity and their role in adolescent health in both males and females.

Disclosures: **R.D. Romeo:** None. **C. Liu:** None. **J. Flores-Galdamez:** None. **S. Minhas:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.13

Topic: E.05. Stress and the Brain

Support: CNPq 454429/2014-2

CNPq 400850/2014-1

CNPq 306271/2014-1

Title: Maternal separation increases cocaine-induced CPP and reduces miRNA-212 expression in the PFC of adolescents

Authors: T. W. VIOLA[1], L. WEARICK-SILVA[1], L. A. AZEREDO[1], F. GARCIA[2], T. W. BREDY[3], *R. GRASSI-OLIVEIRA[1];
[1]PUCRS, Porto Alegre, Brazil; [2]UFMG, Belo Horizonte, Brazil; [3]Univ. of California - Irvine, Irvine, CA

Abstract: MicroRNAs are important posttranscriptional gene expression regulators that are involved in many neurobehavioral disorders. Recently, it has been suggested that the risk for cocaine addiction and maintenance of drug-seeking behavior are particularly related to the activity of microRNA-212 in the brain. Furthermore a variety of environmental experiences, such as early life stress exposure, might contribute to vulnerability to cocaine abuse and dependence, although the molecular mechanisms underlying this relationship still not completely understood. We investigated the expression of miRNA-212 in the prefrontal cortex (PFC) and hippocampus of adolescent mice exposed to an early life stress model and trained for cocaine-induced conditioned place preference (CPP). Male BALB/c litters were randomly assigned to one of three groups: maternal separation (MS), standard rearing (SR - controls) and drug naïve animals. The MS animals were subjected to daily 3-h maternal separation from postnatal day (PND) 2 to 15. The CPP was performed with a cocaine dose of 20mg/kg, following three sequential phases: habituation (PND 34), conditioning (PND 35 to PND 44) and post-conditioning test (PND 45). Tissue extraction occurred 2 hours after the CPP test and levels of miRNA-212 were determined by qPCR. We found that after CPP training, MS animals exhibited higher time spent in the drug-paired chamber in comparison with SR animals. Furthermore CPP treatment decreased miRNA-212 expression in PFC only in MS animals, while no differences were found in the hippocampus. Additionally, we performed another experiment with drug-naïve animals exposed to maternal separation and also found reduced expression of miRNA-212. Given that decreased levels of miRNA-212 has been related with more cocaine consumption and higher risk for cocaine addiction, our data suggest that miRNA-212 expression in the PFC during adolescence could play an important role in the maternal separation effects on cocaine-induced CPP.

Disclosures: **T.W. Viola:** None. **L. Wearick-Silva:** None. **L.A. Azeredo:** None. **F. Garcia:** None. **T.W. Bredy:** None. **R. Grassi-Oliveira:** None.

Nanosymposium

375. Persistent Effects of Early Life Adversity

Location: S404

Time: Monday, October 19, 2015, 1:00 PM - 4:30 PM

Presentation Number: 375.14

Topic: E.05. Stress and the Brain

Support: NSERC Alexander-Graham-Bell Canada Graduate Scholarship (CGS-D)

NSERC Grant #493091

Title: Maternal programming of adult behavior and metabolism by prenatal predator odor exposure

Authors: ***S. ST-CYR**, S. ABUAISH, K. C. WELCH, Jr,, P. O. MCGOWAN;
Cell and Systems Biol., Univ. of Toronto, Scarborough, ON, Canada

Abstract: We investigated maternal programming of offspring phenotype using predator odor, a stressor that is evolutionarily and ecologically relevant to mice, uniform in its intensity, psychological and unconditioned. Pregnant mice dams were exposed to 3 different predator odors daily or distilled water (control) over the second half of their pregnancy when the fetal stress axis is developing. We previously showed increased behavioral aversiveness (anti-predatory behavior) and increased corticosterone responsivity to predator odor in prenatally predator odor exposed offspring, especially in females. Furthermore, we showed that these changes in females were associated with increased Corticotropin-releasing hormone receptor 1 (CRHR1) expression in the amygdala and decreased Brain-derived neurotrophic factor (BDNF) expression in the hippocampus. Increased hippocampal BDNF expression among prenatally-exposed female offspring was correlated with levels of *Bdnf* exon *IV* methylation, suggesting an epigenetic basis for the shaping of the adult offspring phenotype following prenatal exposure to predator odor. In the current study, adult mice were prenatally exposed to predator odor to assess its impact on anxiety-like behavior, social affiliation, growth and metabolic rate. First, the mice were exposed to a variety of stressors to examine whether anxiety-like behavior in the adult offspring adjusts in response to the type or strength of the stressor applied. Second, we submitted our new cohort to a social recognition test to examine social affiliation. Third, growth, activity levels and metabolic rate recordings over 24 hours were used to examine metabolic differences. Our preliminary data indicate that the phenotype of the adult offspring prenatally exposed to

predator odor include modulation of the anxiety-like behavior, increased social affiliation and higher metabolic rate.

Disclosures: **S. St-Cyr:** None. **S. Abuaish:** None. **K.C. Welch:** None. **P.O. McGowan:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.01

Topic: F.01. Human Cognition and Behavior

Support: UK Economic and Social research council postgraduate funding

Royal Society Wolfson Research Merit Award

NIH R01 MH 081990

Title: Cortical reading and picture comprehension extensively overlaps sensory-motor maps

Authors: ***M. I. SERENO**[1,2], M. SOOD[3];
[1]Cognitive Sci., Univ. Calif San Diego, La Jolla, CA; [2]Exptl. Psychology, Univ. Col. London, London, United Kingdom; [3]Psychological Sci., Birkbeck Col. Univ. London, London, United Kingdom

Abstract: Two decades of neuroimaging research have provided ample evidence that language processing extends beyond the classical frontotemporal regions in left hemisphere. In parallel, cortical mapping techniques using fMRI have been instrumental in identifying primary and higher-level sensory-motor maps in humans. In this study, we provide a quantitative estimate of overlap between cortical regions involved in reading comprehension and those that have a sensory or motor map. Using the latest advances in surface-based cortical mapping methods, we first obtained a complete set of visual, auditory, and somatomotor maps for each subject across multiple scanning sessions. Then, within the same group of subjects, we used a language comprehension task where subjects made naturalistic but controlled saccades (by occluding all but one word at a time with a gray rectangle) to read interesting and coherent 64-word passages. We were then able to directly measure the overlap between naturalistic reading comprehension and all sensory-motor maps. The data comes from nearly 80 individual sessions of fMRI on 20 subjects and has been analyzed using a cortical surface based stream from start to finish. Our results suggest that nearly 80% of the activation in the left hemisphere specific to language understanding falls within cortical areas containing topological sensory-motor maps. The same

participants then participated in a picture-story comprehension task, where they viewed a series of pictures that told a coherent story (no text captions of any kind). Saccades by participants across each single- or multi-frame picture frame were controlled by 'saccading' a transparent Gaussian 'bubble'-style mask (at 1 Hz) to relevant points in the images chosen by offline comprehension testing. Initial data collected for picture-story task indicates that the pattern of activation for comprehension here is centered around the same occipital, temporal and frontal regions as in reading comprehension. The substantial overlap between areas containing sensory and motor maps, and areas involved in reading comprehension and the similarities with picture based comprehension suggest that language comprehension is not as isolated from other brain functions as has sometimes been suggested, but instead has been built in substantial part upon a mosaic of areas, many similar to those known from non-human primates.

Disclosures: M.I. Sereno: None. **M. Sood:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.02

Topic: F.01. Human Cognition and Behavior

Support: Welcome Trust (093957)

MRC (WMCR_P39389)

Title: Network dysfunction predicts speech production after left-hemisphere stroke

Authors: *F. GERANMAYEH, R. LEECH, R. J. S. WISE;
Imperial Col. London, London, United Kingdom

Abstract: Objective: Recovery after a stroke resulting in aphasia is often discussed in terms of intact ipsilesional or contralesional regions ‘taking over’ the lost domain-specific functions. However, domain-general processes, mediated by multiple distributed brain networks, also have a role.[1,2] These include the default mode (DM), fronto-temporo-parietal (FTP) and cingulo-opercular (CingOper) networks. **Methods:** This functional MRI study, investigated the effects of a previous left hemisphere stroke on functional connectivity both within and between these networks, as patients described pictures (Speech). Fifty-two patients and 24 age-matched controls were recruited. Data were acquired during overt speech production (Speech) as participants described objects and performed several baseline tasks; counting (Count), a visual

non-verbal decision task (Decision) and a Rest baseline. The relative activity between the DM network and each of the CingOper, left and right FTP networks was calculated during Speech. These were entered into a hierarchical multiple regression model in order to identify functional imaging predictors of speech production. The functional connectivity between the networks was assessed. **Results:** The patients showed a significant reduction in performance on several measures of speech production ($P < 0.005$). Although activity within individual networks was not predictive of speech production, the relative activity between networks was a predictor of both within-scanner and out-of-scanner language performance, over and above that predicted from lesion volume and other demographic factors (age, sex, years of education). Specifically, the robust functional imaging predictors were the differential activity between the default mode network and both the left (standardized beta = 0.54, $P < 0.001$) and right (standardized beta = 0.49, $P = 0.001$) fronto-temporo-parietal networks, respectively activated and deactivated during speech. The between-network functional connectivity of these networks was also altered in patients. **Conclusions:** The demonstration that speech production is dependent on complex interactions between widely distributed brain networks, indicates that recovery depends on more than the restoration of local domain-specific functions. The systems neuroscience of recovery of function after focal lesions is not adequately captured by notions of brain regions 'taking over' lost domain specific functions, but is best considered as the interaction between what remains of domain-specific networks and the domain-general systems that regulate behavior. 1.Fedorenko. rends Cogn Sci.2014 2.Geranmayeh. Brain. 2014.

Disclosures: F. Geranmayeh: None. **R. Leech:** None. **R.J.S. Wise:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.03

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R00 HD065839

Title: Using lexical semantic ambiguity to distinguish information-specific from domain-general processing

Authors: *W. W. GRAVES, S. R. SMOLIN, E. J. ALEXANDER;
Psychology, Rutgers Univ., Newark, NJ

Abstract: Word recognition usually involves processing word meanings, yet it is unclear whether the neural basis of meaning search and retrieval is distinct from semantic feature storage. We elicited word recognition using lexical decision: participants indicated whether a letter string was a word. Words varied in meaning relatedness: words with multiple unrelated meanings (bank) are thought to elicit greater semantic search and retrieval processes compared to words with related meanings (paper). This was crossed with imageability: highly imageable words have richer semantic feature representations compared to less imageable words. A second hypothesis was neural effects of these variables would differ depending on similarity of the nonword background to the words. Foils were either pronounceable nonwords (pseudowords, PW, brab) or pseudohomophones (PH, karv). Words and nonwords may differently engage task-positive or default-mode networks, depending on level of stimulus discriminability. With PW foils, low- vs. high-imageability words activated areas found in meta-analyses to be associated with semantics, including bilateral posterior cingulate (PC), dorso-medial prefrontal cortex, and left middle temporal gyrus. A very different pattern was seen for this contrast with PH foils: activation was limited to left orbital inferior frontal gyrus, and right inferior temporal gyrus. Relatedness showed no activation against a PW background, but low- vs. high-relatedness words with PH foils showed activation in left angular gyrus (AG). Thus, imageability is associated with activation in semantic areas when lexical decisions can be made using semantic information alone, but relatedness is associated with activation in semantic regions when lexical decisions require more detailed search. The lexicality contrast (words - nonwords) showed activation for words in task-positive network areas: inferior frontal junction, intraparietal sulcus, and ventral occipitotemporal sulcus (vOT); whereas nonwords activated resting-state or putative semantic regions such as AG and PC. An interaction of lexicality with nonword type was significant, including left AG and PC for (words - PW) > (words - PH), and the opposite pattern in vOT. That is, lexicality contrasts with more semantic content but also more difficult discrimination led to less activation in AG and PC, and more activation in vOT. This supports the second hypothesis: areas previously interpreted as supporting semantic processing are instead responding to domain-general processing demands. Overall, this study clarifies conditions where information-specific and domain general effects co-occur.

Disclosures: W.W. Graves: None. **S.R. Smolin:** None. **E.J. Alexander:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.04

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant AG017586

IARPA, Knowledge Representation in Neural Systems

Title: Assessing the information content of semantic processing areas using sparse canonical correlation analysis

Authors: *J. S. PHILLIPS[1], J. SEDOC[2], S. TUBRIDY[4], A. T. VU[5], M. E. PHILLIPS[6], R. BHATTACHARYYA[6], T. M. GURECKIS[4], L. UNGAR[2], M. GROSSMAN[1], B. B. AVANTS[3]; [1]Neurol., [2]Computer and Information Sci., [3]Radiology, Univ. of Pennsylvania, Philadelphia, PA; [4]Psychology, New York Univ., New York, NY; [5]Radiology, Univ. of Minnesota, Minneapolis, MN; [6]HRL Laboratories, LLC, Malibu, CA

Abstract: Sentence comprehension requires the integration of multiple concepts into a meaningful proposition. However, the anatomical basis of this integration is unclear: some theories attribute it to amodal representations in the anterior temporal lobe (ATL), while other theories propose that semantic integration depends on modality-specific representations represented in perceptual-motor cortices and heteromodal association areas (HAAs) such as the angular gyrus (AG). Sentence comprehension additionally involves a core language network of left-lateralized peri-Sylvian inferior frontal cortices. We used functional magnetic resonance imaging (fMRI), multivariate statistical methods, and neural decoding to determine which subset of brain areas provided a sufficient basis for modeling sentence comprehension. The stimulus set comprised 240 simple, declarative English sentences, presented an average of 15 times each over multiple fMRI sessions. The study design maximized within-subject statistical power (average of 6 hours of fMRI data per subject). Participants (n=3) read sentences silently in the scanner and answered yes/no questions about them. Sparse canonical correlation analysis (SCCA) was used to map neuroanatomical and semantic features to a low-dimensional feature space for each participant. The resulting model was then used to decode brain activity in held-out test data. We performed SCCA with 3 sets of anatomical priors to determine the minimal set necessary for accurate decoding. The first set comprised bilateral ATL; accurate decoding with this set would not rule out the involvement of other regions in sentence comprehension, but would establish that ATL contained sufficient information for representing target sentences. The second set comprised HAAs in posterior superior temporal and inferior parietal cortices, and the third set comprised the core language network, testing the possibility that syntactic processing in the language network was necessary to inform semantic integration in ATL. Decoding accuracy moderately exceeded chance in ATL and AG, suggesting that each set of regions contained partial semantic information. Optimal decoding accuracy was achieved by combining ATL, AG, and the core language network into a single prior set.

Disclosures: **J.S. Phillips:** None. **J. Sedoc:** None. **S. Tubridy:** None. **A.T. Vu:** None. **M.E. Phillips:** None. **R. Bhattacharyya:** None. **T.M. Gureckis:** None. **L. Ungar:** None. **M. Grossman:** None. **B.B. Avants:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.05

Topic: F.01. Human Cognition and Behavior

Title: Cross-modal representation of spoken and written word meaning in anterodorsal pars triangularis

Authors: ***A. G. LIUZZI**[1], R. BRUFFAERTS[1], P. DUPONT[1], K. ADAMCZUK[1], R. PEETERS[2], S. DE DEYNE[4], G. STORMS[4], R. VANDENBERGHE[5,3];
[1]KU Leuven / Lab. For Cognitive Neurol., Leuven, Belgium; [2]Radiology, [3]Neurol., Univ. Hosp. Leuven, Leuven, Belgium; [4]Lab. of Exptl. Psychology, Leuven, Belgium; [5]Lab. for Cognitive Neurol., Leuven, Belgium

Abstract: INTRODUCTION: For years the commonalities underlying the semantic processing of different input-modalities has been studied by means of univariate analysis but nowadays Representation Similarity Analysis (RSA) provides a new opportunity to better understand the nature of such common processes. In two event-related fMRI experiments we searched for regions with activity patterns reflecting a cross-modal semantic similarity effects between written and spoken word modality. METHODS: 18 and 20 healthy subjects participated in the first and second experiment respectively. 24 concrete nouns were used which refer to animals. Based on a feature generation experiment conducted by De Deyne et al. (2008), the pairwise semantic cosine similarity was calculated for each pair of items (semantic cossimilarity matrix). During fMRI subjects performed a property verification task in spoken and written modality. The fMRI data of the first experiment were modelled using a General Linear Model (GLM). Clusters showing a significant main effect of task in the first experiment were used as VOI in the second experiment. The cosine similarity matrix based on fMRI data of the second experiment was generated by calculating the pairwise cosine similarity between every pair of cross-modal trials (cross-modal cossimilarity matrix). Finally we conducted the RSA between the semantic cossimilarity matrix and the cross-modal cossimilarity matrix. RESULTS: The main effect of task (uncorrected $p<0.001$ combined with a cluster-level corrected $p<0.05$) yielded 7 clusters: left ventral occipitotemporal transition zone (vOT), left ventromedial temporal cortex,

retrosplenial cortex, pars orbitalis bilaterally, left anterodorsal pars triangularis and frontal pole. The left anterodorsal pars triangularis showed a significant effect of semantic similarity cross-modally: activity patterns were more similar for word pairs that were more semantically similar, even though the words were presented in two different modalities (Cosine Similarity (CS) = 0.029, P = 0.0004). When the RSA was conducted between the semantic cossimilarity matrix and the cossimilarity matrix based on fMRI data generated by calculating the pairwise cosine similarity between every pair of trials belonging to the written input-modality (written cossimilarity matrix), 3 clusters showed a significant semantic similarity effect: vOT (CS = 0.933, P = 0.008), left ventromedial temporal cortex (CS = 0.879, P=0.008) and left pars orbitalis (CS = 0.138, P = 0.027). CONCLUSIONS: The cross-modal effect confirms the role of anterodorsal pars triangularis in amodal semantic processing.

Disclosures: **A.G. Liuzzi:** None. **R. Bruffaerts:** None. **P. Dupont:** None. **K. Adamczuk:** None. **R. Peeters:** None. **S. De Deyne:** None. **G. Storms:** None. **R. Vandenberghe:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.06

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant AG017586

NIH Grant 5T32AG000255

Title: Neural mechanisms for object semantics: fine-grained feature statistics for object representation

Authors: ***A. R. PRICE**[1], M. BONNER[1], J. PEELLE[2], M. GROSSMAN[1];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Washington Univ. in St. Louis, St. Louis, MO

Abstract: Based on our experience in the world, we store conceptual information about the objects in our environment and the features that define them. Many studies have examined how object knowledge is distributed in the brain by examining the neural representation of categories of objects. However, little is known about the visual mechanisms that encode the semantic attributes of specific objects within a category. For example, how do we know that a red apple is similar in meaning to a green apple but not to a blue apple? Here, we address this question by examining the neural coding of feature statistics and object meaning in the real world. In an

fMRI experiment, 16 subjects viewed images that were systematically manipulated in color and shape information while they performed an unrelated object detection task. The stimuli included three different conceptual categories (apples, leaves, and roses). They were each combined with five different colors (red, pink, blue, green, and yellow) to sample a range of co-occurrence statistics across the objects (Fig A). This co-occurrence metric was used to build a semantic similarity model within each object (Fig B). Using representational similarity analysis, we identified regions where patterns of neural activity were correlated with this semantic similarity model for each object category (Fig B). We found that perirhinal cortex, a region at the highest level of the ventral visual system, encodes abstract feature statistics that underlie semantic representations within each category (Fig C, $p<0.01$). In contrast, more posterior regions such as early visual cortex, lateral-occipital complex, inferior-temporal cortex, and V4 encode the individual features of shape and color but not the co-occurrence statistics of these feature conjunctions. These findings reveal a cortical mechanism for the coding of high-level visual statistics in perirhinal cortex. The visual codes in this region could support both abstract semantic inference and the fine-grained differentiation of items within a category.

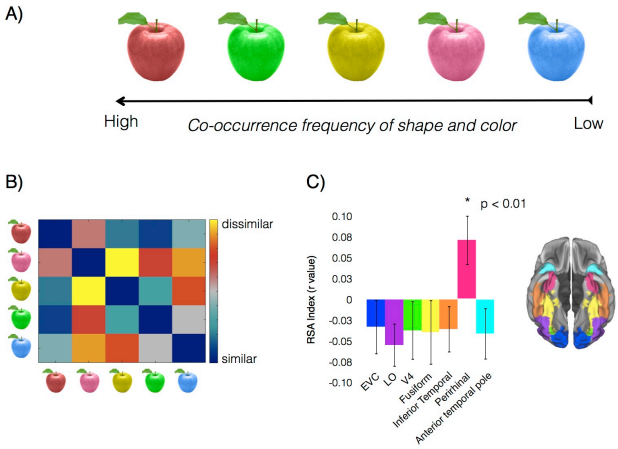


Figure (A) Example color combinations for the example object "apple", arranged from highest to lowest co-occurrence frequency. For each set of combinations the shape of the object concept was the same, only the color was changed. The co-occurrence frequencies were based on a text-based measure from a large lexical corpus from Google. A separate norming study demonstrated that this metric was strongly correlated with subjective ratings of semantic similarity. **(B)** An example of the model representational dissimilarity matrix for the category "apple." This model predicts that "red apple" and "green apple" would have highly similar neural representations, whereas "red apple" and "pink apple" would be dissimilar. Importantly, the co-occurrence of object and color information was always independent of the frequencies of each feature alone (i.e., shape and color). Additionally, each object concept in the experiment had a unique semantic similarity matrix. These high-level relationships are hypothesized to be represented in regions that encode high-level combinatorial information about object knowledge, while more posterior regions like V4 and lateral occipital complex (LOC) encode individual features, such as color and shape. **(C)** Perirhinal cortex was the only region of interest along the ventral visual stream that showed a correlation with with the semantic model of feature combinations across all objects (*$p < 0.01$). Bar colors correspond to colored brain regions of interest.

Disclosures: **A.R. Price:** None. **M. Bonner:** None. **J. Peelle:** None. **M. Grossman:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.07

Topic: F.01. Human Cognition and Behavior

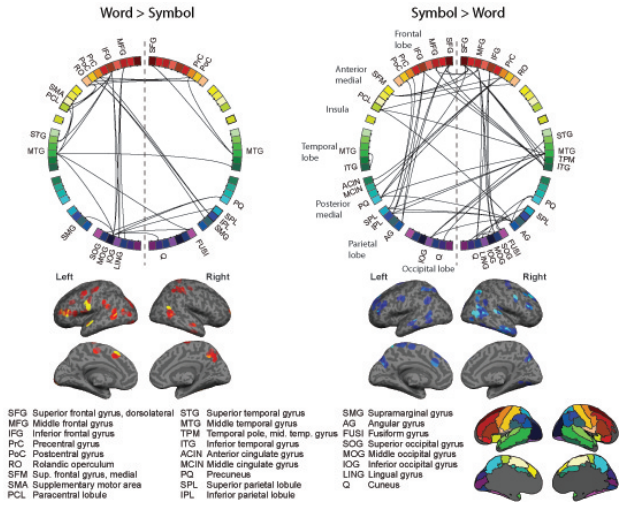
Support: Academy of Finland

BRAHE

Title: Large-scale functional networks connect differently for processing words and symbol strings

Authors: *M. LILJESTRÖM[1], J. VARTIAINEN[2], J. KUJALA[1], R. SALMELIN[1];
[2]Dept. of Neurosci. and Biomed. Engin., [1]Aalto Univ., Espoo, Finland

Abstract: Large-scale cortical networks are thought to support the dynamic integration of information across functionally specialized brain regions. We recorded magnetoencephalography (MEG) data from 15 participants performing a one-back task on written words or symbol strings (Vartiainen, Liljeström, Koskinen, Renvall, Salmelin, J Neurosci 31:1048-58, 2011). Modulations in coherence between cortical regions following stimulus presentation (50-800 ms) were determined by contrasting spatial filtering results for words and symbols ($p<0.05$, FWE corrected) in pre-specified frequency bands between 3 and 90 Hz (Liljeström, Kujala, Stevenson, Salmelin, Hum Brain Mapp 36:1202-16, 2015), and visualized in a circular diagram with nodes based on an anatomical parcellation scheme (see Figure). Whole-cortex mapping of coherence revealed spectrally and spatially distinct connectivity patterns for words and symbols. For words, increased coherence was detected mainly in alpha (8-13 Hz) and high gamma (60-90 Hz) frequency bands, but for symbol strings in the low gamma (30-45 Hz) range. Word reading enhanced coherence in a left-lateralized network with nodes in classical language regions: left inferior frontal, middle/superior temporal, and occipito-temporal cortex (see Figure, Word>Symbol, summary network across frequencies). The bilateral network recruited when processing symbols (see Figure, Symbol>Word) included fronto-parietal connections, typically associated with directing spatial attention and visual working memory. The left frontal cortex was a major part of both networks, but with different connectivity patterns for the two stimulus types. The spatial distribution of the network nodes agrees well with existing activation- and lesion-based views of language and visual recognition. The present study demonstrates the formation of task-relevant, frequency-resolved large-scale network patterns driven by input stimulus, and provides novel evidence that global functional networks are dynamically modulated by task or stimulus to support goal-directed behavior.



Disclosures: **M. Liljeström:** None. **J. Vartiainen:** None. **J. Kujala:** None. **R. Salmelin:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.08

Topic: F.01. Human Cognition and Behavior

Title: The effect of literacy acquisition on cortical and subcortical networks: A longitudinal approach

Authors: ***F. EISNER**[1], U. KUMAR[2], R. K. MISHRA[3], V. N. TRIPATHI[4], A. GULERIA[2], J. P. SINGH[5], F. HUETTIG[6];
[1]Donders Inst. for Brain, Cognition, and Behaviour, Radboud Univ., Nijmegen, Netherlands; [2]Ctr. of Biomed. Res. (CBMR), Sanjay Gandhi Postgraduate Inst. of Med. Sci. Campus, Lucknow, India; [3]Ctr. for Neural and Cognitive Sci., Univ. of Hyderabad, Hyderabad, India; [4]Dept. of Psychology, [5]Ctr. of Behavioural and Cognitive Sci., Univ. of Allahabad, Allahabad, India; [6]Psychology of Language, Max Planck Inst. for Psycholinguistics, Nijmegen, Netherlands

Abstract: How do human cultural inventions such as reading result in neural re-organization? Previous cross-sectional studies have reported extensive effects of literacy on the neural systems for vision and language (Dehaene et al [2010, Science], Castro-Caldas et al [1998, Brain], Petersson et al [1998, NeuroImage], Carreiras et al [2009, Nature]). In this first longitudinal study with completely illiterate participants, we measured brain responses to speech, text, and other categories of visual stimuli with fMRI before and after a group of illiterate participants in

India completed a literacy training program in which they learned to read and write Devanagari script. A literate and an illiterate no-training control group were matched to the training group in terms of socioeconomic background and were recruited from the same societal community in two villages of a rural area near Lucknow, India. This design permitted investigating effects of literacy cross-sectionally across groups before training (N=86) as well as longitudinally (training group N=25). The two analysis approaches yielded converging results: Literacy was associated with enhanced, mainly left-lateralized responses to written text along the ventral stream (including lingual gyrus, fusiform gyrus, and parahippocampal gyrus), dorsal stream (intraparietal sulcus), and (pre-) motor systems (pre-central sulcus, supplementary motor area), thalamus (pulvinar), and cerebellum. Significantly reduced responses were observed bilaterally in the superior parietal lobe (precuneus) and in the right angular gyrus. These positive effects corroborate and extend previous findings from cross-sectional studies. However, effects of literacy were specific to written text and (to a lesser extent) to false fonts. Contrary to previous research, we found no direct evidence of literacy affecting the processing of other types of visual stimuli such as faces, tools, houses, and checkerboards. Furthermore, unlike in some previous studies, we did not find any evidence for effects of literacy on responses in the auditory cortex in our Hindi-speaking participants. We conclude that learning to read has a specific and extensive effect on the processing of written text along the visual pathways, including low-level thalamic nuclei, high-level systems in the intraparietal sulcus and the fusiform gyrus, and motor areas. The absence of an effect of literacy on responses in the auditory cortex in particular raises questions about the extent to which phonological representations in the auditory cortex are altered by literacy acquisition or recruited online during reading.

Disclosures: **F. Eisner:** None. **U. Kumar:** None. **R.K. Mishra:** None. **V.N. Tripathi:** None. **A. Guleria:** None. **J.P. Singh:** None. **F. Huettig:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.09

Topic: F.01. Human Cognition and Behavior

Support: National Institute of Neurological Diseases and Stroke grant R01 NS33576

National Institutes of Health General Clinical Research Center grant M01 RR00058

National Institute of General Medical Sciences grant T32 GM89586

Title: Decoding conceptual information from heteromodal cortex

Authors: *L. FERNANDINO[1], C. J. HUMPHRIES[1], M. S. SEIDENBERG[3], W. L. GROSS[2], L. L. CONANT[1], J. R. BINDER[1];
[1]Neurol., [2]Anesthesiol., Med. Col. of Wisconsin, Milwaukee, WI; [3]Psychology, Univ. of Wisconsin, Madison, WI

Abstract: Neuroimaging studies have implicated a network of heteromodal cortical areas in conceptual processing, but the role of this "general semantic network" (GSN) is not well understood. We propose that at least a subset of the GSN contributes to conceptual processing by encoding patterns of co-activation over modality-specific cortices. In other words, these areas may function as convergence-divergence zones, integrating sensory-motor information from multiple modalities during perception/action and coordinating the reactivation of sensory-motor areas during concept retrieval. Alternatively, the GSN could encode exclusively abstract conceptual representations whose informational structure bears no direct relation with sensory-motor representations. We investigated this hypothesis using predictive machine learning on the fMRI data from Fernandino et al. (2015), in which participants performed a concreteness decision task on a set of 900 written English words and 300 pseudowords. In the present study, we predicted fMRI activation patterns for individual words using an encoding semantic model based on the relative relevance of five semantic attributes - all directly related to sensory-motor processes - to the meaning of the word: sound, color, shape, manipulability, and visual motion. The model was trained via multiple regression on a set of 820 words, and tested on a separate set of 80 words. Model performance was evaluated separately in voxels located in the GSN (according to the ALE meta-analysis from Binder et al., 2009) and in voxels located in control regions (defined by the contrast pseudoword > word). The semantic model was able to successfully decode activation patterns associated with individual words from voxels in the GSN ($p = .004$), but not from voxels in control regions. Follow-up analyses determined that GSN areas in the lateral temporoparietal cortex provided the highest decoding accuracy. Conversely, a different model based on five word-form attributes (length, neighborhood and bigram statistics) was able to decode neural activity in control areas, particularly from voxels in early visual cortex ($p = .001$), but not from GSN voxels. These results demonstrate that semantic information encoded in temporoparietal heteromodal areas during concept retrieval is directly related to sensory-motor attributes of experience, consistent with a role for these areas in coordinating the reactivation of sensory-motor representations in modality-specific cortices. References Binder, J. et al. (2009) Cereb. Cortex, 19 (12), pp. 2767-2796 . doi:10.1093/cercor/bhp055 Fernandino, L. et al. (2015). Cereb. Cortex. doi:10.1093/cercor/bhv020

Disclosures: L. Fernandino: None. **C.J. Humphries:** None. **M.S. Seidenberg:** None. **W.L. Gross:** None. **L.L. Conant:** None. **J.R. Binder:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.10

Topic: F.01. Human Cognition and Behavior

Title: An algebraic architecture for semantic composition in left-mid superior temporal cortex: defining the variables and interpreting the code

Authors: S. M. FRANKLAND, *J. D. GREENE;
Harvard Univ., Cambridge, MA

Abstract: Human brains flexibly combine the meanings of words (e.g. “bite”, “dog”, and “man”) to form more complex, structured ideas (e.g. of a dog biting a man or a man biting a dog). Recent research has identified distinct regions of the left-mid Superior Temporal Cortex (lmSTC) that represent two abstract semantic role variables: the agent (“who did it?”) and the patient (“to whom was it done?”) (Frankland & Greene, under review). Agent information is represented in a medial region of superior temporal sulcus, while an adjacent, lateral region of superior temporal gyrus encodes patient information. These neighboring regions represent the fluctuating values of these semantic variables using patterns of activity that are reused across sentences. This variable/value representational architecture is thus analogous to that of algebraic expressions (Marcus, 2001). Here, we extend this work in two ways: First, we study the semantic roles of a different class of verbs, known as psychological verbs (e.g., “frightened”/“noticed”) as a means to understanding the broader semantic structure of event representations. Psych verbs have different semantic roles from agent and patient, called the “experiencer” (e.g., “who noticed”?) and the “stimulus” (e.g., “what was noticed?”). Psych verbs are unique in that the experiencer may be realized as the subject (“Jane noticed that⋯”) or the direct object (“⋯frightened Jane.”). This allows us to dissociate a sentence’s grammatical relations from the semantic relations of the event described. We find that a medial portion of lmSTC treats the agent and stimulus variables identically, while a lateral region treats the patient and experiencer identically. The patterns of activity within these regions are invariant to the syntactic position of the experiencer/stimulus semantic roles in the sentence. These results are consistent with the lmSTC’s composing structured representations of events based on their causal or temporal structure. Second, we investigate the similarity structure of noun representations in these sub-regions: Do these patterns encode phonological similarity relationships (“hog” is like “hawk”), semantic similarity relationships (“hog” is like “pig”), or neither? The answer appears to be neither. We can, however, identify other regions that represent phonological and semantic similarity relationships, indicating that our methods are adequate to detect such patterns. These findings are consistent with the hypothesis that lmSTC uses efficient, compressed codes for

representing the fluctuating values of semantic variables. Such codes may serve as pointers to richer semantic representations elsewhere in cortex.

Disclosures: S.M. Frankland: None. **J.D. Greene:** None.

Nanosymposium

376. Neuroimaging of Language

Location: N227

Time: Monday, October 19, 2015, 1:00 PM - 3:45 PM

Presentation Number: 376.11

Topic: F.01. Human Cognition and Behavior

Title: Face information is dynamically incorporated into transmission and receptive language processes during interpersonal communication

Authors: *J. HIRSCH[1,2,3,4], A. NOAH[1], X. ZHANG[1], S. YAHIL[1], J. PARK[1], D. RODRIGUEZ MORENO[1];
[1]Dept. of Psychiatry, [2]Neurobio., [3]Comparative Med., Yale Sch. of Med., New Haven, CT; [4]Biomed. Engin., Univ. Col. London, London, United Kingdom

Abstract: Social interaction and direct communication between two or more individuals are fundamental human functions that can be investigated with simultaneous recordings of BOLD signals from two interacting individuals using near-infrared spectroscopy (NIRS). We have previously shown cross-brain coherence between Wernicke's and Broca's Areas during interpersonal interactions associated with dialogue [1], suggesting a mechanism for interactive communication that involves dynamic modulation of processes specialized for reception (Wernicke's Area) and transmission (Broca's Area) across brains. In this study we test the hypothesis that face information is dynamically incorporated into this receptive/transmission system during interactive communication. If so, then findings would be supportive of a mechanism whereby facial and spoken information are integrated within the canonical language system. BOLD signals were acquired at a temporal resolution of 33 msec with a spatial resolution of 3 cm using a Shimadzu LabNIRS system. Dyads of 34 subjects participated in 15 sec alternating epochs of talking and listening during either face-to-face or face-occluded conditions. Wavelet analysis [2] was used to quantify coherence between two brains for all pairs of cross-brain regions. Coherence during face-to-face conditions exceeded coherence during face-occluded conditions ($p<0.005$) for two pairs of cross-brain regions: [Fusiform Gyrus - DLPFC] at a wavelength of 4.2 secs, and [DLPFC - Broca's Area] at a wavelength of 8.5 secs. Face processing (Fusiform Gyrus) covaried with verbal transmission mechanisms (Broca's Area) via an intermediate stage involving DLPFC consistent with integration of facial input with

transmission and receptive communication functions. Further, the synchronous exchange of facial information between two individuals occurred more often (shorter wavelength) than the synchronous exchange of verbal information. The relatively frequent face-related processes embedded into the canonical language system during interactive conversation suggest "real-time" information-updating functions based on facial cues. 1. Hirsch, et al.2014 Neural specialization for interpersonal communication. SFN no5914 (204.13). 2. Torrence and Compo 1998 A practical guide to wavelet analysis. Bull of the Am Meteorological Soc, 79,1,61-78.

Disclosures: **J. Hirsch:** None. **A. Noah:** None. **X. Zhang:** None. **S. Yahil:** None. **J. Park:** None. **D. Rodriguez Moreno:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.01

Topic: F.02. Animal Cognition and Behavior

Support: AG028488

Title: Over-expression of the L-type voltage-gated calcium channel $Ca_V1.3$ mimics age-related changes in cognition and neuronal dysfunction

Authors: ***G. G. MURPHY**[1], S. MOORE[2], J. KRUGER[2];
[1]MBNI/Physiology, [2]MBNI, Univ. of Michigan, Ann Arbor, MI

Abstract: Under normal circumstances, neurons in the mammalian nervous system exhibit a remarkable capacity to maintain nominal levels of intracellular calcium. There is considerable evidence suggesting that calcium homeostasis becomes dysregulated during aging and calcium dysregulation has been implicated as a feature of Alzheimer's disease. Previous work in rodent models has shown that aging is associated with an up-regulation of L-type voltage-gated calcium channels (LVGCCs) and that this increase is correlated with age-related memory impairments in hippocampus-dependent learning and memory tasks. We have generated a novel transgenic mouse line in which the αCamKII promotor drives exogenous expression of an HA-tagged subtype of LVGCCs ($Ca_V1.3$) to directly examine the relative contribution of increased LVGCCs to cognitive and neuronal function. Over-expression of $Ca_V1.3$ results in cognitive impairments that are similar to, but less severe than, those observed in aged mice. In addition, recordings made from pyramidal neurons in the CA1 region of the hippocampus reveal that the $Ca_V1.3$ over-expressing mice exhibit an enhanced slow afterhyperpolarization (sAHP) similar to that

observed in aged mice. Taken together, our results suggest that an age-dependent up-regulation of the LVGCC $Ca_V1.3$ contributes to cognitive deficits in learning and memory and thus may represent a novel therapeutic target for the amelioration of age-related cognitive decline.

Disclosures: G.G. Murphy: None. **S. Moore:** None. **J. Kruger:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.02

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant AG039511

AFAR Grant RAG14141

Title: Cell-type specific changes in TrpC3 expression are associated with memory decline in a model of Alzheimer's disease

Authors: *C. C. KACZOROWSKI[1], K. A. HOPE[1], L. A. WILMOTT[1], K. M. S. O'CONNELL[2], S. C. CHAN[3], S. M. NEUNER[1];
[1]Dept. Anat. and Neurobio., [2]Dept. Physiol., Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [3]Physiol., Northwestern Fienberg Sch. of Med., Chicago, IL

Abstract: Memory deficits in Alzheimer's Disease (AD), the leading cause of age-related dementia, differ in some ways from those associated with 'normal' aging. AD memory deficits are more severe, devastate multiple cognitive domains, and coincide with distinct neuropathologies. Despite these differences, similarities in hippocampus-dependent memory deficits in aging humans and AD patients suggest a common mechanism. Therefore, mechanisms driving 'normal' aging-related memory impairments might provide a feasible target for early intervention against AD. To this point, recent work from our laboratory demonstrated that the transient receptor potential cation channel C3 (TRPC3) is enriched in hippocampal neurons of aging mice with impaired memory. This upregulation of TRPC3 contributes to a decrease in neuronal excitability, thereby providing a mechanistic explanation for memory deficits in 'normal' aging models. Given some evidence that 'normal' aging and AD may share common mechanism(s), we hypothesized that TRPC3 expression would be enriched in hippocampal neurons in AD models. Immunocytochemistry confirmed that TRPC3 is upregulated in AD hippocampus; however, TRPC3 is predominantly expressed in reactive astrocytes located in

areas undergoing neurodegeneration. To test the functional significance of this upregulation, targeted intrahippocampal knockdown of Trpc3 using AAV9-shRNA was performed on presymptomatic male 5XFAD mice (4 mo). Working memory was tested at 9 mo using the Y-maze test of spontaneous alternations. Trpc3 knockdown was sufficient to attenuate memory deficits typically seen in this model (Ctrl = 45.3 ± 5.51%, TRPC3 KD = 58.2 ± 3.51%, p=0.04). Both groups displayed a similar number of total arm entries and traveled the same total distance, confirming that differences observed were not due to gross changes in motor function. As we show TRPC3 is also significantly enriched in the hippocampus of human AD patients relative to age-matched non-demented controls, therapeutics designed to reduce expression and/or function of TRPC3 early in the disease process may prove useful in slowing the onset of cognitive decline in human populations. Future work will examine the exact mechanism of this upregulation of TRPC3 in reactive astrocytes in AD and whether it is a cause or consequence of AD-related neurodegeneration.

Disclosures: **C.C. Kaczorowski:** None. **K.A. Hope:** None. **L.A. Wilmott:** None. **K.M.S. O'Connell:** None. **S.C. Chan:** None. **S.M. Neuner:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.03

Topic: F.02. Animal Cognition and Behavior

Support: NIH

Mitchell Center for Neurodegenerative Diseases

Mohn Foundation

Title: Context discrimination in Alzheimer’s disease model mice reveals adult-neurogenesis mechanism

Authors: *D. CORTEZ[1,2,3,4], L. DENNER[1,5,4], K. T. DINELEY[1,6,3,4,2];
[2]Ctr. for Addiction Res., [3]Neurosci. and Cell Biol., [4]Mitchell Ctr. for Neurodegenerative Dis., [5]Intrnl. Medicine-Endocrinology, [6]Neurol., [1]UTMB, Galveston, TX

Abstract: The Tg2576 mouse model recapitulates early Alzheimer’s disease (AD) pathology including hippocampal cognitive deficits, Aβ oligomer accumulation, and central insulin resistance. The insulin-sensitizing drug and peroxisome proliferator activated receptor γ

(PPARγ) agonist, rosiglitazone (RSG), improves Tg2576 cognitive performance in hippocampus-dependent memory tasks. Context discrimination fear conditioning is a hippocampus-dependent learning and memory task designed to test an animal's ability to distinguish between two similar yet different environments in which context 'A' is paired with a foot shock and context 'B' is the safe context. Since adult-born neurons arising from neurogenesis within the dentate gyrus (DG) sub-granular zone are thought to be necessary for context discrimination and RSG restores DG mature/immature neuronal population ratios to wild type levels, we postulated that RSG-treated Tg2576 would perform better in a context discrimination task compared to untreated Tg2576 and wildtype mice. Interestingly, we found that untreated Tg2576 mice exhibited superior context discrimination compared to all other groups and RSG treatment improved wild type performance over that of untreated. Furthermore, RSG-treated Tg2576 context discrimination performance was equivalent to RSG-treated wildtype mice. Stages of adult-neurogenesis such as proliferation and differentiation are increased in human AD and AD mouse models, which may explain the superior context discrimination exhibited byTg2576. We postulate that improved context discrimination performance observed in untreated Tg2576 mice and RSG-treated groups is via distinct influences on adult-neurogenesis. We will use immunohistochemistry staining to quantify proliferation, differentiation and survival of adult born neurons to establish these mechanisms.

Disclosures: **D. Cortez:** None. **L. Denner:** None. **K.T. Dineley:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.04

Topic: F.02. Animal Cognition and Behavior

Support: VA Merit Award BX001638

NIH P50 AG033514

NIH GM103542

Thome Memorial Foundation

Title: Improved proteostasis in the secretory pathway rescues Alzheimer's disease but not Huntington's disease or Amyotrophic Lateral Sclerosis

Authors: *L. PUGLIELLI[1], Y. PENG[1], M. KIM[2], R. HULLINGER[1], K. J. O'RIORDAN[1], C. BURGER[1], M. PEHAR[2];
[1]Med. (Geriatrics & Gerontology), Univ. Wisconsin-Madison Med. Sch., Madison, WI; [2]Med. Univ. of South Carolina, Charleston, SC

Abstract: The aberrant accumulation of toxic protein aggregates is a key feature of aging as well as many neurodegenerative diseases, including Huntington disease (HD), amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD). As such, improving normal proteostatic mechanisms is an active target for biomedical research. Although they might share common pathological features, protein aggregates can form in different subcellular locations. Our group has recently reported that reduced acetylation of Atg9A in the lumen of the endoplasmic reticulum (ER) stimulates ERAD(II)/autophagy (J Biol Chem 2012; 287:29921; J Neurosci 2014; 34: 6772). ER acetylation requires a membrane transporter, SLC33A1/AT-1, that translocates acetyl-CoA from the cytosol into the lumen of the ER (J Cell Sci 2010;123:3378; J Neurosci 2014;34:6772), and two acetyltransferases, ATase1 and ATase2 (J Biol Chem 2009;284:2482; J Biol Chem 2012; 287:8424). Here, we used mouse embryo fibroblasts (MEF) with normal or reduced ER acetylation to study disposal of toxic protein aggregates that form in different cellular compartments. The results indicate that inhibition of the ER acetylation machinery specifically improves autophagy-mediated disposal of toxic protein aggregates that form within the secretory pathway but not those that form in the cytosol or nucleus. Consequently, genetic and biochemical inhibition of the ER acetylation machinery in the mouse rescued the AD, but not the HD or the ALS, phenotype. These results are consistent with the fact that the ER acetylation machinery is activated in an age-dependent fashion and is "hyperactive" in the brain of AD patients (J Biol Chem 2009;284:2482; J Cell Sci 2010;123:3378; J Biol Chem 2012;287:8424). In conclusion, our results support therapies targeting ER-specific acetyltransferases, ATase1 and ATase2, for a specific subset of chronic neurodegenerative diseases.

Disclosures: L. Puglielli: None. **Y. Peng:** None. **M. Kim:** None. **R. Hullinger:** None. **K.J. O'Riordan:** None. **C. Burger:** None. **M. Pehar:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.05

Topic: F.02. Animal Cognition and Behavior

Support: VA Merit Award BX001638

NIH P50 AG033514

NIH GM103542

Title: Interplay between APP, Delta40p53, and tau in the cognitive decline associated with aging and Alzheimer's disease

Authors: *M. PEHAR[1], M. LI[2], K. J. O'RIORDAN[3], C. BURGER[3], L. PUGLIELLI[2,4]; [1]Cell and Mol. Pharmacol., Med. Univ. of South Carolina, Charleston, SC; [2]Med., [3]Neurol., Univ. of Wisconsin-Madison, Madison, WI; [4]Geriatric Res. Educ. Clin. Ctr., VA Med. Ctr., Madison, WI

Abstract: The transcription factor p53, originally described as a tumor suppressor, has recently emerged as an important regulator of the aging process. p53 levels and activity are regulated by different post-translational modifications and by the differential expression of multiple isoforms. Delta40p53 (also referred to as p44) is a short isoform of p53 regulated in an age-dependent manner. When overexpressed in the mouse it causes a progeroid phenotype that includes premature cognitive decline, synaptic defects and hyperphosphorylation of tau (Genes Dev 2004;18:306-19; Aging Cell 2010; 9:174-90).The abnormal tau metabolism observed in p44 overexpressing mice was directly linked to altered p53 transcriptional activity caused by the imbalance in full length p53:p44 ratio (Aging Cell 2014; 13:449-56). Here, we show that the APP intracellular domain (AICD), which results from the processing of the amyloid precursor protein (APP), regulates translation of p44 through a cap-independent mechanism that requires direct binding to the second internal ribosome entry site (IRES) of the p53 mRNA. Moreover, haploinsufficiency of *Tp53* gene, which encodes all p53 isoforms, rescues the synaptic deficits of mice overexpressing APP ($APP_{695/swe}$). $APP_{695/swe}$ mice displayed tau hyperphosphorylation linked to an increased in the mRNA levels of Dyrk1A, GSK3β, p35, and p39. These changes in tau metabolism were prevented by *Tp53* haploinsufficiency. Our study reveals a novel aspect of AICD and p53/p44 biology and provides a possible molecular link between, APP, p44 and tau.

Disclosures: M. Pehar: None. **M. Li:** None. **K.J. O'Riordan:** None. **C. Burger:** None. **L. Puglielli:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.06

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant R00 AG039511

AFAR Grant RAG14141

Title: Systems genetics of 'normal' aging identifies novel candidates misregulated in Alzheimer's disease

Authors: *S. M. NEUNER[1], M. DE BOTH[4], B. GARFINKEL[5], J. INGELS[2], L. LU[2], L. WILMOTT[3], T. SHAPAKER[3], R. WILLIAMS[2], G. KEMPERMANN[6], J. ORLY[5], M. HUENTELMAN[4], C. KACZOROWSKI[3];
[2]Genetics, Genomics, and Informatics, [3]Anat. and Neurobio., [1]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [4]Neurogenomics Div., Translational Genet. Res. Inst., Phoenix, AZ; [5]Biol. Chemistry, The Alexander Silberman Inst. of Life Sci., The Hebrew Univ. of Jerusalem, Jerusalem, Israel; [6]Ctr. for Regenerative Therapies, Technische Univ. Dresden, Dresden, Germany

Abstract: 'Normal' age-associated cognitive decline is generally less severe than that seen in pathological dementias such as Alzheimer's disease (AD), and occurs in the absence of gross neuropathological changes. However, we recently identified several candidates that are known to confer risk for AD (*Trem2 & Inpp5d*) as significantly associated with memory status in a 'normal' aging murine genetic reference group (BXD panel). This led to the hypothesis that common mechanisms underlie both 'normal' aging and AD-related memory deficits. Using standard contextual fear conditioning, we obtained an average memory index for each of 15 aging BXD strains tested (age=14±0.7mo). Memory index varied across the population (range=0-61.4% freezing during memory test) and genetic interval mapping identified an area on chromosome 4 that suggestively modulates memory function during aging. Heterochromatin protein 1 binding protein 3 (*Hp1bp3*) was identified as a top candidate responsible for aging- and AD-related memory decline given that: 1) age-matched BXD hippocampal transcript data identified *Hp1bp3* as *cis*-regulated, 2) HP1BP3 protein is enriched in the hippocampus of aging impaired mice, 3) disruption of *Hp1bp3* in *Hp1bp3*$^{-/-}$ mice disrupts hippocampus-dependent working memory function as measured on the T-maze test of spontaneous alternation [WT=91 ± 4%, KO= 49 ± 7%, $t(12)=5.095$, $p<.001$)], 4) *HP1BP3* transcript is enriched in the hippocampus of human AD patients as compared to age-matched non-demented controls, and 5) *Hp1bp3* is known to directly interact with amyloid precursor protein (APP), a well-known gene product harboring causal mutations linked to overproduction of Aβ and AD. Our systems genetics approach allowed for the identification of expression QTLs (eQTLs) that mapped to the *Hp1bp3* locus. One such eQTL was *Wdfy3*, an autophagy protein found to be enriched in impaired murine hippocampal proteome and human AD hippocampal transcriptome. Utilization of existing GWAS data confirmed *WDFY3* is nominally significantly associated with late-onset AD across a diverse human population. As dysfunction in autophagic processes has been linked to memory

decline in both aging and AD, we provide a functional link between *Hp1bp3*, its downstream effector *Wdyfy3*, and memory deficits in both conditions. These genes and additional candidates identified via our systems genetics approach will be combined with multi-layered omics data in order to create network models that better predict and understand the common mechanisms underlying memory decline in both 'normal' aging and AD.

Disclosures: **S.M. Neuner:** None. **M. de Both:** None. **B. Garfinkel:** None. **J. Ingels:** None. **L. Lu:** None. **L. Wilmott:** None. **T. Shapaker:** None. **R. Williams:** None. **G. Kempermann:** None. **J. Orly:** None. **M. Huentelman:** None. **C. Kaczorowski:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.07

Topic: F.02. Animal Cognition and Behavior

Support: NIH NIA R37 AG06647

NIH NIA P01 AG16765

Intramural Research Program of the NIA

Title: Presynaptic mitochondria in the monkey PFC: implications for normal aging, menopause, and working memory

Authors: ***Y. HARA**[1], F. YUK[2], R. PURI[2], W. G. M. JANSSEN[2], P. R. RAPP[3], J. H. MORRISON[2];
[1]Neurosci., [2]Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Natl. Inst. on Aging, Baltimore, MD

Abstract: Humans and nonhuman primates are vulnerable to age- and menopause-related decline in working memory. Rhesus monkeys provide a valuable model for studying the basis of normal cognitive aging, because they do not develop Alzheimer's disease and therefore the effects of aging and menopause can be examined uncontaminated by neurodegenerative disease. Working memory is a cognitive function thought to be one of the most vulnerable to aging and is mediated by the energy-demanding excitation of dorsolateral prefrontal cortex (dlPFC) neurons. Here, we tested the hypothesis that the number and morphology (straight, curved, and donut-shaped) of mitochondria in presynaptic inputs to dlPFC are altered with aging and menopause and that these metrics correlate with working memory (i.e., delayed response (DR) accuracy). In

contrast to what is observed in neurodegenerative models, aging did not result in a loss of mitochondria in dlPFC boutons. However, DR accuracy positively correlated with the number of total and healthy straight presynaptic mitochondria, consistent with the energy-demanding nature of this task. In contrast, DR accuracy inversely correlated with the frequency of boutons harboring malformed donut-shaped mitochondria, which exhibited smaller active zone size and fewer docked vesicles than those with straight or curved mitochondria. Surgically-induced menopause (ovariectomy) resulted in working memory impairment and a concomitant increase in presynaptic donut-shaped mitochondria, both of which were reversed with estradiol treatment. Our findings suggest that hormone replacement therapy may benefit cognitive aging, in part, by promoting mitochondrial and synaptic health in the PFC.

Disclosures: **Y. Hara:** None. **F. Yuk:** None. **R. Puri:** None. **W.G.M. Janssen:** None. **P.R. Rapp:** None. **J.H. Morrison:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.08

Topic: F.02. Animal Cognition and Behavior

Support: SIU Neuroscience Research Center

Title: Mouse models of Alzheimer’s disease: what are they modelling?

Authors: *G. M. ROSE, E. HAYASHI, P. R. PATRYLO;
Neurosci. Res. Ctr., Southern Illinois Univ., Carbondale, IL

Abstract: Alzheimer’s disease (AD) can be a pernicious consequence of aging. There is currently no cure, and marketed symptomatic treatments have, at best, limited and temporary effects. Initial efforts to develop pharmacotherapies for AD were stimulated by descriptions of cholinergic neuron loss in the basal forebrain. It was thought that boosting brain acetylcholine levels by using acetylcholinesterase inhibitors to slow metabolism of the neurotransmitter would be beneficial, similar to the strategy used to respond to reduced dopamine levels in Parkinson’s disease. However, this approach has turned out to have practical utility in only a minority of cases. The development of transgenic mouse models containing mutant human genes was heralded as a breakthrough because it offered the opportunity to examine the genesis of major aspects of AD-associated neuropathology: the amyloid plaques, and, in later models, the neurofibrillary tangles composed of hyperphosphorylated tau protein. A reasonable expectation

was that the presence of these neuropathologies would result in the profound cognitive deficits that are the major symptom of AD. Unfortunately, this has not turned out to be the case. While statistically significant deficits in learning and memory tests have been described for many of the transgenic models, they do not approach the magnitude usually observed in aged rodents that have not had genetic manipulations. Because the deficits in the AD models are usually mild, they are often restricted to a particular measure on a particular behavioral task, and are not always reproducible either within or between laboratories. This outcome is seen despite the presence of heavy plaque loads, particularly in hippocampal and neocortical regions. Further, while many experimental treatments have been shown to improve learning or memory in transgenic AD models, none that have progressed to human clinical trials have been successful. Thus, current transgenic AD models lack both face and predictive validity. Why? It seems clear that presence of amyloid in these models is, by itself, insufficient to grossly impair cognition. An important question is whether amyloid is involved at all, or whether it is simply a biomarker for some other deleterious process. Cognitive impairments frequently develop in aging, which sometimes progresses to AD. Neuronal death, profoundly present in the AD brain but essentially absent in transgenic mouse models, may be the key transitional factor. Understanding the cause(s) of this process, and reproducing it in AD mouse models, will likely be a critical step in differentiating AD from normal aging.

Disclosures: **G.M. Rose:** None. **E. Hayashi:** None. **P.R. Patrylo:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.09

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant AG037868

NIH Grant AG034605

Title: Transcriptional signatures of brain aging and Alzheimer’s disease: what are our animal models telling us?

Authors: *E. M. BLALOCK;
Dept Pharmacol, Univ. Kentucky Coll Med., Lexington, KY

Abstract: Aging is the single biggest risk factor for developing idiopathic Alzheimer's disease (AD). Recently, the NIH released AD research recommendations that include: appreciating normal brain aging, expanding data-driven research, using more open-access resources and evaluating experimental reproducibility. Despite publically available transcriptome data sets that already satisfy many the NIH's AD research recommendations, little work has been done to determine the potential interrelatedness of molecular signatures across human and animal models of aging and AD. To address this, in the present work, I performed meta-analyses contrasting aging and AD transcriptional profiles from different experimental animal and human brain samples, testing the hypothesis that similar conditions across species would be reflected by similar deflections in their molecular signatures. Despite the profound inter-species differences in the chronological time point at which aging is established, the transcriptional profile of normal aging was consistent across human, rat, mouse, and canine brain tissue. This similarity largely was driven by a common core of increased immune/ inflammatory mRNA expression. However, although end-stage idiopathic AD also showed increased immune/ inflammatory changes, the magnitude of those changes, the molecular entities involved, and the relative proportion of expression among those entities was a poor match with normal brain aging. This suggests that idiopathic AD represents a separate (albeit age-associated) pathology. Intriguingly, the transcriptional profiles of transgenic AD mouse models did match well with one another, but not with human idiopathic AD. These results suggest that normal human brain aging is well-modeled by research mammals. However, the transgenic mouse does not appear to recapitulate the full spectrum of human idiopathic AD's molecular phenotype. This latter point raises the interesting possibility that transgenic AD models may need to be aged similarly to humans in order to provide a closer molecular match, and/ or that idiopathic and familial AD may represent fundamentally separate disorders with a common pathological outcome.

Disclosures: E.M. Blalock: None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.10

Topic: F.02. Animal Cognition and Behavior

Support: R.E.A.C.H. Undergraduate Grant

Title: Testing the effects of diabetes mellitus on cognitive ability in a mouse model of Alzheimer's disease

Authors: *E. HAYASHI, C. GRIFFITH, H. ZHANG, B. OZMENT, P. PATRYLO, G. ROSE; Southern Illinois Univ., Carbondale, IL

Abstract: Alzheimer's Disease (AD) is the primary cause of dementia in the elderly and a growing concern for society. AD is characterized by severe memory impairments and brain neuropathology that includes amyloid plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. The cause of AD is unknown, though certain genes have been identified that predispose or lead to the development of AD. Diabetes mellitus is an endocrine pathology that impairs glucose utilization and is considered a risk factor for AD. Glucose utilization is known to decline in brain regions associated with memory in AD patients. The goal of this project was to determine whether experimentally induced diabetes mellitus would exacerbate memory impairments or brain neuropathology in a transgenic mouse model of AD. The 3xTg mouse model for AD contains human genes that cause plaques and tangle deposition in memory-associated brain regions in an age-related manner. Diabetes was induced in 13-month old 3xTg mice using streptozotocin (STZ; 90 mg/kg on two successive days), a drug that selectively destroys insulin-producing pancreatic beta cells. Hyperglycemia was verified by sampling blood glucose levels. Mice that received STZ injections maintained high blood glucose levels throughout the study (>250 mg/dL), in contrast to mice that received vehicle injections (<120 mg/dL). Three months after injection, all mice were trained in the Morris water maze, a test of hippocampus-dependent spatial learning, and cued/contextual fear conditioning, a test that can assess both hippocampal and hippocampal-independent memory. Results indicated no difference in memory performance between the groups. After behavioral testing was completed, brain immunohistochemistry was performed to assess cell loss, amyloid plaque accumulation, and hyperphosphorylated tau. Though behavioral performance was not statistically different between groups, STZ-treated animals showed significantly more amyloid plaques in the subiculum, the only hippocampal region where plaques were seen in either group. These results indicate that amyloid plaques, per se, are not sufficient to cause memory impairments. Further, while diabetes mellitus can enhance this aspect of brain pathology, the combination of disrupted glucose metabolism and the transgenes is still not sufficient to cause the cognitive impairments associated with AD.

Disclosures: E. Hayashi: None. **C. Griffith:** None. **H. Zhang:** None. **B. Ozment:** None. **P. Patrylo:** None. **G. Rose:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.11

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant AG036800

NIH Grant AG037984

The Evelyn F. McKnight Brain Research Foundation

Title: Rodent models of synaptic senescence: Relevance to discovery of AD therapies

Authors: *T. C. FOSTER;
Dept Neurosci., Evelyn F. and William L. McKnight Brain Inst. Univ. Florida, Gainesville, FL

Abstract: Alzheimer's disease (AD) is a progressive disease of aging. Cognitive aging and AD are associated with weakening of episodic memory and executive function which progresses to more severe cognitive impairments and dementia. The evolution of cognitive decline is linked to the progression of pathology, such that, the initial onset of impaired episodic memory is better characterized by neuroinflammation and synaptic loss; and clinical dementia is more likely related to cell death. On the surface, it would appear that aging rodents would provide a poor model of AD due to an absence of neuritic amyloid plaques and neocortical neurofibrillary tangles. However, it is important to emphasize that the primary risk factor for AD is age. Thus, aging rodents provides a model for investigation of modulatory factors that determine the specificity of cognitive impairments, the mechanism for synaptic loss, and selective cellular vulnerability. This talk will focus on alterations in synaptic function with aging that may contribute to the onset and progression of cognitive decline. Impaired executive function and episodic memory deficits emerge in middle-age in association with senescent neural physiology, including a decline in NMDA receptor synaptic function in the medial prefrontal cortex and CA1 region of the hippocampus, respectively. The decreased NMDA receptor function is due to an oxidized intracellular redox state providing a link between a rise in neuroinflammation and oxidative stress and a weakening of memory mechanisms. In turn, the decrease in NMDA receptor activity may underlie altered transcription associated with aging and cognitive decline. Specifically, expression of genes for cell health and maintenance are altered, expression of synaptic genes decrease, and expression of immune response genes increase. Importantly, the decline in synaptic genes is associated with impaired memory. As such, altered transcription due to a decrease in synaptic NMDA receptor activity could contribute to the progression of cognitive decline through synaptic loss and increase neuronal vulnerability to cell death.

Disclosures: T.C. Foster: None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.12

Topic: F.02. Animal Cognition and Behavior

Support: Intramural Research Program of the NIA

AG10606

Title: Characterization of GABAergic basal forebrain neurons in young and aged behaviorally characterized rhesus monkeys

Authors: *C. BANUELOS[1], E. J. PEREZ[1], J. M. LONG[1], M. T. ROBERTS[2], S. FONG[2], P. R. RAPP[1];
[1]NIH-NIA, Baltimore, MD; [2]California Natl. Primate Res. Ctr., Univ. of California, Davis, Davis, CA

Abstract: Corticopetal basal forebrain projections are anatomically positioned to influence a broad range of cognitive capacities including attention, executive function and memory. Although basal forebrain dysfunction has long been implicated in cognitive aging, prior research has focused predominantly on cholinergic cell groups, and their precise contribution to age-related decline remains controversial. The medial septal nucleus (MS) and the nucleus of the diagonal band (nDB) originate the primary cholinergic input to the hippocampus, while cholinergic neurons in the nucleus basalis of Meynert (nBM) project to the dorsolateral prefrontal cortex, an area essential for working memory. In rodents, GABAergic neurons in these basal forebrain nuclei are numerically more prominent, where they are also positioned to impact the cognitive processing capacities of their projection targets in the hippocampus and prefrontal cortex. To date, however, the distribution and organization of basal forebrain GABAergic neurons in monkeys have received limited attention. Here we used immunohistochemical techniques to visualize cholinergic (ChAT+) and GABAergic (GAD67+) neurons in an evenly spaced series of histological sections through the MS, nDB and the nBM in brains from behaviorally characterized young and aged rhesus monkeys. In both age groups, distinct GABAergic neuronal populations were co-extensive and partially intermingled with cholinergic neurons throughout the extent of the basal forebrain, spanning over 14 mm, emerging rostrally at the MS and nDB and continuing through the caudal portion of the nDB. While cholinergic neurons tended to be clustered, GABAergic neurons were more homogeneously distributed throughout the region. GABAergic neurons exhibited diverse morphologies including multipolar, fusiform and oval cell bodies that were, on average, ~70% the size of cholinergic neurons. Overall, the findings of this study describe a distinct, robustly immunolabeled GABAergic neuronal population in the primate basal forebrain that is co-extensive with cholinergic cell

groups known to project to the hippocampus and prefrontal cortex. Ongoing stereological quantification will test, for the first time in the monkey, whether basal forebrain contributions to individual differences in cognitive aging are mediated by combined or independent changes in GABAergic and cholinergic integrity.

Disclosures: **C. Banuelos:** None. **E.J. Perez:** None. **J.M. Long:** None. **M.T. Roberts:** None. **S. Fong:** None. **P.R. Rapp:** None.

Nanosymposium

377. Learning and Memory: Aging and Alzheimer's Disease

Location: N228

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 377.13

Topic: F.02. Animal Cognition and Behavior

Support: NIH/NIGMS T32GM007507

NSF Graduate Research Fellowship

Title: Learning impairments identified early in life are predictive of future impairments associated with aging

Authors: ***C. BURGER**[1], R. HULLINGER[2];
[1]Dept Neurol., [2]Neurosci. Training Program, Univ. Wisconsin, Madison, WI

Abstract: The Morris Water Maze (MWM) behavioral paradigm is commonly used to measure spatial learning and memory in rodents. It has been suggested that impairments in this task develop at around 12-18 months in rats. However, young rats ubiquitously perform very well on established versions of the water maze, suggesting that more challenging tasks may be required to reveal subtle differences in young animals. Therefore, we have used a one-day water maze and the novel object recognition to test whether more sensitive tests of memory in young animals could identify subtle cognitive impairments early in life that might become accentuated later with senescence. We have found that these two independent tasks reliably separate young rats into inferior and superior learners, are highly correlated, and that performance on these tasks early in life is predictive of performance at 12 months of age. Furthermore, we have found that repeated training in this task selectively improves the performance of inferior learners, suggesting that behavioral training from an early age may provide a buffer against age-related cognitive decline.

Disclosures: **C. Burger:** None. **R. Hullinger:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.01

Topic: F.03. Motivation and Emotion

Support: NIMH

Title: Cell-type specific epigenetic reprogramming of the Fosb gene controls depression-related behaviors

Authors: *E. A. HELLER[1], P. J. HAMILTON[2], D. BUREK[2], H. M. CATES[2], C. J. PENA[2], E. J. NESTLER[2];
[1]Systems Pharmacol. and Translational Therapeut., Univ. of Pennsylvania, Perelman Sch. of Med., Philadelphia, PA; [2]Fishberg Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Genome-wide histone posttranslational modifications have been shown to underlie the pathophysiology of stress exposure, leading to the characterization of many highly relevant genes. For instance, we have found that Fosb gene expression is repressed in the nucleus accumbens of both depressed human subjects and mice subjected to long-term social isolation. This repression is associated with increased histone methylation at the Fosb promoter. In order to causally link transcriptional regulation and the chromatin state of Fosb to downstream stress phenotypes it is necessary to manipulate the epigenome solely at this locus. We have targeted histone methylation specifically to the Fosb gene promoter using an engineered zinc-finger protein fused to the histone methyltransferase, G9a. We found that NAc expression of FosB-ZFP-G9a methylates histone H3 specifically at the FosB promoter, leading to a reduction in both basal and induced expression of FosB/deltaFosB. This manipulation was sufficient to produce a social avoidance phenotype in mice undergoing a sub-threshold social defeat stress, as well as reduced exploratory behavior of the open arms of the elevated plus maze. While social isolation represses deltaFosB protein in total NAc, we have shown that social defeat stress increases deltaFosB expression, an effect specific to Drd2-expressing medium spiny neuron in susceptible mice. We have thus targeted this cell type using Cre-dependent HSVs expressing FosB-ZFPs coupled to the p65 transcriptional activation domain to activate FosB expression via increased histone acetylation. We found that this cell-type and locus-specific epigenetic manipulation of FosB expression is sufficient to drive depressive behaviors. Engineered transcription factors are a novel tool to study the function of epigenetic reprogramming at a single gene in a single brain region *in vivo* for the study of neuropsychiatric disease and beyond.

Disclosures: **E.A. Heller:** None. **P.J. Hamilton:** None. **D. Burek:** None. **H.M. Cates:** None. **C.J. Pena:** None. **E.J. Nestler:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.02

Topic: F.03. Motivation and Emotion

Support: NIH Grant R01DA038613-01

Title: Dichotomous behavioral outcomes of egr3 expression in nucleus accumbens medium spiny neuron subtypes

Authors: ***T. C. FRANCIS**[1,2], R. CHANDRA[3], P. KONKALMATT[4], A. KLAUSING[4], M. ENGELN[3], M. LOBO[4];
[1]Dept. of Anat. and Neurobio., [2]Program in Neurosci., Univ. of Maryland, Baltimore, Baltimore, MD; [3]Anat. and Neurobio., [4]Univ. of Maryland SOM, Baltimore, MD

Abstract: The Nucleus Accumbens is a principle integrator of reward related information within the brain and is highly implicated in depression. The NAc consists primarily of two projection neuron subtypes, medium spiny neurons (MSNs), which are differentiated by dopamine receptor expression, either dopamine 1 receptors (D1) or dopamine 2 receptors (D2). Social defeat stress (SDS), a well-validated stress paradigm to induce depression-like symptoms, promotes dichotomous behavioral, electrophysiological, and molecular outcomes in these MSN subtypes. SDS produces two distinct behavioral phenotypes: mice susceptible to SDS (i.e., displaying depression-like symptoms) or mice resilient to SDS. We found repeated high frequency 473 nm optogenetic stimulation (≥50 Hz stimulation) of NAc D1-MSNs promotes resilience to a 10 day chronic (C)SDS, while repeated stimulation of D2-MSNs promotes susceptibility to subthreshold (S)SDS. Quantitative real-time PCR revealed repeated stimulation of either MSN subtype reduces NAc expression of the transcription factor early growth response 3 (Egr3). Egr3 is a primary target of brain-derived neurotrophic factor (BDNF) TrkB signaling. Disrupting this signaling pathway from the VTA-NAc circuit promotes resilience. Given the known effects of BDNF disruption on SDS behavior and the opposing outcomes of MSN subtype stimulation, we hypothesized reduction of Egr3 expression in D1-MSN subtypes would promote resilience to SDS and reduction in D2-MSN subtypes, susceptibility. To mimic stimulation induced down-regulation of Egr3 in cell subtypes, a conditional double inverted open reading frame (DIO) adeno-associated virus (AAV) expressing an Egr3-miRNA was injected in the NAc of D1-Cre

and D2-Cre mice. Egr3 miRNA knockdown in D1-MSNs enhanced resilience to CSDS, while Egr3 miRNA knockdown in D2-MSNs induced susceptibility to SSDS. These results suggest Egr3 knockdown mimics MSN subtype-specific stimulation-induced outcomes to SDS. To examine the consequence of enhanced Egr3 expression in MSN subtypes, we injected a DIO-AAV construct to overexpress Egr3. In contrast to knockdown of Egr3, overexpression of Egr3 in D1-MSNs promoted susceptibility to SSDS, while overexpression in D2-MSNs produced enhanced resilience to CSDS. Preliminary electrophysiological recordings suggest enhancing Egr3 expression reduce excitatory input to MSN subtypes. Our results suggest Egr3 manipulation in MSN subtypes oppositely mediates outcomes to SDS. Further, these changes are likely due to alterations in excitatory synaptic transmission which may underlie the behavioral outcomes to SDS.

Disclosures: **T.C. Francis:** None. **R. Chandra:** None. **P. Konkalmatt:** None. **A. Klausing:** None. **M. Engeln:** None. **M. Lobo:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.03

Topic: F.03. Motivation and Emotion

Support: NIH Intramural Program

Nancy Nossal Fellowship Award

Title: Direct and indirect pathway neurons bidirectionally modulate affective state in the dorsal striatum

Authors: ***K. H. LEBLANC**[1], D. M. FRIEND[1], K. P. NGUYEN[1], A. V. KRAVITZ[1,2]; [1]NIH/NIDDK, Bethesda, MD; [2]NIH/NIDA, Baltimore, MD

Abstract: Recent evidence suggests that the direct and indirect pathway neurons of the dorsal striatum are important for positive and negative affect, in addition to their role in movement. Stimulation of direct pathway medium spiny neurons (dMSNs) in the dorsal striatum is reinforcing, while stimulation of indirect medium spiny neurons (iMSNs) is aversive. In addition, a number of disorders involving the striatal dopamine system, such as Parkinson's disease, addiction, and obesity, are comorbid with anxiety and depression. Based on this evidence, we hypothesized that iMSNs and dMSNs also play a role in anxiety, whereby

stimulating iMSNs would have anxiogenic effects while stimulating dMSNs would have anxiolytic effects. Using *in vivo* electrophysiology we found that the firing rates of a subset of MSNs in the dorsal striatum was substantially higher in either the open or closed arms of the elevated zero maze, suggesting that the firing of these neurons may be linked to anxiety state. In addition, optogenetically stimulating iMSNs in the dorsal striatum decreased the percent of time spent in the open arms of an elevated zero maze, consistent with an anxiogenic-like effect. Conversely, stimulating dMSNs had the opposite effect, increasing the percent of time in the open arms. Stimulating dMSNs also increased sucrose preference and time in the food zone in a novelty-induced hypophagia task, both consistent with a more positive affective state. Our results support a role for iMSNs and dMSNs in the striatum in affective states, which has implications for a number of disorders, including Parkinson's disease, OCD, addiction and obesity.

Disclosures: K.H. Leblanc: None. **D.M. Friend:** None. **K.P. Nguyen:** None. **A.V. Kravitz:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.04

Topic: F.03. Motivation and Emotion

Support: NIMH Grant K99 MH099243

NIMH Grant 4R00 MH099243

Title: Striatal synapses as a central node for ASD pathophysiology

Authors: *M. V. FUCCILLO;
Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Autism spectrum disorders (ASD) are clinically characterized by two central and seemingly unrelated symptom domains – deficits in social interaction and communication and restrictive, repetitive patterns of behavioral output. Whether the diverse nature of ASD symptomology represents a distributed, global dysfunction of brain networks or abnormalities within specific neural circuits is currently unclear. We hypothesize that alterations in striatal physiology may serve as a common node in mediating a range of autism-related behaviors, consistent with its diverse functions in regulating action selection, organizing motor programs and integrating reward-related information to shape behavior. Here we use two related genetic

models of ASD, mice with mutations in the Neuroligin3 (Nlgn3) synaptic adhesion molecule, to explore the underlying circuit and physiological pathogenesis of motor and reward processing abnormalities. Using the accelerating rotarod to study the acquisition of pattered motor output, we find that Nlgn3 mutants have enhanced rotarod learning, a common behavioral phenotype in several mouse autism models. This enhanced performance directly correlates with a more rapid formation of stereotyped motor output in mutants as compared to wildtypes. Using viral and genetic loss-of-function approaches, we demonstrate that altered Nlgn3 function within D1 Dopamine receptor positive medium spiny neurons (D1R+ MSNs) of the ventral striatum (nucleus accumbens) is causal for the enhanced rotarod earning. Furthermore, electrophysiology in acute striatal slices revealed a D1R+ MSN specific deficit in inhibitory synaptic tone, suggesting a physiological mechanism whereby perturbed circuit dysfunction can produce behavioral abnormalities. In addition to enhanced motor learning and repetitive, stereotyped behaviors, Nlgn3 mutants also demonstrate altered reward processing in both operant tasks of behavioral flexibility and Pavlovian conditioning paradigms. Efforts are currently underway to see whether these diverse behavioral phenotypes stem from common physiological abnormalities of inhibitory tone in nucleus accumbens circuits. Going forward, exploration of striatal circuits in other mouse ASD genetic models should provide a unique opportunity to illuminate canonical behavioral circuits whose dysfunction directly contributes to discrete aspects of ASD symptomology.

Disclosures: **M.V. Fuccillo:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.05

Topic: F.03. Motivation and Emotion

Support: NIDA R01DA037152

NIMH F31 MH101956

NIDA K99DA038725

DOE DE-FG02-07ER46471

NINDS R01NS081707

DOE DE-FG02-07ER46453

Title: Wireless optofluidic systems for programmable *in vivo* pharmacology and optogenetics

Authors: ***J. G. MCCALL**[1], J.-W. JEONG[3], G. SHIN[4], Y. ZHANG[5], R. AL-HASANI[1], M. KIM[4], S. LI[4], J. SIM[6], K.-I. JANG[4], Y. SHI[5], D. Y. HONG[1], Y. LIU[4], G. P. SCHMITZ[1], L. XIA[1], Z. HE[5], P. GAMBLE[2], W. Z. RAY[2], Y. HUANG[5], J. A. ROGERS[4], M. R. BRUCHAS[1]; [1]Anesthesiol., [2]Washington Univ., Saint Louis, MO; [3]Electrical, Computer, and Energy Engineerring, Univ. of Colorado, Boulder, CO; [4]Univ. of Illinois at Urbana-Champaign, Urbana, IL; [5]Northwestern Univ., Evanston, IL; [6]Electronics and Telecommunications Res. Inst., Daejeon, Korea, Republic of

Abstract: *In vivo* pharmacology and optogenetics hold tremendous promise for dissection of striatal neural circuits, cellular signaling and manipulating neurophysiological systems in awake, behaving animals. Existing neural interface technologies, such as metal cannulas connected to external drug supplies for pharmacological infusions and tethered fiber optics for optogenetics, are not ideal for minimally invasive, untethered studies on freely behaving animals. Here we introduce wireless optofluidic neural probes that combine ultrathin, soft microfluidic drug delivery with cellular-scale inorganic light-emitting diode (μ-ILED) arrays. These probes are orders of magnitude smaller than cannulas and allow wireless, programmed spatiotemporal control of fluid delivery and photostimulation. We demonstrate these devices in freely moving animals to modify gene expression in the dorsal striatum, deliver peptide ligands to the ventral tegmental area dopaminergic system, and provide concurrent photostimulation with antagonist drug delivery to manipulate mesoaccumbens reward-related behavior. These completely self-contained devices allow for combinatorial optogenetic, pharmacological, and viral approaches with a high degree of spatial resolution and limited disruption to sensitive neural tissues such as striatal circuitry. The minimally invasive operation of these probes is ideal for investigation of neuropsychiatric disorders and forecasts utility in other organ systems and species, with potential for broad application in biomedical science, engineering, and medicine.

Disclosures: **J.G. McCall:** None. **J. Jeong:** None. **G. Shin:** None. **Y. Zhang:** None. **R. Al-Hasani:** None. **M. Kim:** None. **S. Li:** None. **J. Sim:** None. **K. Jang:** None. **Y. Shi:** None. **D.Y. Hong:** None. **Y. Liu:** None. **G.P. Schmitz:** None. **L. Xia:** None. **Z. He:** None. **P. Gamble:** None. **W.Z. Ray:** None. **Y. Huang:** None. **J.A. Rogers:** None. **M.R. Bruchas:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.06

Topic: F.03. Motivation and Emotion

Support: T32 NS007375

R01 MH086828

Title: Mechanisms of synaptic plasticity at excitatory hippocampal inputs to the nucleus accumbens

Authors: *T. A. LEGATES, S. M. THOMPSON;
Physiol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The nucleus accumbens (NAc) is a central component of the reward system and is responsible for integrating information from cortical and limbic brain regions to drive goal directed behavior. The ventral hippocampus provides excitatory input to the NAc shell, which is thought to be important for modulating NAc activity and providing contextual information to reward processing. This synapse has received increased attention due to its potential role in mood regulation, specifically in response to reward and motivation to seek rewards, which are altered in mood disorders including depression. However, the mechanistic understanding of activity-dependent synaptic plasticity at this synapse remains limited. We used whole-cell electrophysiological recordings in the NAc shell to dissect the mechanisms underlying activity dependent synaptic plasticity of the excitatory input from the hippocampus to the NAc shell. Our data show that this synapse is capable of undergoing activity-dependent long-term potentiation (LTP) via a postsynaptic mechanism. The induction of LTP was blocked by APV and KN62 indicating that this is an N-methyl-D-aspartate (NMDA) receptor - and Ca2+/calmodulin-dependent kinase type II (CaMKII)-dependent process. Furthermore, we found that there is no change in the stoichiometry of GluA1 and GluA2 synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor composition after LTP induction, as assayed with rectification and sensitivity to N-acetyl-spermine. We verified the specificity of this response by using optogenetic stimulation of this synapse allowing us to assay the behavioral consequence of *in vivo* manipulation of this synapse. These experiments provide the first detailed electrophysiological characterization of the excitatory input from the hippocampus to the NAc and are crucial for proper understanding of the dysfunction in these neural circuits that contribute to mood dysregulation.

Disclosures: T.A. LeGates: None. **S.M. Thompson:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.07

Topic: F.03. Motivation and Emotion

Support: NIH R01-NS064577-07

Wakeman Fellowship

NIH T32 GM007171

Trice-Holland Fellowship

Title: A novel role for the metabotropic glutamate receptor mGluR5 in regulating striatal synapse maturation

Authors: *S. BHAGAT, Y. WAN, R. HERNANDEZ-MARTINEZ, N. CALAKOS;
Duke Univ., Durham, NC

Abstract: A highly conserved method for appropriate development of connectivity across diverse brain regions involves synaptic pruning preceded by synaptic proliferation. The period of synaptic proliferation is characterized by a large proportion of immature "silent synapses" that lack stable signaling via AMPA-type glutamate receptors. In the cortex and hippocampus, these immature synapses also have relatively high levels of NR2B, and low levels of NR2A subunits of NMDA-type glutamate receptors. Studies from these brain regions support a role for diheteromeric NR1/NR2B glutamate receptors in preventing premature synapse maturation, whereas trihetereomeric NR1/NR2A/NR2B or diheteromeric NR1/NR2A receptors may promote synapse maturation. However, in the striatum, NR2A remains low even in adulthood while NR2B expression persists at high levels, suggesting that the striatum may have a unique mechanism for preventing premature synapse maturation. Here we present evidence for such a novel mechanism in the striatum. We find that constitutive, glutamate-independent mGluR5 signaling prevents premature synapse maturation in the early postnatal period, promoting maintenance of silent synapses through a PKC and protein synthesis dependent mechanism. These findings broaden our understanding of the roles of mGluR5 in normal development and have implications for the consequences of targeting this receptor pharmacologically in neurodevelopmental disorders such as autism.

Disclosures: S. Bhagat: None. **Y. Wan:** None. **R. Hernandez-Martinez:** None. **N. Calakos:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.08

Topic: F.03. Motivation and Emotion

Support: R01MH090264

F30MH100835

Title: Neuroligin-2 knockdown in the nucleus accumbens modulates social behavior

Authors: ***M. HESHMATI**[1], H. ALEYASIN[1], C. MENARD[1], M. E. FLANIGAN[1], M. L. PFAU[1], P. H. GOFF[1], G. E. HODES[1], A. LEPACK[1], L. BICKS[1], I. S. MAZE[1], S. A. GOLDEN[2], S. J. RUSSO[1];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Natl. Inst. of Drug Abuse, Baltimore, MD

Abstract: Dysregulation of excitatory/inhibitory balance is suggested to be a common mechanism of neuropsychiatric disease. Neuroligin-2, a postsynaptic cell adhesion protein, supports the functional integrity of the inhibitory synapse and may play a role in the inhibitory balance. While the neuroligin gene family has been implicated in autism, little is known about the role of neuroligin-2 in social behavior. We found that after chronic social defeat stress, neuroligin-2 protein is reduced in the nucleus accumbens (NAc) of male mice that are susceptible to stress. Next, using a Cre-conditional RNA interference approach, we knocked down neuroligin-2 in the NAc of mice expressing Cre in either dopamine D1 receptor-positive or dopamine D2 receptor-positive cells. We then explored the contribution of neuroligin-2 in the NAc to social behavior. We demonstrate that neuroligin-2 knockdown in D2-positive cells stimulates increased home cage aggression and heightened dominance. Knockdown in D1-positive cells promotes susceptibility to social defeat stress with no significant change in baseline aggression. Together, these findings suggest a novel, cell-type specific role of NAc neuroligin-2 in aggression and stress-induced social interaction.

Disclosures: M. Heshmati: None. **H. Aleyasin:** None. **C. Menard:** None. **M.E. Flanigan:** None. **M.L. Pfau:** None. **P.H. Goff:** None. **G.E. Hodes:** None. **A. Lepack:** None. **L. Bicks:** None. **I.S. Maze:** None. **S.A. Golden:** None. **S.J. Russo:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.09

Topic: F.03. Motivation and Emotion

Support: NARSAD Young Investigator award

Title: Genetic dissection of striatal neural circuits in a conditional BAC transgenic mouse of VIPR2 CNV: a susceptibility allele of schizophrenia

Authors: *X. LU[1], A. RICHARD[2], W. YANG[3], N. GOEDERS[2];
[1]Dept. of Pharmacology, Toxicology & Neurosci., [2]LSU Hlth. Sci. Ctr., Shreveport, LA; [3]UCLA, Los Angelse, CA

Abstract: The lack of a credible mouse model of schizophrenia hinders the understanding of its pathogenic mechanisms and the development of therapeutics. We took advantage of a recently identified VIPR2 Copy Number Variant (CNV) in schizophrenia patients from large-scale GWAS studies and generated conditional Bacterial Artificial Chromosome (BAC) transgenic mice to model the susceptibility allele. Importantly, the transgene can be "switched off" in desired temporal and spatial patterns controlled by crossing with mice expressing Cre recombinase. To investigate whether genetic overexpression of VIPR2 in striatal circuitry in mouse causes abnormal cognition, sociability, dopamine hyperactivity and other traits associated with schizophrenia, we are emplying a Cre-LoxP strategy to conditionally "switch off" VIPR2 transgene expression in striatonigra and straitopallidal neurocircuits. Our study may yield critical mechanistic insights on the pathogenesis of schizophrenia and generate indispensable animal models. The identified cellular substrates of will shed light on novel therapeutic strategies for schizophrenia patients.

Disclosures: X. Lu: None. **A. Richard:** None. **W. Yang:** None. **N. Goeders:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.10

Topic: F.03. Motivation and Emotion

Title: A novel role for E2F3a and E2F3b in cocaine-elicited behavioral and molecular response

Authors: *H. M. CATES, E. A. HELLER, R. C. BAGOT, E. S. CALIPARI, C. J. PEÑA, D. M. WALKER, E. RIBEIRO, E. J. NESTLER;
Icahn Sch. of Med. At Mt. Sinai, New York, NY

Abstract: The underlying mechanisms of cocaine abuse and eventual addiction have been studied for decades, and findings have demonstrated hereditary predisposition to drug abuse. It has been posited that the transition from casual drug use to compulsive addiction is due in part to epigenetic regulation of genes in the brain, specifically in the mesolimbic dopamine reward system, including the nucleus accumbens (NAc) and prefrontal cortex (PFC). Long-lasting changes in neuronal gene expression in the mesolimbic dopamine system appear to underlie some of the persistent neurophysiological changes in the addicted brain in rodent models. Our group and others have demonstrated that altered expression or activity of several candidate transcription factors in NAc regulates drug sensitivity. However, to achieve a more unbiased view of transcriptional mechanisms underlying persistent changes in gene expression, our laboratory has recently performed ChIP- and RNA-sequencing experiments on mouse NAc tissue after repeated cocaine administration (Feng et al., Genome Biol, 2014). In depth analysis of these genome-wide data deduced members of the E2F family as some of the most prominent upstream regulators of cocaine-induced changes in gene expression and alternative splicing in this brain region. E2F transcription factors are involved in chromatin modification, gene regulation, and RNA processing via direct interaction with and recruitment of histone modifying enzymes as well as transcriptional and splicing machinery. Here we show regulation of E2F3a and E2F3b expression in NAc and/or PFC by cocaine administration, as well as regulation of behavioral responses to cocaine upon manipulating E2F3a and E2F3b expression in these regions. Furthermore, cocaine regulates binding of E2F3 to several predicted target genes, and manipulation of E2F3a or E2F3b expression *in vivo* leads to differences in expression of these target genes in specific brain reward regions. These findings support a crucial role for E2F3a and E2F3b in the regulation of gene expression underlying cocaine-elicited behavioral abnormalities.
Supported by NIDA

Disclosures: **H.M. Cates:** None. **E.A. Heller:** None. **R.C. Bagot:** None. **E.S. Calipari:** None. **C.J. Peña:** None. **D.M. Walker:** None. **E. Ribeiro:** None. **E.J. Nestler:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.11

Topic: F.03. Motivation and Emotion

Support: NIH Grant DA03906

NIH Grant DA12513

NIH Grant DA015369

Title: Redefining the direct and indirect pathways of the ventral striatum

Authors: *Y. M. KUPCHIK[1], R. M. BROWN[2], J. HEINSBROK[3], M. LOBO[4], D. J. SCHWARTZ[3], P. W. KALIVAS[3];
[1]Dept. of Med. Neurobio., The Hebrew Univ., Jerusalem, Israel; [2]Florey Inst. of Neurosci. & Mental Hlth., Univ. of Melbourne, Melbourne, Australia; [3]Dept. of Neurosciences, Med. Univ. of South Carolina, Charleston, SC; [4]Sch. of Med., Univ. of Maryland, Baltimore, MD

Abstract: Motivated behavior is governed by two parallel pathways originating in the nucleus accumbens (NAc). The direct pathway consists of medium spiny neurons (MSNs) that project directly to neurons that send their projections outside of the basal ganglia. The indirect pathway consists of MSNs projecting to neurons that do not leave the basal ganglia. The two pathways are classically encoded by two types of MSNs - those expressing the D1 dopamine receptor (D1-MSNs) and projecting to the ventral mesencephalon (VM) are considered as the direct pathway while D2-MSNs that project to the ventral pallidum (VP) are thought to encode the indirect pathway. Here we demonstrate that dividing the direct and indirect pathways according to the two MSN types is not valid for the NAc. By combining slice electrophysiology with optogenetics and retrograde tracers in D1-Cre and D2-Cre transgenic mice we found that approximately 50% of VP neurons receive input from D1-MSNs. This rate was also observed particularly in VP neurons that project to the VM, thus definitively showing that NAc D1-MSNs participate in the indirect pathway. In addition, a large proportion of VP neurons project outside of the basal ganglia to the mediodorsal nucleus of the thalamus (MDT). We found that all MDT-projecting VP neurons were innervated by D2-MSNs. Thus, NAc D2-MSNs, although not projecting to the VM, do form a direct pathway through the VP. Our findings thus call for a re-evaluation of the canonical encoding of the direct and indirect pathways according to the expressed dopamine receptor.

Disclosures: Y.M. Kupchik: None. **R.M. Brown:** None. **J. Heinsbrok:** None. **M. Lobo:** None. **D.J. Schwartz:** None. **P.W. Kalivas:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.12

Topic: F.03. Motivation and Emotion

Support: R00DA031699

Title: Voltage dependent inhibitory synaptic plasticity in the nucleus accumbens

Authors: *D. GHOSE[1,2,3], E. DELPIRE[6,4], B. A. GRUETER[2,5,4,3];
[1]Dept. of Psychology, [2]Dept. of Anesthesiol., [3]Vanderbilt Brain Inst., [4]Mol. Physiol. and Biophysics, [5]Dept. of Psychiatry, Vanderbilt Univ. Med. Ctr., Nashville, TN; [6]Dept. of Anesthesiol., Vanderbilt Univ., Nashville, TN

Abstract: The nucleus accumbens (NAc) is a key brain structure within the reward circuitry. 90-95% of the neuronal population of NAc comprises of medium spiny neurons (MSNs) which express either D1 receptor and project primarily to the midbrain or express D2 receptors and project via the pallidum to the midbrain, while the rest 5-10% are interneurons (INs). NAc MSNs receive excitatory glutamatergic inputs from cortical, limbic and thalamic sources while inhibition is mainly mediated by GABA-ergic INs and MSN collaterals. A portion of these GABAergic INs are fast spiking and express parvalbumin (PV-INs). PV-INs synapse onto proximal dendrites and cell bodies of the MSNs while neighboring MSN collaterals preferentially synapse onto the distal dendrites of the MSNs. This innervation pattern and fast spiking suggest PV-INs have the potential to exert a strong influence on MSN activity by mediating feedforward inhibition, ultimately shaping MSN output. Thus PV-INs are positioned to play an influential role in integrating timing of cognitive, environmental and emotional information entering the NAc and gating output thus influencing reward- related behavioral outcomes. NAc MSNs are quiescent cells that exist in two states, an “up state” wherein they are depolarized and easily activated and a “down state” wherein they are hyperpolarized and resist activation. As suggested above, since the PV- INs synapse onto proximal dendrites and cell bodies of the MSNs, they are thought to have a great influence on the membrane state of the MSN. Moreover, long term plasticity at these inhibitory synapses onto the MSNs may play an important role in sculpting the output of the two different pathways to favor certain actions while suppressing others. In order to understand NAc circuit function under physiological and pathological conditions such as drug addiction, it is critical to understand the nature of PV-IN mediated inhibitory action onto the two distinct MSN subtypes. In this study, using transgenic mice, ex vivo slice electrophysiology and optogenetics, we investigated synaptic plasticity at PV-IN synapses onto D1/D2 MSN in a voltage dependent manner. We found that low frequency stimulation (1Hz, 80s) elicited long term depression (iLTD) in either D1 or D2 MSNs depending on the membrane state of the MSNs. Moreover, optogenetic stimulation of the NAc using the same paradigm *in vivo* resulted in a striking behavioral outcome. The mechanisms underlying this plasticity are being investigated to determine how PV-INs shape NAc circuit function both in health and disease.

Disclosures: D. Ghose: None. **E. Delpire:** None. **B.A. Grueter:** None.

Nanosymposium

378. Striatal Circuits in Psychiatric Diseases

Location: S403

Time: Monday, October 19, 2015, 1:00 PM - 4:15 PM

Presentation Number: 378.13

Topic: F.03. Motivation and Emotion

Support: NIH MH093672-03S2

Title: Upregulation of dopamine D2 receptors in the nucleus accumbens indirect pathway enhances motivation by disinhibiting the direct pathway

Authors: *E. F. GALLO, J. JAVITCH, C. KELLENDONK;
Psychiatry, Columbia Univ., NEW YORK, NY

Abstract: Dopamine signaling in the nucleus accumbens (NAc) plays a central role in motivation. Medium spiny neurons (MSNs), the main output cells of the NAc, belong to either the direct (dMSNs) or indirect projection pathways (iMSNs). These pathways differ in their expression of dopamine D1 and D2 receptors (D1Rs and D2Rs) and operate in a dynamic balance to mediate appropriate goal-directed actions. Decreased D2R availability in striatum, including NAc, is common in several disorders characterized by motivational abnormalities, including drug addiction, ADHD, and obesity. However, whether D2Rs specifically expressed in NAc iMSNs directly contribute to motivation and to the function of striatal circuits necessary for motivated behavior is poorly understood. We selectively upregulated D2Rs in iMSNs by injecting a Cre-dependent adeno-associated virus into the NAc of D2-Cre transgenic mice. We tested the effect on motivation using a progressive ratio schedule of reinforcement. Mice overexpressing D2Rs (D2R-OENAcInd) pressed significantly more times, earned more rewards and continued to respond longer than EGFPNAcInd controls, suggesting that D2R upregulation in the indirect pathway of the NAc is sufficient to increase motivation. Using whole cell recordings in acute NAc slices we found that iMSNs, but not dMSNs, of D2R-OENAcInd mice are intrinsically hyper-excitable, an effect associated with reduced inward-rectifying potassium channel currents. Conversely, excitatory input onto iMSNs is reduced, as measured by a decrease in the frequency of spontaneous excitatory postsynaptic currents (sEPSCs). To study the role of D2Rs in regulating inhibitory output of iMSNs, we tested whether D2R upregulation alters local inhibition of dMSNs by iMSNs. We evoked inhibitory postsynaptic currents (IPSCs) in putative dMSNs by optogenetic activation of iMSNs from D2R-OENAcInd or EGFPNAcInd mice. The light-evoked IPSC amplitude in dMSNs was significantly reduced in D2R-OENAcInd mice compared to controls. These data raise the possibility that the increased motivation in the D2R-OENAcInd mice may be associated with disinhibition of the direct pathway. Using an hM3Dq-based chemogenetic approach, we showed that direct activation of dMSNs is sufficient to

enhance PR responding to levels seen with D2R-OENacInd mice, suggesting that decreased inhibition of dMSNs could contribute to the increased motivation in D2R-OENacInd mice. These data indicate that D2Rs in iMSNs are key regulators of motivated behavior and striatal circuit function. Overall, our findings suggest that boosting D2R levels in the indirect pathway could be useful in treating motivational dysfunction.

Disclosures: E.F. Gallo: None. **J. Javitch:** None. **C. Kellendonk:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NUHS Seed Grant for Basic Science

Title: ApoE3 expression prevent Abeta inhibition of insulin-stimulated AMPA receptor function

Authors: *B.-S. WONG[1], E. S. CHAN[2];
[2]Physiol., [1]Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Human apolipoprotein E4 (ApoE4) is a major genetic risk factor for Alzheimer's disease (AD), but it is unclear how harbouring ApoE4 causes earlier disease manifestation. ApoE4 is linked to early onset of cognitive decline and lower cerebral glucose metabolism. To examine the connection between ApoE isoforms with brain insulin signaling and cognition in AD, we crossed our mice carrying familial-AD mutant human amyloid precursor protein (APP) with the ApoE3 and ApoE4 mice. Young ApoE4/APP mice have poorer cognitive function as compared to ApoE3/APP and APP mice. Insulin treatment was also observed to stimulate insulin signaling in hippocampal slices from ApoE3/APP, but not ApoE4/APP and APP mice. Similarly, insulin treatment was only able to increase AMPA-GluR1 phosphorylation in (50uM) forskolin-pretreated hippocampal slices from ApoE3/APP but not ApoE4/APP and APP mice. In the absence of Abeta, insulin treatment increased the miniature excitatory postsynaptic current (mEPSC) amplitude in both ApoE3 and ApoE4 hippocampal neurons. Abeta42 (500nM) however, only inhibited insulin-induced mEPSC increases in ApoE4 hippocampal neurons. Immunocytochemistry experiment showed that insulin increased AMPA GluR1 subunit insertion in both ApoE3 and ApoE4 hippocampal neurons in the absence of Abeta42. But, adding Abeta42 only affected new AMPA GluR1 subunit insertion in insulin treated ApoE4 hippocampal neurons. Taken together, our results suggest that ApoE3 expression can prevent Abeta inhibition

of insulin-stimulated AMPA receptor function. This ApoE-specific effect could regulate cognitive impairment in our ApoE/APP mice.

Disclosures: B. Wong: None. **E.S. Chan:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG047644

R01 NS090934

R01 NS034467

JPB Foundation

Title: Human and murine apolipoprotein E differentially facilitate and co-localize with cerebral amyloid angiopathy and amyloid plaques in APP transgenic mouse models

Authors: *F. LIAO[1], T. J. ZHANG[1], H. JIANG[1], K. B. LEFTON[1], G. O. ROBINSON[1], R. J. VASSAR[2], P. M. SULLIVAN[3], D. M. HOLTZMAN[1];
[1]Neurol., Washington Univ. In St. Louis, Saint Louis, MO; [2]Dept. of Cell and Mol. Biol., The Feinberg Sch. of Medicine, Northwestern Univ., Chicago, IL; [3]Dept. of Med. (Geriatrics), Duke Univ. Med. Ctr., Durham, NC

Abstract: The accumulation of extracellular amyloid β (Aβ) plaques is one of the pathological hallmarks of Alzheimer's disease (AD). The vast majority of patients diagnosed with AD also have cerebral amyloid angiopathy (CAA). The ε4 allele of human apolipoprotein E (apoE) is associated with higher amyloid plaque load as well as higher amounts and prevalence of CAA. Whereas apoE may influence deposition of Aβ plaques and CAA through common mechanisms affecting Aβ clearance and aggregation, evidence from animals suggests that apoE may promote amyloid plaque and CAA deposition via some specific mechanisms. Out of 299 amino acids, human apoE4 shares only 70% homology with murine apoE, and human apoE4 and murine apoE facilitate amyloid plaques and CAA differently. As compared to mouse apoE, human apoE4 results in delayed plaque load but increases CAA. This difference is not likely caused by changes in Aβ clearance rate/concentration because a higher or lower Aβ concentration will have the

same impact on plaque burden and CAA. To further investigate the differential effects of mouse apoE and human apoE4, we assessed their co-aggregation/co-localization with Aβ in plaques and CAA. We first confirmed that human apoE4 is associated with lower plaques and higher CAA as compared to mouse apoE in the 5XFAD-line 7031 mice using X-34 staining. Then we co-stained brains using X-34, anti-mouse apoE and anti-human apoE specific monoclonal antibodies in 5XFAD mice expressing one copy of mouse apoE and one copy of human apoE4 under the control of the normal mouse apoE gene regulatory elements (5XFAD/apoE$^{m/4}$). Both human apoE4 and mouse apoE co-localized more with parenchymal plaques than with CAA, suggesting a differential co-aggregation of apoE with Aβ in plaques and CAA. More importantly, plaques contained more mouse apoE which is prone to cause parenchymal plaque formation while parenchymal CAA contained more human apoE4 which is prone to CAA formation. We further confirmed the co-aggregation of mouse apoE with Aβ in plaques by correlating insoluble mouse apoE with insoluble Aβ in PS1APP-21/apoE$^{m/4}$ mice, which develop plaques without having CAA. This data demonstrates that when mouse and human apoE are expressed at the same level they differentially co-aggregate with and influence parenchymal plaque deposition versus CAA. Understanding how this occurs may lead to a better understanding of the causal relationships between apoE and CAA/plaque formation and suggest new therapeutic strategies targeting apoE.

Disclosures: **F. Liao:** None. **T.J. Zhang:** None. **H. Jiang:** None. **K.B. Lefton:** None. **G.O. Robinson:** None. **R.J. Vassar:** None. **P.M. Sullivan:** None. **D.M. Holtzman:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; AstraZeneca, Eli Lilly, C2N Diagnostics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Cure Alzheimer's Fund, JPB Foundation, Tau Consortium. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C2N Diagnostics, LLC. F. Consulting Fees (e.g., advisory boards); C2N Diagnostics, LLC, AstraZeneca, Genentech, Eli Lilly, Neurophage.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.03

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS086924

Title: Sleep deprivation disrupts apoE isoform specific radial diffusion from the penetrating arteries into brain by the glymphatic system: implications for CAA and Alzheimer's disease

Authors: *R. DEANE[1], M. THIYAGARAGAN[1], B. LI[1], W. PENG[1], P. B. VERGHESE[2], E. MCCONNELL[1], A. BENRAISS[1], Y. SHI[3], T. KASPER[1], W. SONG[1], T. TAKANO[1], D. M. HOLTZMAN[4], M. NEDERGAARD[1];
[1]Univ. of Rochester, Rochester, NY; [2]Washington Univ. Sch. of Med., St. Louis, MO;
[3]Washington Univ. Sch. of Med., St. Louis, MO; [4]Washington Univ. Sch. of Med., St.Louis, MO

Abstract: Apolipoprotein E (apoE), the major carrier of cholesterol in brain and in the periphery, has essential and diverse role in the CNS. It's involved in neuritic growth, synaptic plasticity, regeneration and remyelination of axon and cognition. In the brain it's produced by many cell types, but mainly by astrocytes. ApoE is also highly expressed by the choroid plexus and the predominant apolipoprotein in cerebrospinal fluid (CSF). However, the role of apoE in CSF is unclear. Recently, the 'glymphatic system', a system that is functionally analogous to the peripheral lymphatic system, was shown to be fundamental for the convective flow of brain interstitial fluid (ISF). This system consists of CSF inflow via the perivascular space of penetrating arteries, CSF/ISF exchange and astrocytic aquaporin 4 (AQP4)-mediated convective flow of ISF through the parenchyma. We tested the hypothesis that the glymphatic system also serves as delivery and distribution pathway for choroid plexus/CSF-derived human apoE to brain, in mice. We found that CSF-delivered apoE enters brain via the perivascular space and diffuses radially around arteries, but not veins, in an isoform specific manner (apoE2>apoE3>apoE4). This restricted apoE4 diffusion may contribute to the cause of cerebral amyloid angiopathy (CAA) and vascular dementia. Diffusion of apoE around arteries was facilitated by the water channel, aquaporin 4 (AQP4), a characteristic feature of the glymphatic system. ApoE3, delivered by lentivirus to the choroid plexus and ependymal layer but not to the parenchymal cells, was present in the CSF, penetrating arteries, neurons and astrocyte. The inflow of apoE, contained in CSF, into brain was severely suppressed by sleep deprivation, consistent with the data that the glymphatic activity is affected by the sleep/wake cycle. This may deprive neurons of CSF-derived apoE, and may contribute to cognitive impairment. Thus, the glymphatic system performs an essential physiological role in the brain-wide distribution of choroid plexus/CSF-derived apoE, and failure in this system may contribute to apoE isoform-specific disorders, such as CAA, vascular dementia and AD. MT and BL contributed equally.

Disclosures: **R. Deane:** None. **M. Thiyagaragan:** None. **B. Li:** None. **W. Peng:** None. **P.B. Verghese:** None. **E. McConnell:** None. **A. Benraiss:** None. **Y. Shi:** None. **T. Kasper:** None. **W. Song:** None. **T. Takano:** None. **D.M. Holtzman:** None. **M. Nedergaard:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AA NIRP14-304720

VA RR&D 1I21RX001558-01A1

NIH P50Y28-2

VA CDA2-526/151

Title: Apoe4-induced phospholipid dysregulation contributes to apoe4-associated cognitive deficits in Alzheimer's disease pathogenesis

Authors: *D. CAI[1,3], L. ZHU[1,4], M. ZHONG[7], M. OHLEMEYER[8], G. ELDER[3], M. SANO[2,5], S. GANDY[1], C. CARDOZO[6], V. HAROUTUNIAN[2,5], N. ROBAKIS[2];
[1]Neurol., [2]Psychiatry, Icahn Sch. of Med. At Mount Sinai, New York, NY; [3]Neurol., [4]Res. & Develop., [6]Mol. Program, Natl. Ctr. of Excellence for the Med. Consequences of SCI, [5]James J Peters VA Med. Ctr., Bronx, NY; [7]Pathology, New York Med. Col. Westchester Med. Ctr., Vahalla, NY; [8]Structural and Chem. Biol., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: The apolipoprotein E4 (ApoE4) allele is known to be the strongest genetic risk factor for developing late-onset AD. However, the mechanisms that underlie the link between ApoE4 genotype and AD are not yet well understood. Evidence suggests that the effects of ApoE4 allele on Alzheimer disease risk are related to the reduced ability of this allele to metabolize neurotoxic amyloid Aβ and clear it from the brain. Other mechanisms have been implicated as well. We have previously found that the levels of phosphoinositol biphosphate (PIP_2) are reduced in postmortem human brain tissues of ApoE4 carriers, in ApoE4 knock-in (KI) mouse brains, as well as in primary neurons expressing ApoE4 alleles compared to ApoE3 counterparts. These changes are secondary to increased expression of synaptojanin 1 (synj1) in ApoE4 carriers. Further studies indicate that ApoE4 which behaves like ApoE null conditions, fails to degrade synj1 mRNA efficiently unlike ApoE3 does. These data suggest a loss-of-function of ApoE4 genotype in regulating PIP_2 homeostasis. Most importantly, genetic reduction of synj1 in ApoE4 KI mouse models restores PIP_2 levels, and rescues AD-related cognitive deficits. Based on these observations, we have further characterized downstream molecular mechanisms. We screened a siRNA panel of ApoE receptors that are highly expressed in neurons, and identified that two ApoE receptors are likely involved in ApoE-regulated synj1 expression. Moreover, we found that levels of mi-195 and mi-155 are differentially expressed in ApoE3- versus ApoE4-treated neurons, which are likely involved in regulating synj1 mRNA degradation. We also searched for

compounds targeted at reducing synj1 expression, and identified 2 top hits which can reduce synj1 protein levels in ApoE4 neuronal culture. Treating ApoE4 mice with one compound for 1-month can improve cognitive functions of these mice. Together, our studies are the first in-depth mechanistic studies of pathogenic roles of ApoE4 genotype in phospholipid homeostasis. Our observations suggest that these ApoE4-induced changes in the cascade of aberrant molecular events may lead to long-term neurodegenerative process. We are currently studying the mechanistic actions of 2 top hits, developing their structural analogs to explore sites for modification and improvement with respect to potency. More importantly, we are investigating detailed signaling pathways involved in ApoE-regulated phospholipid homeostasis. We believe that the findings provide a basis for the development of new therapeutic interventions for the treatment of late-onset AD.

Disclosures: **D. Cai:** None. **L. Zhu:** None. **M. Zhong:** None. **M. Ohlemeyer:** None. **G. Elder:** None. **M. Sano:** None. **S. Gandy:** None. **C. Cardozo:** None. **V. Haroutunian:** None. **N. Robakis:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Effect of Aβ on release of exosome and apoE from astrocytes in culture

Authors: M. ABDULLAH, H. ENOMOTO, M. NUNOME, J. GONG, *M. MICHIKAWA; Nagoya City University, Sch. of Med. Sci., Nagoya, Aichi, Japan

Abstract: Exosomes are small extracellular vesicles (30-100 nm) derived from the endosomal system and secreted by variety of cell types such as neurons, astrocytes and oligodendrocytes. Exosomes are suggested to play important roles in amyloid β (Aβ) deposition and clearance. Aβ is well known to induce neuronal cell death, whereas little is known about its effect on astrocytes. The limited information of the effect of Aβ on astrocytes led us to perform experiments to study the effect of Aβ on release of exosome from astrocytes. The astrocytes were prepared from the SD-rat brains. We characterized and analyzed release of exosomes and apoE, both of which are known to remove/clear Aβ from the brain, in the culture medium of astrocytes. Exosome release was determined by western blot analysis using exosome specific marker proteins, flotillin and HSP90. We found that exosome and apoE-HDL were successfully separated by density gradient ultracentrifugation. Their release was confirmed by distribution of

their specific markers and lipids, and electron microscopic analysis. Exosome release was significantly reduced by Aβ1-42 treatment in cultured astrocytes accompanied by an increased JNK phosphorylation. Whereas, apoE-HDL release remained unchanged. A JNK inhibitor recovered the decreased levels of exosome induced by Aβ treatment to levels similar to those of control, suggesting that Aβ1-42 inhibits exosome release via stimulation of JNK signal pathway. Because, exosome is shown to remove Aβ in the brain, our findings suggest that increased Aβ levels in the brain may impair the exosome-mediated Aβ clearance pathway.

Disclosures: M. Abdullah: None. **H. Enomoto:** None. **M. Nunome:** None. **J. Gong:** None. **M. Michikawa:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG0053834A1

Title: Expression of CR1 in Alzheimer's disease brain: lack of association with disease

Authors: *M. I. FONSECA[1], S. CHU[1], A. PIERCE[1], W. BRUBAKER[2], R. HAUHART[3], D. MASTROENI[4], J. ROGERS[2], J. P. ATKINSON[3], A. J. TENNER[1];
[1]Univ. California, Irvine, CA; [2]SRI, Menlo Park, CA; [3]Washington Univ. Sch. of Med., St. Louis, MO; [4]Banner Sun Hlth. Res. Inst., Sun City, AZ

Abstract: Chronic activation of the complement system and induced inflammation are associated with neuropathology in Alzheimer’s disease (AD). Recent large genome wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in the C3b/C4b binding receptor (CR1 or CD35) that are associated with late onset AD. In order to characterize the role of CR1 in AD, we have studied CR1 localization by immunohistochemistry (IHC) in control and AD brain using antibodies (Abs) directed against different epitopes of the receptor. Most of the Abs tested by IHC stained erythrocytes in blood vessels (CR1, the immune adherence receptor, is expressed on RBCs) but not neurons or glial cells. However, two monoclonal anti-CR1 Abs (8C9.1 and J3B11) labelled astrocytes in all of the cases tested (control and AD), and this reactivity was preabsorbed by recombinant human CR1. Astrocyte staining with both mAbs was supported by immunocytochemistry in human-derived astrocyte cultures and by colocalization with GFAP in tissues and in cell cultures. Staining of neurons with

8C9.1 occurred in tissue from some cases, but was not preabsorbed by recombinant human CR1 indicating non specificity or Ab crossreactivity with other molecular structures. The amount of astrocyte staining varied among the samples, but no consistent difference was conferred by diagnosis, or the GWAS-identified SNPs rs4844609 or rs6656401. Plasma level of soluble CR1 does not correlate with either diagnosis or SNP. However, there was a modest but statistically significant increase in relative binding affinity of C1q to CR1 with the rs4844609 SNP compared to CR1 without the SNP. In addition, C3b binding by CR1 was also significantly increased in the CR1 genotypes containing one or both SNP's (rs6656401, rs4844609). These results demonstrate that further careful functional studies of variants of CR1 are required to determine the role of this receptor in the progression of AD. It remains to be determined if CR1 is involved in the clearance of amyloid beta peptide in blood and/or brain, and/or if CR1 differentially modulates complement-mediated inflammation in AD brains or in the periphery.

Disclosures: M.I. Fonseca: None. **S. Chu:** None. **A. Pierce:** None. **W. Brubaker:** None. **R. Hauhart:** None. **D. Mastroeni:** None. **J. Rogers:** None. **J.P. Atkinson:** None. **A.J. Tenner:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Rs17518584 polymorphism in CADM2 gene accelerates brain and hippocampal atrophy in Alzheimer's disease and Mild Cognitive Impaired patients

Authors: *B. MOHAJER, N. ABBASI, A. ABDOLALIZADEH, M. H. AARABI, A. S. BAYANI ERSHADI, M. PISHNAMAZI;
Student's Scientific Res. Center, Tehran Unive, Tehran, Iran, Islamic Republic of

Abstract: Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder of central nervous system in which patients experience impairment in cognitive processing. Structural imaging studies like Tensor Based Morphometry (TBM) have proved their use in AD. Many SNPs in various genes have been showed to play role in trigger or progression of this disease. Recently in a GWAS study, rs187518584, an intronic SNP of Cell Adhesion Molecule 2 (CADM2) gene, has been shown to have a significant impact on cognitive processing speed in normal population. We found impact of mentioned SNP on (TBM) findings. Methods: Data acquisition: Using Alzheimer's Disease Neuroimaging Initiative (ADNI) project 471 patients

with Alzheimer's and MCI were included. SNP extracted from chromosome 3 by VCFtools. Imaging data: Tensor Based Morphometry with Symmetric Diffeomorphic Image Normalization (TBM-SyN) Based scores from 12 month (M12) follow-up images were used to obtain TBM changes during one year. The TBM-SyN Scores represent annualized atrophy rates computed from the subject's baseline scan to each follow-up, and summarized by averaging over the 31 ROIs. Brain, ventricular and hippocampal robust atrophy rate measurement with Boundary Shift Integral (known as KN-BSI) for m12 were also used to calculate brain and ventricular BSI as well as hippocampus. Cognitive assessment: Alzheimer's Disease Assessment Scale (ADAS) questionnaire of baseline and m12 and m24 were used to investigate SNP impact. Statistical analysis: we used IBM SPSS 22 for univariate analysis to investigate SNP's effect adjusted for sex, age and education on having the risk allele (C). Significant results with p-value <.05 are reported. Results: Using General Linear Model we found significantly more loss in TBM-SyN from M12 (p-value=.026) with recessive allele (estimated mean -.013 compared to -.017). Also left and right hippocampus boundary shift integrals were significantly higher (whit p-values .037 and .045 respectively). M12 and M24 ADAS changes from baseline, as well as brain and ventricles BSI, have not shown any significant changes, considering the form of SNP. Discussion: Firstly our study is the first one to show the effect of mentioned SNP on brain structure. In a recent GWAS study it has been shown that, this SNP has a highly significant impact on cognitive process speed. Secondly our findings demonstrated that having the risk allele significantly increase hippocampal atrophy, beside the atrophy found in TBM. It is important to note all of these imaging findings are in the absence of cognitive changes. Further evaluation with clinical data in patients with AD is suggested.

Disclosures: **B. Mohajer:** None. **N. Abbasi:** None. **A. Abdolalizadeh:** None. **M.H. Aarabi:** None. **A.S. Bayani Ershadi:** None. **M. Pishnamazi:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Investigator FCT 2012

334366 TrafficInAD FP7-PEOPLE-2012-CIG

FRM "Fondation pour la Recherche Medicale en France"

SFRH/BPD/94186/2013

Title: The Alzheimer's risk factors Bin1 and CD2AP differentially regulate the endocytic generation of amyloid-β

Authors: F. UBELMANN, T. BURRINHA, *C. G. ALMEIDA;
NOVA Med. Sch. - UNL, CEDOC - Chronic Dis. Res. Ctr., Lisbon, Portugal

Abstract: Bin1 and CD2AP are putative genetic risk factors for Alzheimer's disease (AD). The most frequent gene variants possibly associate with loss of function. Little is known on how Bin1 and CD2AP increase the risk for AD. We found that upon Bin1 or CD2AP knockdown endogenous Aβ production rises in the axon or in dendrites, respectively. We asked if Bin1 and CD2AP affect APP and BACE1 trafficking to endosomes, where Aβ is produced. We report that BACE1 recycling to the axonal plasma membrane is reduced by Bin1 depletion and that BACE1 gets trapped in enlarged endosomal tubules. Thus Bin1 is essential for BACE1 recycling from axonal early endosomes, probably by controlling scission of recycling carriers. On the other hand, CD2AP depletion reduced APP degradation mainly in dendrites, accumulating APP in early endosomes at the limiting membrane whereas in control neurons APP is at the endosomal lumen, likely escaping processing. Overall, Bin1 and CD2AP modulate Aβ endosomal generation by controlling BACE1 recycling and APP degradation, respectively. Our data contribute to validate Bin1 and CD2AP as AD risk factors and imply that their modulation may have therapeutic potential in AD.

Disclosures: F. Ubelmann: None. **T. Burrinha:** None. **C.G. Almeida:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.09

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 NS074804

Bright Focus A2015296S

Alzheimer's Association 2014 IIRG

Title: TREM2 deficiency results in exacerbated MAPT pathology in the hTau mouse model of tauopathy

Authors: *S. M. BEMILLER[1], G. XU[2], G. WILSON[3], O. KOKIKO-COCHRAN[1], S. CRISH[3], B. LAMB[1];
[1]Neurosciences, [2]Cleveland Clin. Lerner Res. Inst., Cleveland, OH; [3]Neurosciences, NEOMED, Rootstown, OH

Abstract: Pathological hyperphosphorylation of microtubule-associated protein tau (MAPT) is an invariant feature of AD as well as other neurodegenerative disorders collectively known as tauopathies. A strong body of literature exists linking inflammation and innate immunity to AD pathogenesis through the use of genomic approaches and animal models. Recent coding variants of Triggering Receptor Expressed on Myeloid Cells-2 (TREM2), a key regulator oif innate immune processes, have has been shown to dramatically confer increased risk of developing late-onset (AD). Initial characterization of TREM2 deficient APPPS1 mice by the Lamb lab revealed complete elimination of $CD45^{hi}Ly6C^{hi}F4/80^{+}$ plaque associated macrophages with decreased pro-inflammatory cytokine production and a modest reduction in amyloid burden. The focus of the current study is to determine the role of TREM2 signaling and expression in a pathological MAPT mouse model of AD tauopathy. Our data reveals that deficiency of microglial TREM2 results in earlier and increased phosphorylation of several MAPT epitopes, earlier MAPT aggregation, altered microglial activation, and cognitive dysfunction. Analysis of the underlying mechanisms linking TREM2 deficiency to MAPT phosphorylation revealed dysregulation of multiple MAPT kinases including GSK3β, ERK1/2, and JNK. Strikingly, we have determined that cell autonomous TREM2 signaling results in opposing effects between amyloid and tau pathologies, thereby exacerbating amyloid pathology while suppressing tau pathology. We posit that the observed effects are due to a reduction in critical neuronal-microglial cross-talk resulting in a lack of suppression signaling which detrimentally alters inflammatory signaling, or that microglia lacking TREM2 are unable to effectively clear extracellular MAPT. The current study will add critical knowledge to the function of TREM2 and innate immune pathways in AD and other neurodegenerative tauopathies, and may reveal novel therapeutic targets beneficial to human patients. Keywords: Tau, Alzheimer’s Disease, Neuroinflammation

Disclosures: S.M. Bemiller: None. **G. Xu:** None. **G. Wilson:** None. **O. Kokiko-Cochran:** None. **S. Crish:** None. **B. Lamb:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG045775

Bright Focus

Title: Translating CD33 genetics to an Alzheimer's disease prophylactic

Authors: *S. ESTUS, M. MALIK, J. SIMPSON, J. TURCHAN;
Sanders-Brown Ctr. Aging, Lexington, KY

Abstract: Genome-wide association studies identified the single nucleotide polymorphism (SNP) rs3865444, located near CD33, as a modulator of Alzheimer's Disease (AD) risk. CD33 is a sialic-acid binding inhibitory receptor, postulated to have an immunosuppressive effect on microglia in brain. To elucidate the SNP actions, we identified CD33 isoforms expressed in human brain as a function of genotype. We found a significant association between rs3865444 genotype and CD33 exon 2 exclusion and intron 1 retention. This action was allele dose dependent, with homozygosity for the minor allele associated with a 45% reduction in mRNA encoding typical CD33 and a 0.82 AD odds ratio. We interpret this finding as suggesting that a more robust CD33 inhibitor may reduce AD risk further, within an overall model wherein CD33 inhibition enables microglial activation. Considering possible inhibitors, we note that CD33 antibodies such as Lintuzumab were safe in humans but ineffective when tested in acute myeloid leukemia trials. We found that Lintuzumab is effective and potent in downregulating CD33 from the cell surface *in vitro*. We are currently evaluating Lintuzumab effects on microglial cell line function, with readouts including phagocytosis and cytokine production. Overall, this prototypic approach exemplifies our long-term goal of elucidating the mechanisms underlying protective SNP alleles and developing pharmacologic mimics with enhanced efficacy for AD.

Disclosures: **S. Estus:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Abbvie. **M. Malik:** None. **J. Simpson:** None. **J. Turchan:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH P01AG030128-06

NIH R21 AG044682-01A1

Title: Targeting apoE lipidation via nuclear receptor agonists

Authors: *C. C. SMITH[1], L. M. TAI[1], S. GHURA[1], G. R. THATCHER[2], M. LADU[1]; [1]Anat. & Cell Biol., Univ. of Illinois At Chicago, Chicago, IL; [2]Col. of Pharm., Univ. of Illinois at Chicago, Chicago, IL

Abstract: APOE4 is the greatest genetic risk factor for sporadic Alzheimer's disease (AD), increasing risk up to 15-fold compared to APOE3, while increased levels of amyloid-β42 (Aβ42) causes familial AD. Levels of amyloid beta (Aβ) in the brain are influenced by APOE genotype. Transgenic mice co-expressing five familial AD mutations (5xFAD) in the presence of human APOE alleles (ϵ2, ϵ3 or ϵ4) (EFAD mice) exhibit APOE genotype-specific differences in Aβ accumulation, suggesting an interaction between APOE and AD pathology. Compared to apoE3, apoE4-containing lipoproteins are less lipidated, leading to reduced apoE4/Aβ levels and increased levels of neurotoxic oligomeric Aβ (oAβ). Increased apoE4 lipoprotein association/lipidation via increasing ATP-binding cassette transporter (ABCA1) transport of lipids to apoE-containing lipoproteins may be a mechanism for reducing soluble Aβ levels. Using EFAD mice we recently demonstrated that Aβ levels and APOE genotype determine the effect of retinoid X-receptor (RXR) agonists on Alzheimer's disease (AD) pathology. In E4FAD mouse brain regions with the greatest level of Aβ pathology at time of treatment, RXR agonists increased ABCA1 levels, apoE lipidation but not apoE levels, increased apoE/Aβ complex, reduced soluble Aβ and Aβ42 and oAβ) and increased synaptic protein expression. However, RXR agonists also induced hepatomegaly, confounding further interpretation of the data. Thus, targeting ABCA1 without the side effect profile of RXR agonists is a critical aspect of developing an NR agonist for the prevention and treatment of AD, particularly for the fragile elderly population. We propose an approach with a counter screen to identify tissue-specific nuclear receptor agonists that upregulate ABCA1 in glial cells in the CNS, and minimize a toxic gene expression profile in hepatocytes (for example, increase SREBP decrease INSIG-1). We treated primary mixed glial cells (astrocyte, microglia) with NR family subtypes (PPARγ, PPARβ/δ, LXR, RXR, FXR, and RAR agonists) and measured mRNA and protein levels of ABCA1 and apoE, cholesterol levels (by enzymatic assays), and apoE lipidation state. In primary mouse hepatocytes treated with NR ligands, the following were assessed: toxicity (caspase levels, MTT assay), expression of genes/proteins considered beneficial (INSIG-1, CYP7A1) and detrimental (SREBP1c, CREBP), lipid metabolism (HMG-CoA) and cholesterol levels (as above). We identified an FXR and PPARγ agonist as candidate tissue-specific NR modulators. Further development of related compounds using the candidate drugs as scaffolds will likely improve the tissue selectivity of a second-generation drug.

Disclosures: **C.C. Smith:** None. **L.M. Tai:** None. **S. Ghura:** None. **G.R. Thatcher:** None. **M. LaDu:** None.

Nanosymposium

461. Alzheimer's Disease: Risk Factors

Location: S403

Time: Tuesday, October 20, 2015, 8:00 AM - 11:00 AM

Presentation Number: 461.12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01AG047644

EMBO Long term fellowship ATLF-815-2014

Title: Using a series of novel genetically encodable tools to characterize apolipoprotein epsilon domain interaction through a förster resonance energy transfer-based assay

Authors: *E. KARA[1], E. HUDRY[2], Z. FAN[2], S. WEGMANN[2], M. MAESAKO[2], O. BEREZOVSKA[2], B. T. HYMAN[2];
[1]Massachusetts Alzheimer Dis. Res. Ctr., Boston, MA; [2]Massachusetts Alzheimer Dis. Res. Center, Massachusetts Gen. Hosp., Boston, MA

Abstract: Introduction: The Apolipoprotein E (apoE) gene encodes a 34kDa protein that binds to plasma lipoproteins. There are three apoE isoforms (E2, E3, E4) differing in two single nucleotide polymorphisms at codons 112 and 158, with apoE4 being associated with a profound increase in the risk for development of Alzheimer's disease (AD). The isoform-specific modulation of disease risk could be attributed to conformational differences. Interestingly, apoE4 adopts a closed conformation in comparison to apoE2 and apoE3, owing to the formation of a salt bridge between Arg-61 and Glu-255. It is thought that these structural differences mainly impact on the properties of secreted apoE. However, these conformational differences, along with possible modulation by disease modifiers, have not been studied in detail. Methods: We cloned a series of apoE2, E3 and E4 constructs carrying a N-terminus RFP tag and a C-terminus GFP tag, placing the 18 aminoacid signaling peptide that mediates protein secretion before the RFP tag. The constructs were transiently transfected in HEK293 cells, fixed 24-48h later, and imaged on a Zeiss Meta510 scope for Förster resonance energy transfer (FRET) and fluorescence lifetime imaging microscopy (FLIM) by measuring around 100 and 40 cells per construct, respectively. In a separate series of experiments, transiently transfected HEK293 cells were dissociated, fixed and analyzed for FRET on a flow cytometry BD LSRFortessa instrument by measuring 30,000 cells per construct. Results were analyzed with two-sided t-tests followed by Bonferroni correction for multiple testing. Results: FRET and FLIM assays demonstrated that all three isoforms exhibit domain interaction within cells. Substantially increasing the number of cells measured using FRET-flow cytometry confirmed presence of FRET but also revealed the presence of subtle conformational differences between isoforms, with apoE4 adopting a more closed conformation (higher FRET efficiency) than apoE2 and apoE3 (p-values <0.0001 and

0.003, respectively). The difference between apoE2 and apoE3 was more subtle, with apoE2 exhibiting a slightly more open conformation (lower FRET efficiency) than apoE3 (p-value 0.046). Conclusion: Here, we describe a series of genetically encodable tools that robustly recapitulate *in vitro* the differences in domain interaction between apoE isoforms. Future studies could elucidate how amyloid and AD risk factors modulate domain interaction to increase susceptibility to disease.

Disclosures: E. Kara: None. **E. Hudry:** None. **Z. Fan:** None. **S. Wegmann:** None. **M. Maesako:** None. **O. Berezovska:** None. **B.T. Hyman:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.01

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS044266

NIH Grant AG017586

Wyncote Foundation

Title: Fronto-parietal network efficiency accurately classifies underlying pathology in corticobasal syndrome

Authors: *J. D. MEDAGLIA[1,2], W. HUANG[3], S. SEGARRA[3], C. OLM[3], J. GEE[3], M. GROSSMAN[3], A. RIBEIRO[3], C. MCMILLAN[3], D. BASSETT[3];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Moss Rehabil. Res. Inst., Elkins Park, PA; [3]The Univ. of Pennsylvania, Philadelphia, PA

Abstract: Corticobasal syndrome (CBS) is a clinically homogeneous but pathologically heterogeneous neurodegenerative disease resulting from either frontotemporal lobar degeneration (FTLD) or Alzheimer's disease (AD). Multimodal neuroimaging studies have demonstrated that a combination of gray matter MRI and diffusion tensor imaging (DTI) of white matter can reliably distinguish between AD and FTLD pathology. However, these studies have typically included clinically heterogeneous patient cohorts and therefore may have been confounded by the spatial heterogeneity of the circuits involved in these neurodegenerative diseases. Here we assess the reliability of neuroimaging to discriminate between pathological sources in clinically homogeneous corticobasal syndrome (CBS) using graph theoretical methods sensitive to

alterations in distributed brain circuits. We parcellate the brain into 119 regions based upon the labeled OASIS dataset. We construct structural brain networks in individuals with FTLD (N=19) or AD (N=21) by linking all regions with the number of white matter streamlines identified in a deterministic tractography analysis. Pathology was confirmed by autopsy or a cross-validated cerebrospinal fluid total-tau to beta-amyloid ratio. We then identify regions in a large fronto-parietal network with reduced gray matter volume in CBS (N=40) relative to age-matched controls (N=40) and characterize white matter networks with 5 graph-based statistics within this system. To evaluate classification power, we apply leave-one-out cross validation using supervised support vector machine (SVM) separately for (i) gray matter volume, and (ii) each network statistic in the fronto-parietal system. The SVM procedure demonstrated that gray matter volumes poorly discriminated between FTLD and AD with only 52% sensitivity and specificity. In contrast, local efficiency, a measure of how a region contributes to the information across the network, was the most sensitive and specific (84%) network statistic in the fronto-parietal system. A majority vote combination of network statistics achieved a marginally better sensitivity/specificity of 85%. Our results demonstrate that the underlying pathological sources of CBS can be classified more accurately using graph-theoretical statistics derived from patterns of white matter microstructure in the fronto-parietal system than by regional gray matter volume alone, highlighting the importance of a multimodal approach to diagnostic neuroimaging analyses of CBS.

Disclosures: **J.D. Medaglia:** None. **W. Huang:** None. **S. Segarra:** None. **C. Olm:** None. **J. Gee:** None. **M. Grossman:** None. **A. Ribeiro:** None. **C. McMillan:** None. **D. Bassett:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.02

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSERC 418489

CIHR 126127

OMHF Fellowship

Ontario Premier's Discovery Award

CFI John R. Evans Leaders Fund 34213

Canadian Consortium on Neurodegeneration in Aging

Title: Searching for treatable links between stroke and Alzheimer's disease in a new rat model: Quantitative imaging of ganglioside expression using MALDI mass spectrometry

Authors: *N. WEISHAUPT[1], D. F. CECHETTO[1], V. HACHINSKI[2], S. N. WHITEHEAD[1]; [1]Anat. and Cell Biol., Univ. of Western Ontario, London, ON, Canada; [2]London Hlth. Sci. Ctr., London, ON, Canada

Abstract: Alzheimer's Disease (AD) is diagnosed in a rapidly increasing number of elderly individuals. No single factor has been identified to cause late onset AD, however, vascular risk factors seem to play a substantial role in the development of dementia. Specifically, there seems to be a critical but poorly understood relationship between stroke and AD. While evidence indicates that stroke may render neurons more vulnerable to AD pathology, how this occurs on a cellular level is unknown. In search of a potential mechanism behind the interaction of stroke and AD, we focus on the cell membrane. Membrane lipids such as gangliosides are critically implicated in neuronal functions and survival, and it has been suggested that they can influence a cell's vulnerability to external stressors. We know that stressors such as stroke can change ganglioside expression patterns, and ganglioside GM-1 supplementation has shown neuroprotective effects in various models of neurodegenerative diseases. Taken together, this evidence points towards gangliosides as potential players in harmful interactions between stroke and AD pathology. Based on this, **we hypothesize that stroke triggers changes in ganglioside expression, which render neurons in the elderly rat brain more vulnerable to developing pathological and behavioural characteristics of AD**. To test this hypothesis, we use APP21 transgenic rats, which express the human form of $APP_{Swe/Ind}$. These rats do not spontaneously exhibit histological hallmarks of AD but they are susceptible to developing characteristics of AD when challenged. In a subset of adult transgenic and wildtype animals, we induce striatal stroke by intracerebral endothelin-I injection. Control animals receive an injection of saline instead. At 28 days post-stroke, brains are harvested and ganglioside (GM1, GM2, GM3, GD1, GD2) expression patterns are analyzed in brain sections using matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI-IMS). This technique allows us to measure the expression of different ganglioside species in an anatomical context both in the vicinity of the stroke and in remote brain regions. In addition, brain sections are screened for histopathological correlates of AD. Preliminary results indicate that ipsilesional changes in ganglioside expression may occur even in strategic brain regions remote from the stroke core, with few but distinct differences between transgenic and wildtype animals.

Disclosures: N. Weishaupt: None. **D.F. Cechetto:** None. **V. Hachinski:** None. **S.N. Whitehead:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.03

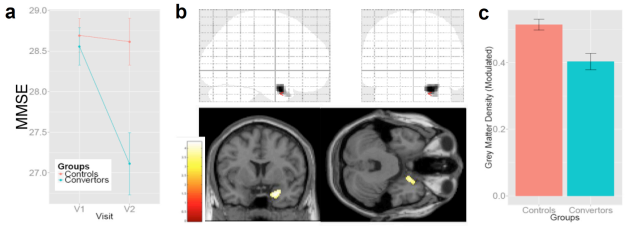
Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Structural MRI predicts conversion from healthy elderly individual to mild cognitive impairment (MCI)

Authors: A. SIERRA-MARCOS[1], *C. LONG[1,2], E. ALFAYATE[1], M. MEDINA[3,4], B. STRANGE[5,4];
[1]Neuroimaging, Queen Sofia Fndn. Alzheimers Ctr., Madrid, Spain; [2]Sloan Neuroeconomics Lab., MIT, Cambridge, MA; [3]Ctr. de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Madrid, Spain; [4]Neuroimaging, Queen Sofia Fndn. Alzheimer Ctr., Madrid, Spain; [5]Lab. for Clin. Neuroscience, CTB, Technial Univ. of Madrid, Madrid, Spain

Abstract: The pathophysiology of Alzheimer's disease (AD) is known to start before the appearance of clinical symptoms. In particular, the entorhinal cortex (EC), a key component of the episodic memory system, shows early signs of tau pathology in AD. However, there is currently no method to reliably assess the likelihood of developing AD from a healthy state. The potential value of a pre-MCI marker would be improved efficacy of therapeutic or preventive interventions. Here, we examined anatomical differences in two matched groups of healthy elderly individuals (N=27/27), one of which went on to exhibit MCI in the subsequent visit. Before exclusions, our sample had 1087 subjects (63.5% female) aged 70-85, with yearly follow-ups as part of a 5 year longitudinal study. The control group was matched using age, gender, APOE ε4, MiniMental State Examination (MMSE) and years of education, and constrained to yield one control per “converter”. We analysed structural MRI T1-sequences (1mm isotropic resolution on a 3T GE MRI, 8-channel head coil) acquired at visit 1 (V1), using the group labels indicating presence/absence of MCI obtained from neurological/neuropsychological evaluations at visit 2 (V2). Voxel-Based Morphometry (VBM) analysis, using SPM12, proceeded as follows. For each subject, grey matter tissue maps were extracted and a nonlinear spatial registration technique (Dartel) applied. Following this spatial standardization, the grey matter density (GMD) maps were entered into an unpaired voxelwise t-test, corrected for multiple comparisons. This VBM analysis yielded a highly focal difference between groups. Figure 1 shows: a) Significant decrease in MMSE score for the converter group from V1 to V2. b) Significant differences in GMD between the two groups at V1 (height thresholded $p<0.001$; extent threshold 50 contiguous voxels) and shown on a “glass” brain and in orthogonal sections. c) GMD values extracted from the peak voxel located at Zmax in (right EC) for each group. Error bars indicate s.e.m. In

conclusion, GMD in the EC may be predictive of conversion to MCI in healthy elderly populations.



Disclosures: **A. Sierra-Marcos:** None. **C. Long:** None. **E. Alfayate:** None. **M. Medina:** None. **B. Strange:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.04

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association

UW CHDD small animal imaging core

Title: White matter dysintegrity in aging and mice transgenic for Alzheimer's pathology revealed by diffusion tensor imaging

Authors: ***D. J. CROSS**[1], M. M. CLINE[1], G. G. GARWIN[1], C. G. CROSS[2], S. MINOSHIMA[3]; [1]Univ. of Washington, Seattle, WA; [2]Brown Univ., Providence, RI; [3]Univ. of Utah, Salt Lake City, UT

Abstract: Using MR imaging with manganese (MEMRI) to examine axonal transport rates *in vivo*, we reported previously decreased transport in mice transgenic (Tg) for Alzheimer's disease (AD). For this study, we hypothesized 3xTg-AD mice would show decreased fractional anisotropy (FA) on diffusion tensor imaging (DTI) indicating loss of white matter integrity as part of the neuropathological cascade in AD. Methods: Mice, (3xTg-AD, n=15 and wild-type (WT) n=8) were imaged at 10 weeks and again at 6 mos. of age. DTI (14T Bruker Biospin Corp) was acquired over the entire brain using a 4-shot echo-planar imaging (EPI) sequence applied along 30 non-colinear diffusion-gradient directions; voxel size 0.195x0.195x0.5 mm3, 35 slices, FA/TR/TE: 90deg/8750ms/17.8ms. DTI processing included a custom algorithm, to eliminate

image frames contaminated by motion artifacts, followed by eddy current and B0 corrections. FA maps were constructed from DTI by FSL software (Analysis Group, FMRIB, Oxford, UK). Regions of interest were manually drawn in the right and left external capsules and averaged across 3 consecutive slices to estimate white matter integrity by a researcher blinded to groups. Results: 3xTg-AD mice have significantly reduced fractional anisotropy (FA), a marker of white matter integrity as early as 10 wks. of age (Wild-type: 0.38±0.02 vs. 3xTg-AD: 0.32±0.03, 16% decreased $p \leq 0.01$). WT had a modest, but significant aged-related decrease in FA (10wks: 0.38±0.02 versus 6mos: 0.37±0.02, 5% decrease $p=0.05$). However, 3xTg-AD mice did not have a further significant aged-related decrease (10wks: 0.32±0.03 versus 6mos: 0.32±0.02). Conclusions: Axon-related deficits are an early feature in the AD neuropathological cascade that precedes traditional AD pathology of amyloid plaques and neurofibrillary tangles and may underlie the specific vulnerability of neuronal populations with long axons to the disease process. This finding may be a result of early aggregating proteins (abeta oligomers and phosphorylated tau), however further research is needed to investigate the underlying mechanisms.

Disclosures: D.J. Cross: None. **M.M. Cline:** None. **G.G. Garwin:** None. **C.G. Cross:** None. **S. Minoshima:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.05

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Indiana University Dean's fund

Title: White-matter shape attributes as biomarkers for Alzheimer’s disease

Authors: *T. GLOZMAN[1], R. LE[1], L. GUIBAS[1], F. PESTILLI[2];
[1]Stanford Univ., Stanford, CA; [2]Indiana Univ., Bloomington, IN

Abstract: Introduction: Alzheimer’s disease (AD) is the most common form of dementia in adults over 65. Although many studies have measured the effect of tissue degeneration for subcortical structures such as the hippocampi, amygdala, and the ventricles, little is known about the changes that occur in the structure of the white matter (WM) during the course of AD. We describe an automatic framework for classification of AD patients and Normal Controls (NC), based solely on the three dimensional shape of the twenty major WM tracts. Our framework automatically identifies twenty major human WM tracts from diffusion-weighted magnetic

resonance imaging data using fiber tracking, calculates the shape attributes of each tract and employs machine learning methods to train a classifier able to distinguish between AD and NC subjects. We evaluate our framework on a cohort of 49 AD and 57 NC subjects available through the Alzheimer's Disease Neuroimaging Initiative. Results: The shape of each tract was summarized using only two values, namely the "root" and "canopy" support measure of the tract, which was estimated by calculating the volume of the cube encapsulating the endpoints on each end. Intuitively, this provides us with the measure of the cortical termination and the origin volume of the tract. As the tissue degeneration progresses, this cortical termination is expected to shrink. Our support descriptor is thus coarse enough to overcome the uncertainty in tractography output near the cortex region (viewed by many researchers as non-robust and noisy), while still being accurate enough to capture the shape variability in the white matter caused by degeneration, as illustrated in figure 3. We employ a simple feature ranking method and train a radial basis function kernel based support vector machine classifier. We achieved 92.07% accuracy in classification of AD patients vs. NC subjects. Discussion: We show that white matter shape attributes provide important information that can be used to identify early onset of AD. These biomarkers of AD have been largely ignored in the literature. We plan to continue exploring the shape individuality and variability in WM in different stages of dementia and analyzing available data sets to establish identification methods for prodromal AD.

Disclosures: **T. Glozman:** None. **R. Le:** None. **L. Guibas:** None. **F. Pestilli:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.06

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NS 062184

MH 087660

GM 08273

Harvey Family Endowment

Title: Axonal transport is dependent on intact kinesin-1 in the important memory circuit from hippocampus to basal forebrain: A magnetic resonance imaging study

Authors: *C. MEDINA[1], O. BIRIS[3], T. L. FALZONE[4], X. W. ZHANG[5], R. E. JACOBS[6], E. L. BEARER[2];
[1]Pathology, [2]Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [3]Div. of Engineering, Brown Univ., Providence, RI; [4]IBYME-CONICET; IBCN, Facultad de Medicina, Univ. de Buenos Aires, Buenos Aires, Argentina; [5]Beckman Inst. at California Inst. of Technol., Pasadena, CA; [6]4Beckman Inst. at California Inst. of Technol., Pasadena, CA

Abstract: Defects in axonal transport are implicated in peripheral neuropathies and in neurodegeneration, yet imaging transport within the living brain has proved challenging. We have developed manganese-enhanced magnetic resonance imaging (MEMRI) to witness transport within axonal bundles in living mice. In previous studies we demonstrated that Mn^{2+} transport is delayed in the optic nerve when kinesin-1 is defective, as occurs in the kinesin light chain 1 knock-out (KLC1-KO) mice. Here we investigate whether similar transport dynamics can be detected and measured in the living brain by MEMRI. We injected 3-5 nL of 600 mM Mn^{2+} into CA3 of the posterior hippocampus and imaged axonal transport *in vivo* by capturing whole-brain 3D magnetic resonance images (MRI) at discrete time points after injection in the 11.7T Bruker scanner. Mn^{2+} is a paramagnetic ion that enters neurons through voltage-gated calcium channels. Once inside the neuron, Mn^{2+} travels down the axon apparently by axonal transport. Since Mn^{2+} causes a reduction in the relaxation time of protons, a hyper-intense area appears in the MR image wherever the Mn^{+2} is present. Statistical parametric mapping comparing intensities at successive time points revealed the position of the Mn^{2+}-enhanced MR signal as it proceeded from the injection site into the forebrain, the expected projection from CA3. Comparisons of results between KLC1-KO mice to their wildtype littermates by visual inspection of statistical maps and by quantitative region of interest analyses demonstrate that distal accumulation of Mn^{2+}-induced intensity changes is delayed by 30% at 6 hr post-injection, and achieved normal levels at 24 hr in the KLC1-KO mice, suggesting a delay in axonal transport consistent with our earlier findings in the optic tract. DTI and correlation histology showed that the KLC1-KO brain is 10% smaller with similar decrease diameter of axonal bundles, which was insufficient to account for the delayed transport. These findings demonstrate that transport in the central nervous system is in part dependent on intact kinesin-1, and that MEMRI has the power to detect differences in transport dynamics within the living brain.

Disclosures: C. Medina: None. **O. Biris:** None. **T.L. Falzone:** None. **X.W. Zhang:** None. **R.E. Jacobs:** None. **E.L. Bearer:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.07

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CNPq, Brazil

CAPES, Brazil

National Institute of Translational Neuroscience, INNT, Brazil

FAPERJ, Brazil

Title: Increased D-serine levels as a potential biomarker in Alzheimer's diaease

Authors: *M. V. LOURENÇO[1], C. MADEIRA[1], C. VARGAS-LOPES[1], C. K. SUEMOTO[2], C. O. BRANDÃO[1], T. REIS[1], R. E. P. LEITE[2], J. LAKS[1], W. JACOB-FILHO[2], C. A. PASQUALUCCI[2], L. T. GRINBERG[2,3], S. T. FERREIRA[1], R. PANIZZUTTI[1];
[1]Fed Univ. of Rio De Janeiro, Rio De Janeiro, Brazil; [2]Univ. of São Paulo, São Paulo, Brazil; [3]Univ. of California San Francisco, San Francisco, CA

Abstract: Alzheimer's disease (AD) is a severe neurodegenerative disorder still in search of effective diagnosis. Altered levels of the NMDA receptor co-agonist, D-serine, have been associated with neurological disorders, including schizophrenia and epilepsy. However, whether D-serine levels are deregulated in AD remains elusive. Here, we first measured D-serine levels in post-mortem hippocampal and cortical samples from nondemented subjects (n = 8) and AD patients (n = 14). We next determined D-serine levels in experimental models of AD, including wild-type rats and mice that received intracerebroventricular injections of amyloid-β oligomers, and APP/PS1 transgenic mice. Finally, we assessed D-serine levels in the cerebrospinal fluid (CSF) of 21 patients with a diagnosis of probable AD, as compared with patients with normal pressure hydrocephalus (n = 9), major depression (n = 9) and healthy controls (n = 10), and results were contrasted with CSF amyloid-β/tau AD biomarkers. D-serine levels were higher in the hippocampus and parietal cortex of AD patients than in control subjects. Levels of both D-serine and serine racemase, the enzyme responsible for D-serine production, were elevated in experimental models of AD. Significantly, D-serine levels were higher in the CSF of probable AD patients than in non-cognitively impaired subject groups. Combining D-serine levels to the amyloid/tau index remarkably increased the sensitivity and specificity of diagnosis of probable AD in our cohort. Our results show that increased brain and CSF D-serine levels are associated with AD. CSF D-serine levels discriminated between nondemented and AD patients in our cohort and might be incorporated in a candidate biomarker panel for early AD diagnosis.

Disclosures: **M.V. Lourenço:** None. **C. Madeira:** None. **C. Vargas-Lopes:** None. **C.K. Suemoto:** None. **C.O. Brandão:** None. **T. Reis:** None. **R.E.P. Leite:** None. **J. Laks:** None. **W. Jacob-Filho:** None. **C.A. Pasqualucci:** None. **L.T. Grinberg:** None. **S.T. Ferreira:** None. **R. Panizzutti:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.08

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Forschungspool Klinische Studien, Medical Faculty, University of Cologne

Title: Dissociable impact of cholinergic system integrity and white matter lesion load on cognition in mild cognitive impairment

Authors: *J. KUKOLJA[1], A. MICHEL[2], N. RICHTER[2], Ö. ONUR[2], L. KRACHT[4], M. DIETLEIN[3], M. TITTGEMEYER[4], B. NEUMAIER[4], G. R. FINK[2];
[2]Dept. of Neurol., [3]Dept. of Nuclear Med., [1]Univ. Hosp. Cologne, Cologne, Germany; [4]Max-Planck-Institute for Metabolism Res., Cologne, Germany

Abstract: The cerebral cholinergic system is a central modulator of attention and episodic memory processes. Its degeneration in Alzheimer's disease is believed to underlie the progressing memory deficits associated with this disease. Although subcortical vascular lesions are frequent in older age, less is known about the link between vascular lesion load and the integrity of the cholinergic system. Recent evidence suggests that vascular white matter lesions (WML) disrupt cholinergic fibre tracts and thereby cause cognitive deficits. Yet unclear is the interrelation between white matter integrity and the cholinergic system and their individual impact on cognitive performance. Healthy old volunteers and patients with mild cognitive impairment (MCI) underwent neuropsychological assessment, brain MRI and PET imaging. In order to assess WML severity, the semiquantitative Scheltens scale was used. N-[11C]-methyl-4-piperidyl acetate (MP4A-) PET imaging allowed to measure cortical Acetylcholinesterase (AChE) activity. Using SPM8, we calculated voxel-wise multiple regression analyses between MP4A-k3-maps, Scheltens scale values and cognitive performance. Severity of WML was inversely correlated with executive functions and visuo-spatial memory. In the MCI group, WML were negatively correlated with attention performance. Cortical cholinergic activity was generally negatively correlated with WML. The highest impact on cholinergic activity, especially in the temporal and parietal cortices, was exerted by periventricular WML load. Multiple regression analyses revealed a dissociation between the effects of cholinergic activity and WML load on cognitive performance. Cortical AChE activity predicted performance across cognitive domains even when WML load was controlled for. However, WML load was negatively associated with memory and executive function only in concert with associated cortical AChE reduction. In conclusion, we found evidence that cerebral cholinergic system

integrity predicts cognitive performance irrespective of WML load. Our results further suggest that WML cause cognitive deficits at least in part via a disruption of cholinergic pathways.

Disclosures: **J. Kukolja:** None. **A. Michel:** None. **N. Richter:** None. **Ö. Onur:** None. **L. Kracht:** None. **M. Dietlein:** None. **M. Tittgemeyer:** None. **B. Neumaier:** None. **G.R. Fink:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.09

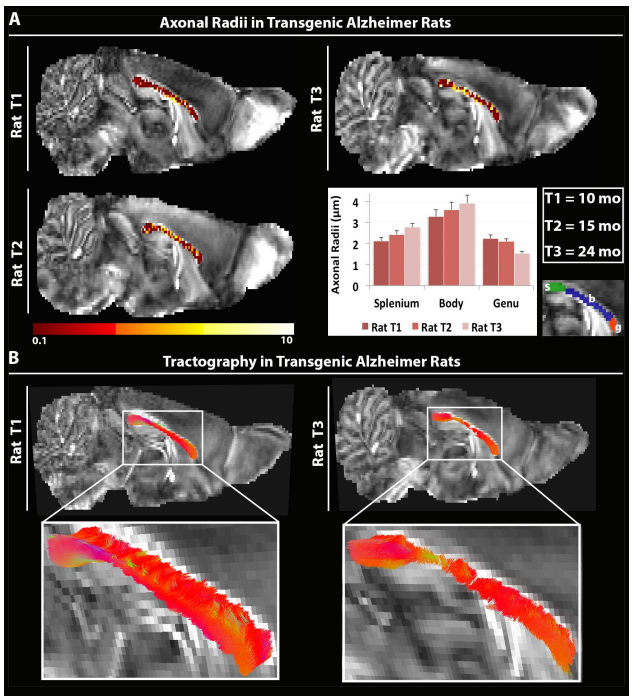
Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Axonal diameter estimated with 7-tesla hybrid diffusion imaging in transgenic Alzheimer's rats

Authors: ***M. DAIANU**[1], Z. ABARYAN[2], R. E. JACOBS[4], T. TOWN[3], P. M. THOMPSON[2]; [1]Inst. for Neuroimaging and Informatics, USC, Marina Del Rey, CA; [2]USC, Marina del Rey, CA; [3]USC, Los Angeles, CA; [4]Caltech, Pasadena, CA

Abstract: Alzheimer's disease (AD) is the most common form of dementia in the elderly. AD pathology involves the abnormal accumulation of amyloid plaques and neurofibrillary tangles, but white matter (WM) changes also occur, including myelin breakdown, and loss of connectivity. Complementing methods to tau and amyloid imaging, diffusion-weighted MRI is sensitive to subtle changes in WM microstructure. Here we used 7-Tesla hybrid diffusion imaging to scan 3 transgenic (Tg) rats ex vivo at 10, 15 and 24 months, bearing mutant human amyloid precursor protein and presenilin 1. We acquired 300 DWI volumes across 5 q-sampling shells (b=1000, 3000, 4000, 8000, 12000 s/mm2). We computed fractional anisotropy measures - reflecting the directionality of molecular displacement by diffusion, at each b-value in the corpus callosum (CC). The diffusion signal had highest signal-to-noise ratio from the first three shells versus the last two (2-tailed t-test P=0.04). From the top three b-value shells, we reconstructed axonal diameter maps (using ActiveAx, http://cmic.cs.ucl.ac.uk/) and WM tractography with diffusion tensor imaging in the CC (genu, body and splenium) of the three Tg rats. As expected, axonal diameter was larger in the CC body than the genu and splenium (see Figure). Axonal diameters increased across the three time points (except in the genu), possibly indicating neuritic dystrophy - characterized by enlarged axons and dendrites (as seen on electron microscopy in the cortex and hippocampus of Tg rats in a study by Terrence Town and colleagues). Tractography detected fewer fibers in the CC at 10 versus 24 months. These preliminary findings are in

preparation for larger scale connectivity analyses and offer great potential to provide technical and scientific insight into the neurobiology of disease.



Disclosures: **M. Daianu:** None. **Z. Abaryan:** None. **R.E. Jacobs:** None. **T. Town:** None. **P.M. Thompson:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AG043503

AG017586

ALS Association

Wyncote Foundation

Title: Cerebrospinal fluid provides a prognostic marker for amyotrophic lateral sclerosis

Authors: *C. MCMILLAN[1,2], S. XIE[2], D. IRWIN[2], K. RASCOVSKY[2], X. HAN[2], E. MORAN[2], K. FIRN[2], J. WOO[2], L. SHAW[2], L. ELMAN[2], L. MCCLUSKEY[2], M. GROSSMAN[2];
[1]Neurol., [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurodegenerative disease with a typical range of survival between 2-5 years. Prognostic markers are needed to improve management of clinical care and provide quantitative endpoints in the context of clinical trials. Cerebrospinal fluid (CSF) measures of total-tau (ttau) are hypothesized to provide a marker of neuronal degeneration in neurodegenerative diseases but the potential prognostic utility has not been evaluated in ALS. We also evaluate phosphorylated tau at threonine 181 (ptau) as a control biomarker that has previously been demonstrated to be elevated in tauopathies but not involved in ALS. CSF ttau and ptau were measured using the Luminex/XMAP platform in 71 ALS patients [13 (+/- 12) month disease duration; 57 (+/- 11) years old]. Disease progression was measured using rates of survival (months from onset to death), rates of functional decline using the ALS functional rating scale (FRS-R), and rates of physical decline using body mass index (BMI). We also related CSF ttau to MRI measure of grey matter density (GMD) in a subset of ALS patients (N=27). Statistical analyses included age of onset and onset site (bulbar vs. limb) as nuisance covariates since these factors have been demonstrated to contribute to survival. A cox regression analysis revealed that CSF ttau was significantly associated with survival [Hazard Ratio=1.016; p=0.009]: for every 10 pg/ml of CSF ttau there is a 16% increased risk of death. Linear mixed effects regression models evaluated longitudinal decline for all 71 patients across a total of 396 clinical visits: elevated CSF ttau was associated with increased rate of FRS-R decline [B=-0.009; p<0.0001] and increased rate of BMI decline [B=-0.002-; p<0.0001]. Imaging regression analyses related reduced GMD to CSF ttau and observed an association in left supplementary motor and dorsal inferior frontal cortex (BA9) along with right middle temporal cortex (BA21; all peak p<0.05 FDR). All analyses of CSF ptau did not reach significance. Together these findings provide converging evidence that CSF ttau, and not CSF ptau, provides a prognostic biomarker in ALS related to survival, functional decline, physical decline, and neuroanatomic disease severity. We suggest that CSF ttau provides a prognostic quantitative endpoint for future clinical trials related to ALS.

Disclosures: C. McMillan: None. **S. Xie:** None. **D. Irwin:** None. **K. Rascovsky:** None. **X. Han:** None. **E. Moran:** None. **K. Firn:** None. **J. Woo:** None. **L. Shaw:** None. **L. Elman:** None. **L. McCluskey:** None. **M. Grossman:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01 AG037376

R01 AG040271

P01 AG017586

P30 AG010124

Title: *In vivo* and *ex vivo* imaging in the same subjects of the human hippocampal formation

Authors: *L. WISSE[1], D. H. ADLER[1], R. ITTYERAH[1], J. B. PLUTA[1,2], J. L. ROBINSON[3], T. SCHUCK[3], J. Q. TROJANOWSKI[3], M. GROSSMAN[3], S. R. DAS[1], D. A. WOLK[2], P. A. YUSHKEVICH[1];
[1]Radiology, [2]Neurol., [3]Pathology and Lab. Med., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Introduction: Hippocampal subfields play a major role in memory and dementia. Delineation of these subfields *in vivo* relies on heuristic rules, as most histological boundaries are difficult to discern on *in vivo* scans. However, the validity of these heuristic rules is under debate. Ultimately a translation from histology to ex vivo MRI to *in vivo* MRI is needed. In this study, we will focus on the translation from ex vivo to *in vivo* MRI and compare hippocampal size and structure on *in vivo* and ex vivo MRI in the same subjects. Methods: Pairs of 0.2x0.2x0.2 mm3 ex vivo and 0.4x0.4x2.6 mm3 *in vivo* T2-weighted MRI scans (time between scans 2.2±0.7 years) from nine subjects (age at death 66.4±8.9; 56% men; Mild Cognitive Impairment n=2, Frontotemporal dementia n=3, Semantic, Alzheimer's dementia, Primary Progressive Aphasia, aphasia n=1) were aligned using Histolozee (by DHA). Thickness was measured in one coronal slice, one slice posterior to the uncus. Height of the hippocampus proper (HP), subiculum (SUB) and dentate gyrus (DG) and cornu ammonis (CA) 3, and width of the HP, CA1 and DG&CA3 were measured (fig) and compared using non-parametric tests. Results: We were able to closely align the *in vivo* and ex vivo scans. Several features, e.g. the shape of the HP and of the white matter band, were similar in the *in vivo* and ex vivo images, though several differences, e.g. thickness of CA, could also be observed (fig). Thickness measurements revealed stat. significant differences between *in vivo* and ex vivo images for HP height (6.40±0.48 vs 6.81±0.61 mm), and HP (8.31±0.85 vs 8.85±1.02), CA1 (0.68±0.08 vs 1.28±0.23) and DG&CA3 width (6.78±0.94 vs 6.32±1.15), but not for SUB (1.58±0.43 vs 1.77±0.57) and DG&CA3 height (4.30±0.58 vs 4.31±0.64). Conclusions: This is the first study to compare a set of same subject *in vivo* and ex vivo image pairs of the human hippocampus. The close alignment and similarities of the *in vivo* and ex vivo images indicate that mapping

cytoarchitectonic information from ex vivo to *in vivo* MRI is feasible, though a strategy needs to be developed that accounts for differences in structure and size.

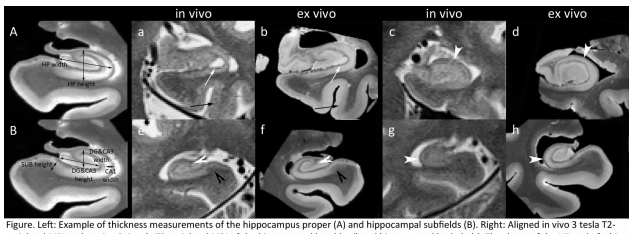


Figure. Left: Example of thickness measurements of the hippocampus proper (A) and hippocampal subfields (B). Right: Aligned in vivo 3 tesla T2-weighted MRI and ex vivo 9.4 tesla T2-weighted MRI of the hippocampal head (a-d) and hippocampal body (e-h). The shape of the HP and of white matter band (white arrows in a and b) can be appreciated in both the in vivo and ex vivo images, as well as the endfolial pathway (white arrow heads in e and f), different subicular layers (black arrow heads in e and f) and different perirhinal cortical layers (black arrows in a and b). On the other hand, compared to ex vivo images, on in vivo images CA appears smaller (closed white arrrow heads in c, d, g, h), the hippocampus appears slightly larger (especially c and d) and cysts appear larger (white arrows in a and b).

Disclosures: L. Wisse: None. **D.H. Adler:** None. **R. Ittyerah:** None. **J.B. Pluta:** None. **J.L. Robinson:** None. **T. Schuck:** None. **J.Q. Trojanowski:** None. **M. Grossman:** None. **S.R. Das:** None. **D.A. Wolk:** None. **P.A. Yushkevich:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.12

Topic: C.05. Aging

Title: Functional brain activation patterns associated with preclinical Alzheimer's disease

Authors: *B. T. GOLD, J. HAKUN, C. BROWN, L. BROSTER, Y. JIANG;
Univ. of Kentucky, Lexington, KY

Abstract: Alzheimer's disease (AD) has a long preclinical stage. However, relatively little is known about the potential link between accumulating Aβ and tau protein levels and non-invasive functional brain activation patterns in cognitively normal (CN) older adults. Here we explored this potential relationship by correlating functional magnetic resonance imaging (fMRI) data during a visual working memory task with CSF protein levels in CN older adults. Thirty seven CN older adults (mean age = 76.2, SD = 7.5; 21 females) completed a short-term memory task while fMRI was performed using a 3T Siemens TIM scanner. Tensor-based independent components analysis (ICA) was conducted using FSL's MELODIC to identify task-related regions of interest (ROIs) for correlation with CSF protein levels. For fMRI magnitude analyses, BOLD signal in each ROI was averaged over all trials in each task epoch relative to baseline for each participant. For fMRI connectivity analyses, correlations were performed on trial by trial percent signal-change estimates between each ROI for each participant. Connectivity between

the left MFG and each LOC region was then averaged to create a single fronto-occipital fC estimate per task phase for each participant. Lumbar CSF was drawn and Aβ1-42, total tau (t-tau) and phosphorylated-tau181 (p-tau181) were measured according to standard protocols (Olsson et al., 2005). Partial correlation analyses were performed to assess relationships between fMRI data and levels of AD risk assessed by CSF protein levels (higher risk is associated with lower levels of CSF Aβ42 and higher levels of CSF tau) controlling for age and sex. Results indicated negative partial correlations between BOLD magnitude in the left DLPFC/LOC ROI and CSF Aβ42 ($r = -0.52$, $p = 0.002$), and the Aβ42/tau ratio ($r = -0.45$, $p = 0.007$), and a positive correlation with the Tau/Aβ42 ratio ($r = 0.41$, $p = 0.01$) when controlling for age and sex. In contrast, there were positive partial correlations between left DLPFC/LOC functional connectivity scores and CSF Aβ42 ($r = 0.39$, $p = 0.020$), Aβ42/tau ratio ($r = 0.39$, $p = 0.02$) and Aβ42/pTau ratio ($r = 0.43$, $p = 0.01$) when controlling for age and sex. Our results provide evidence for an association between patterns of fMRI brain activation patterns and preclinical AD biomarkers in CN older adults. Whereas increased BOLD magnitude in fronto-occipital regions was associated with increasing risk of preclinical AD, increased functional connectivity between those fronto-occipital regions was associated with lower risk of future AD.

Disclosures: **B.T. Gold:** None. **J. Hakun:** None. **C. Brown:** None. **L. Broster:** None. **Y. Jiang:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.13

Topic: C.05. Aging

Support: William E. Mabie and Grace S. Mabie Fund

Title: Small vessel disease is a prominent feature of Alzheimer's disease

Authors: *R. S. MILETICH[1], D. WACK[1], M. HOURIHANE[2], B. AJTAI[2];
[1]Nuclear Med., UB, SUNY, Buffalo, NY; [2]Dent. Neurologic Inst., Amherst, NY

Abstract: The most widely accepted etiology of Alzheimer's disease (ALZ), the Amyloid Cascade Hypothesis, proposes that accumulation of beta-amyloid sets into motion a toxic, detrimental cascade of effects leading to neurodegeneration. The Stressed Homeostasis Hypothesis (SHH) acknowledges the importance of multiple interactive and additive factors, including vascular disease, in causing ALZ. We reasoned that because the signal of SPECT

requires cellular uptake of bicisate, that SPECT will be more sensitive for the detection of small vessel disease (SVD) than structural MRI or lumen-based measures of perfusion, including MRP, CTP, and ASL. We examined over 6,000 brain perfusion bicisate SPECTs from the NMIC database at University at Buffalo. Three ordinal levels of cognitive impairment were studied: memory loss alone, mild cognitive impairment and dementia. The diagnosis of ALZ was based on the clinical presentation and outcome and by the grey matter perfusion profile of ALZ. We discovered that white matter SVD is a constant feature of late onset ALZ (LOAD), but is not always present in the phenotypically similar early onset ALZ (EOAD). Furthermore, white matter SVD progressively worsens with increasing degrees of cognitive impairment, no matter what grey matter patterns may be present. As compared to psychiatric illness or other neurodegenerative processes, white matter SVD is a more prominent covariate of the grey matter pattern of ALZ. These findings indicate that white matter SVD plays an important role in cognitive impairment and lend support to SHH as a better explanation for ALZ etiology. SVD appears not only capable of directly impairing cognition, but also is contributory to the neurodegenerative process called Alzheimer's disease. These findings support the use of basal physiologic functional imaging of perfusion or metabolism as a useful biomarker for the risk of developing and for the differential diagnosis of cognitive impairment. Creation of effective therapy for ALZ will first require identification of the relative strengths of the multiple factors causing ALZ.

Disclosures: **R.S. Miletich:** None. **D. Wack:** None. **M. Hourihane:** None. **B. Ajtai:** None.

Nanosymposium

462. Imaging and Biomarkers in Neurodegenerative Disease

Location: N226

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 462.14

Topic: C.05. Aging

Support: National Institute on Aging (AG045571)

The Davee Foundation

Northwestern University Alzheimer's Disease Center (AG013854)

Title: Resistance to Alzheimer's pathology in elderly with superior cognitive capacity

Authors: P. ABBASSIAN, A. REZVANIAN, J. SHI, S. WEINTRAUB, E. BIGIO, E. J. ROGALSKI, M.-M. MESULAM, *C. GEULA;
Cogn Neurol & Alzhei Dis Cent, Northwestern Univ. Med. Sch., Chicago, IL

Abstract: A majority of individuals who live to old age display cognitive functional decline. This is reflected in age-appropriate adjustments in norms for neuropsychological tests. Some elderly, on the other hand, perform significantly better than their peers on cognitive tests. We have coined the term 'SuperAger' to refer to individuals over the age of 80, whose performance on tests of memory is at least equivalent to healthy 50-65 year-olds, and on tests of other cognitive domains at least equivalent to their cognitively normal aged peers. Amyloid plaques (AP) and neurofibrillary tangles (NFT) are present in the brains of virtually all normal elderly in limited density and distribution, but display higher density and wider distribution in mild cognitive impairment (MCI) and Alzheimer disease (AD). We investigated the distribution and density of AP and NFT in the entorhinal cortex, the site in which NFT appear first, in five SuperAged individuals and five age-matched cognitively normal elderly controls. Mature AP and NFT were visualized using the Thioflavin-S (TS) stain and pre-NFT / NFT were immunostained using the PHF-1 antibody, which recognizes tau phosphorylated at Ser396/404 - Thr181. The Braak staging of NFT in SuperAgers ranged between 0 and III whereas the range in normal elderly was between II and IV. Unbiased stereological analysis revealed 180% lower density of TS-stained NFT in SuperAgers than the control group ($p=0.003$). A similar pattern was observed for PHF-1 immunoreactive pre-NFT / NFT, where the density in SuperAgers was ten-fold lower when compared with controls ($p<0.03$). The density of TS-positive mature plaques was more variable, but also was significantly lower in SuperAgers than the control group ($p=0.02$). Our findings suggest that SuperAgers may be resistant to the age-related accumulation of AD pathology. Thus pre-NFT / NFT, and to a smaller degree mature AP, appear to display an inverse relationship with cognitive status in the SuperAged-normal aged-MCI-AD continuum.

Disclosures: P. Abbassian: A. Employment/Salary (full or part-time); Northwestern University. **A. Rezvanian:** A. Employment/Salary (full or part-time); Northwestern University. **J. Shi:** A. Employment/Salary (full or part-time); Northwestern University. **S. Weintraub:** A. Employment/Salary (full or part-time); Northwestern University. **E. Bigio:** A. Employment/Salary (full or part-time); Northwestern University. **E.J. Rogalski:** A. Employment/Salary (full or part-time); Northwestern University. **M. Mesulam:** A. Employment/Salary (full or part-time); Northwestern University. **C. Geula:** A. Employment/Salary (full or part-time); Northwestern University.

Nanosymposium

463. Therapeutics of Parkinson's Disease: Preclinical Studies

Location: N230

Time: Tuesday, October 20, 2015, 8:00 AM - 10:15 AM

Presentation Number: 463.01

Topic: C.03. Parkinson's Disease

Title: Cell replacement therapy in Parkinson's disease utilizing trans-differentiation of mesenchymal stem cells

Authors: *R. WELCHKO[1,2], G. SHALL[1,2], L. SIEGEL[1,2], T. HULSE[1,2], S. PARKER[1,2], A. WADDLES[1], A. WRIGHT[1,2], M. LU[1,2], X. LEVEQUE[1], J. ROSSIGNOL[1,3], G. DUNBAR[1,2,4]; [1]Field Neurosciences Inst. Lab. For Restorative Neurol., Mount Pleasant, MI; [2]Central Michigan Univ., Mt. Pleasant, MI; [3]Central Michigan Univ. Col. of Med., Mount Pleasant, MI; [4]Field Neurosciences Inst., Saginaw, MI

Abstract: Parkinson's disease (PD) is a progressive and continuous neurodegenerative disorder. Transplantation of human embryonic dopaminergic progenitors within the striata of PD patients has provided encouraging results, but ethical concerns and tissue availability limit this approach. The use of mesenchymal stem cells (MSCs) and induced pluripotent stem cells offers an alternative cell source for transplantation that circumvents the ethical issues, and provides a readily available source of cells, as they are derived from adult tissue. This two part study (*in vitro* and *in vivo*) explored the use of MSCs as a cell source for DA neuronal induction prior to transplantation as a means to increase integration within the striatum. To this end, our lab developed a novel adenovirus for the polycistronic expression of multiple genes (Ascl1, Lmx1a, and Nurr1) that are involved in DA neuron differentiation and used gfp to track transfection. MSCs were cultured with the adenovirus, which resulted in morphological changes as well as expression of GFP as evidenced by fluorescence microscopy. The presence of the viral DNA within the transfected cells was confirmed with PCR. Immunocytochemistry and RT-PCR analyses revealed that, cells expressing GFP have nuclear co-labeling of ASCL1, LMX1a and, NURR1, as well as an up-regulation of these genes, along with an up-regulation of downstream gene targets, such as tyrosine hydroxylase, and the dopamine transporter. These results are indicative of active ASCL1, LMX1a and, NURR1 promoting dopaminergic differentiation. Furthermore these induced DA neuronal-like cells produced dopamine which has been quantified utilizing high performance liquid chromatography. Our *in vitro* results suggest that the approach used in this study may provide a new means of facilitating cell replacement therapy. Following the *in vitro* study, the *in vivo* study consisted of transplanting induced DA neuronal-like cells into the unilateral 6-hydroxydopamine (6-OHDA) lesion rat model of PD. The unilateral 6-OHDA lesion was assessed utilizing the cylinder test and amphetamine rotation. Induced DA neuron like cells, were transplanted into the dorsal striatum of rats at 8 weeks, following verification of the 6-OHDA lesion. There was a significant improvement in behavior in both behavioral tasks, in addition to cellular integration following cellular transplantation; thus indicating a potential clinical utility for this method.

Disclosures: **R. Welchko:** None. **G. Shall:** None. **L. Siegel:** None. **T. Hulse:** None. **S. Parker:** None. **A. Waddles:** None. **A. Wright:** None. **M. Lu:** None. **X. Leveque:** None. **J. Rossignol:** None. **G. Dunbar:** None.

Nanosymposium

463. Therapeutics of Parkinson's Disease: Preclinical Studies

Location: N230

Time: Tuesday, October 20, 2015, 8:00 AM - 10:15 AM

Presentation Number: 463.02

Topic: C.03. Parkinson's Disease

Support: Fritz Thyssen Stiftung

DFG Center for Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB)

Fundação para a Ciência e Tecnologia

Santa Casa da Misericórdia

Title: Adenosine A2A receptors as potential targets for Parkinson's disease-related cognitive deficits

Authors: ***T. F. OUTEIRO**[1], D. G. FERREIRA[1,2,3], V. L. BATALHA[2], H. VICENTE-MIRANDA[2], J. E. COELHO[2], F. Q. GONÇALVES[4], J. REAL[4], R. A. CUNHA[4,5], A. ALBINO-TEIXEIRA[3,6], L. V. LOPES[2];
[1]Univ. Med. Ctr. Goettingen, Goettingen, Germany; [2]Inst. de Medicina Molecular, Fac. of Medicine, Univ. of Lisbon, Lisbon, Portugal; [3]Dept. of Pharmacol. and Therapeut., Fac. of Medicine, Univ. of Porto, Porto, Portugal; [4]CNC-Center for Neurosci. and Cell Biology, Univ. of Coimbra, Coimbra, Portugal; [5]Fac. of Medicine, Univ. of Coimbra, Coimbra, Portugal; [6]MedInUP - Ctr. for Drug Discovery and Innovative Medicines, Univ. of Porto, Porto, Portugal

Abstract: The deposition of alpha-synuclein (aSyn) in Lewy bodies is the neuropathological hallmark of Parkinson´s disease (PD). In addition to the characteristic motor symptoms, cognitive disturbances are also common in PD. These cognitive deficits, which can predict the development of dementia in later stages, do not respond to dopamine therapies, and represent an unmet need in the treatment of PD. Recently, adenosine A2A receptors (A2AR) emerged as an attractive non-dopaminergic target for the treatment of both motor as well as non-motor symptoms of PD. Nevertheless, the precise molecular mechanisms underlying neuroprotection and the effects of blocking A2AR on synaptic plasticity and cognition in a PD context remain

unknown. Based on our previous data showing that aSyn oligomers impair long-term potentiation (LTP), we set out to investigate whether A2AR blockade prevented synaptic dysfunction. We found that hippocampal slices preincubated with the selective A2AR antagonist SCH58260 (110 min, 50 nM) did not lose the ability to sustain LTP when preincubated with aSyn oligomers (90 min, 500 nM) ($n=5-9$, $P<0.01$). Consistently, aSyn oligomers also failed to impair LTP in A2AR KO mice ($n=3-4$, $P<0.05$). This neuroprotection was achieved through the prevention of NMDA receptors basal overactivation caused by aSyn oligomers. We then tested a novel selective blocker of adenosine A2AR, KW6002, in the Thy1-driven human aSyn transgenic mice (Thy1-aSyn), in order to establish its potential to rescue memory and cognitive function. Thy1-aSyn mice and their WT littermates were treated for 1 month with KW6002 administered in the drinking water (3 mg/kg/day) and tested for hippocampal-dependent tasks using the Morris Water maze (MWM) and Y-maze tests. In the MWM, Thy1-aSyn mice presented a slower learning during acquisition and a lack of preference by the target quadrant during probe test. These deficits were reverted by A2AR blockade ($n=6-11$, $P<0.05$). In the Y-maze, Thy1-aSyn performed worse than WT mice, revealing no preference for the novel arm. When treated with the A2AR antagonist, short-term memory was restored ($n=6-11$, $P<0.05$). Overall, these results reveal the involvement of A2AR in the aSyn-associated synaptic and memory impairments by showing that long-lasting synaptic and behavioural effects of aSyn can be reverted by targeting adenosine A2AR. These findings provide a novel evidence for the use of adenosine A2AR antagonists as potential therapeutic targets in PD-related cognitive deficits.

Disclosures: **T.F. Outeiro:** None. **D.G. Ferreira:** None. **V.L. Batalha:** None. **H. Vicente-Miranda:** None. **J.E. Coelho:** None. **F.Q. Gonçalves:** None. **J. Real:** None. **R.A. Cunha:** None. **A. Albino-Teixeira:** None. **L.V. Lopes:** None.

Nanosymposium

463. Therapeutics of Parkinson's Disease: Preclinical Studies

Location: N230

Time: Tuesday, October 20, 2015, 8:00 AM - 10:15 AM

Presentation Number: 463.03

Topic: C.03. Parkinson’s Disease

Support: Michael J Fox Target Validation Grant 2014-2016

BID PICT 2011-1758

Title: Addressing a new target for L-DOPA induced dyskinesias

Authors: *S. SANZ-BLASCO[1], A. DAMIANICH[2], M. SABORIDO[1], G. GOMEZ[1], M. BORDONE[1], M. A. BERNARDI[1], S. CAMPANA[1], I. TARAVINI[1], D. HANGER[3], M. AVALE[2], O. GERSHANIK[1], J. FERRARIO[1];
[1]Exptl. Parkinsonism Lab., ININFA-UBA-CONICET, CIUDAD AUTONOMA DE BUENOS AIRES, Argentina; [2]INGEBI-CONICET, CIUDAD AUTONOMA DE BUENOS AIRES, Argentina; [3]Inst. of Psychiatry, King's College London, United Kingdom

Abstract: Symptomatic treatment with the dopamine precursor L-DOPA is at present the most effective therapy for the treatment of Parkinson's disease (PD); however, its long-term administration frequently induces L-DOPA induced dyskinesias (LID). Dyskinesias are a priority within the scientific community because of their impact on the quality of life of PD patients, but the molecular mechanisms underlying L-DOPA-induced dyskinesias are not yet completely understood. Previous results from our lab show that the pleiotrophin receptor, RPTP-z/b is upregulated after L-DOPA treatment in a rodent model of PD (1). This receptor interacts with PSD95 and regulates the tyrosine kinase Fyn in the postsynaptic density complex (2). Fyn has been associated with learning, memory and long-term potentiation through the regulation of the NMDA receptor subunits NR2A and NR2B. After dopamine depletion and L-DOPA treatment, Fyn has been found to participate in NMDA receptors redistribution (3),(4). In addressing Fyn as an intermediate in the development and maintenance of LID, and therefore as a potential novel target for the treatment of LID in PD, we have obtained the following results in our model of rodents with unilateral 6-OHDA lesion: after L-DOPA treatment, the number of pleiotrophin immunopositive striatal neurons and the phosphorilation level of Fyn is increased in dyskinetic rats. In addition, LIDs are reduced in both intensity and duration in Fyn KO mice compared to WT ones with equivalent lesion severity as demonstrated by TH inmunohistochemistry and behavioral tests. Our results show that the kinase Fyn appears to have an important role in LID, highlighting this protein as a novel target of study for the treatment of this side effect of L-DOPA therapy. References: 1) Ferrario JE et al.(2008) Pleiotrophin receptor RPTP-zeta/beta expression is up-regulated by L-DOPA in striatal medium spiny neurons of parkinsonian rats. Journal of neurochemistry 107:443-452. 2) Pariser H et al.(2005) Fyn is a downstream target of the pleiotrophin/receptor protein tyrosine phosphatase beta/zeta-signaling pathway: regulation of tyrosine phosphorylation of Fyn by pleiotrophin. Biochemical and biophysical research communications 332:664-669. 3) Dunah AW et al.(2004) Dopamine D1-dependent trafficking of striatal N-methyl-D-aspartate glutamate receptors requires Fyn protein tyrosine kinase but not DARPP-32. Molecular pharmacology 65:121-129. 4) Trepanier CH et al. (2012) Regulation of NMDA receptors by the tyrosine kinase Fyn. FEBS J. 279(1):12-9.

Disclosures: S. Sanz-Blasco: None. **A. Damianich:** None. **M. Saborido:** None. **G. Gomez:** None. **M. Bordone:** None. **M.A. Bernardi:** None. **S. Campana:** None. **I. Taravini:** None. **D. Hanger:** None. **M. Avale:** None. **O. Gershanik:** None. **J. Ferrario:** None.

Nanosymposium

463. Therapeutics of Parkinson's Disease: Preclinical Studies

Location: N230

Time: Tuesday, October 20, 2015, 8:00 AM - 10:15 AM

Presentation Number: 463.04

Topic: C.03. Parkinson's Disease

Support: Parkinson's Disease Foundation IRG1303

Swedish Research Council

Title: Chemogenetic modulation of dopaminergic fetal grafts in Parkinson's disease elucidates therapeutic potential and a mechanism underlying graft induced dyskinesias

Authors: *T. BJORKLUND[1], P. ALDRIN-KIRK[1], A. HEUER[2], M. LUNDBLAD[2], G. WANG[1], B. MATTSSON[1], M. PARMAR[2];
[1]Mol. Neuromodulation, Wallenberg Neurosci., Lund, Sweden; [2]Developmental and Regenerative Neurobiology, Wallenberg Neurosci. Ctr., Lund, Sweden

Abstract: Transplantation of dopaminergic neuroblasts into the Putamen of patients with Parkinson's Disease is seen as one of the most promising routes for symptomatic treatment of motor symptoms. A number of clinical trials have assessed the therapeutic potential of fetal dopaminergic ventral mesencephalic dopamine neurons in both open label and double-blinded study designs. While some patients have benefitted greatly from the therapy, the outcome has been highly variable and a non-trivial number of the patients developed a new form of involuntary movements termed graft-induced dyskinesias (GIDs). In this study, we have utilized fetal dopamine cells from a novel TH-Cre knock-in driver line transduced *in situ* in the striatum with an inducible AAV8 vector carrying different versions of chemogenetic receptors (DREADDs) potentiating or inhibiting the activity of the transplanted neurons specifically after the systemic delivery of their respective inert ligands. Thanks to a novel DREADD receptor (based on the kappa-opioid receptor and stimulated with the otherwise inert compound Salvinorin B), the same transplant could be activated or inhibited solely dependent on the ligand. We here show for the first time that the recovery in motor function from a fetal transplant can be significantly potentiated through the chemogenetic drive of dopamine cell function and that Gi-based silencing of the same cells can remove all therapeutic activity of the graft in selected behavior tests. Importantly, we have in this model been able to induce GIDs by solely increasing the intracellular cAMP concentrations in the transplanted DA neurons. We have also generated strong evidence that such elevation can be achieved through activation of a subset of serotonin receptors on the graft and thus provide a link between serotonergic system and GIDs that is acting through dysregulation of the transplanted DA neurons.

Disclosures: **T. Bjorklund:** None. **P. Aldrin-Kirk:** None. **A. Heuer:** None. **M. Lundblad:** None. **G. Wang:** None. **B. Mattsson:** None. **M. Parmar:** None.

Nanosymposium

463. Therapeutics of Parkinson's Disease: Preclinical Studies

Location: N230

Time: Tuesday, October 20, 2015, 8:00 AM - 10:15 AM

Presentation Number: 463.05

Topic: C.03. Parkinson's Disease

Support: MJFF SynTAP Research Grant 2013

Title: Preclinical development of a vaccine against alpha-synuclein for the treatment of Parkinson's disease

Authors: ***M. DOUCET**[1], A. EL-TURABI[2], T. DELTHEIL[1], M. CIOROCH[1], M. BACHMANN[2], R. WADE-MARTINS[1];
[1]Dept. of Physiology, Anat. and Genet., Univ. of Oxford, Oxford, United Kingdom; [2]The Jenner Inst., Oxford, United Kingdom

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting 1% of the population over the age of 65. In recent years, over-expression of alpha-synuclein has been shown to play a key role in the pathophysiology of PD, with a 1.5 or 2-fold up-regulation of alpha-synuclein shown to cause familial PD. Treatment of PD is currently limited to dopamine-replacement therapies, which only provide symptomatic relief. Novel drug targets are therefore needed and clearance of alpha-synuclein represents an exciting strategy for the development of the next generation of therapeutics for PD. An emerging possibility to reduce intracerebral alpha-synuclein levels is vaccination against the protein to induce long-lived antibody responses. For vaccine production, short peptides representing the middle (PD1), N-terminus (PD2) and C-terminus (PD3) of human alpha-synuclein were selected and chemically cross-linked onto Qb-based virus like-particles. Pilot studies in mice demonstrated that intravenous delivery of these vaccines led to production of good antibody titres (OD50 >103) and that antibodies from Qb-PD1- and Qb-PD3-treated mice were able to recognise Lewy bodies in post-mortem brain tissue from PD patients. The Qb-PD1 and Qb-PD3 vaccines were then tested for immunogenicity in a mouse model of Parkinson's disease, which over-expresses human alpha-synuclein (the SNCA-OVX mouse). Following subcutaneous administration of these vaccines for 2-3 months, SNCA-OVX mice produced antibodies against alpha-synuclein and peripheral antibody titres were at levels relevant for crossing of the blood-brain barrier. In SNCA-OVX mice, vaccination was well-tolerated and safe, as assessed by examination of

general behaviour and analysis of blood parameters. Biochemical and histochemical studies are currently underway to characterise changes in alpha-synuclein protein levels, and potential reversal of early deficits in dopamine neurotransmission.

Disclosures: **M. Doucet:** None. **A. El-Turabi:** None. **T. Deltheil:** None. **M. Cioroch:** None. **M. Bachmann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Saiba GmbH (Switzerland). **R. Wade-Martins:** None.

Nanosymposium

463. Therapeutics of Parkinson's Disease: Preclinical Studies

Location: N230

Time: Tuesday, October 20, 2015, 8:00 AM - 10:15 AM

Presentation Number: 463.06

Topic: C.03. Parkinson’s Disease

Title: A neural stem cell-based therapeutic approach for Parkinson’s disease

Authors: *R. A. SEMECHKIN[1], R. GONZALEZ[1], I. GARITAONANDIA[1], M. POUSTOVOITOV[1], T. ABRAMIHINA[1], A. CRAIN[2], A. NOSKOV[1], C. R. S. MCENTIRE[3], B. CULP[3], J. ATTWOOD[3], L. C. LAURENT[4], J. D. ELSWORTH[5], E. Y. SNYDER[2], D. REDMOND[5];
[1]Intl. Stem Cell Corp, Carlsbad, CA; [2]Sanford-Burnham Med. Res. Inst., La Jolla, CA; [3]Axion Res. Fndn., Hamden, CT; [4]UCSD, La Jolla, CA; [5]Yale Stem Cell Ctr., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Clinical studies have shown that grafted fetal tissue can achieve considerable biochemical and motor improvements in Parkinson’s disease (PD) patients decades after implantation. The source of fetal tissue is limited, clinically impractical and alternative sources are needed. Human parthenogenetic stem cells (hpSCs) offer a more practical alternative because they are pluripotent stem cells that can be expanded indefinitely *in vitro* and generate an unlimited supply of neural tissue. Unlike human embryonic stem cells, hpSCs are derived from unfertilized oocytes, avoiding the destruction of a potentially viable human embryo. Proof-of-concept studies have shown that human parthenogenetic stem cell derived neural stem cells (hpNSCs) are safe and increase brain dopamine levels in PD animal models. Here we present the results of the comprehensive preclinical development of hpNSCs as a PD therapy. The pharmacology, toxicology, biodistribution, tumorigenicity, safety and efficacy studies demonstrate that nigrostriatal administration of cGMP-manufactured hpNSCs is safe, well tolerated, and does not induce dyskinesia, dystonia, systemic toxicity, host immune rejection,

ectopic tissue, tumors, or hyperproliferation. More importantly, hpNSC-transplanted animals had lower Parkinson's rating scores and higher healthy behavior scores, dopamine levels, number of nigral dopaminergic neurons and striatal fiber density than vehicle control-injected animals. The multimodal actions of hpNSCs, including neuroprotection, neurotrophic support, and cell replacement may have promoted the recovery of the host nigrostriatal system. Overall, these results show that hpNSCs are safe, well tolerated and effective in treating Parkinson's disease and support their testing in clinical trials.

Disclosures: R.A. Semechkin: A. Employment/Salary (full or part-time); International Stem Cell Corp. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Stem Cell Corp. **R. Gonzalez:** A. Employment/Salary (full or part-time); International Stem Cell Corp. **I. Garitaonandia:** A. Employment/Salary (full or part-time); International Stem Cell Corp. **M. Poustovoitov:** A. Employment/Salary (full or part-time); International Stem Cell Corp. **T. Abramihina:** A. Employment/Salary (full or part-time); International Stem Cell Corp. **A. Crain:** None. **A. Noskov:** A. Employment/Salary (full or part-time); International Stem Cell Corp. **C.R.S. McEntire:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; International Stem Cell Corp. **B. Culp:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; International Stem Cell Corp. **J. Attwood:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; International Stem Cell Corp. **L.C. Laurent:** None. **J.D. Elsworth:** None. **E.Y. Snyder:** None. **D. Redmond:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; International Stem Cell Corp.

Nanosymposium

463. Therapeutics of Parkinson's Disease: Preclinical Studies

Location: N230

Time: Tuesday, October 20, 2015, 8:00 AM - 10:15 AM

Presentation Number: 463.07

Topic: C.03. Parkinson's Disease

Support: Mitchell Center for Neurodegenerative Disease

Sealy Center for Vaccine Development

Michael J Fox Foundation

Title: Targeting the toxic synergy of α-synuclein and tau with tau oligomer-specific antibodies

Authors: *J. GERSON[1], D. L. CASTILLO-CARRANZA[2], U. SENGUPTA[2], N. HENSON[3], A. NILSON[1], R. KAYED[2];
[1]Neurosci. and Cell Biol., [2]Neurol., UTMB, Galveston, TX; [3]Univ. of Texas, Austin, TX

Abstract: Parkinson's disease (PD) and Lewy body dementia (LBD) are two of the most common neurodegenerative disorders. As the life expectancy of the aging population grows, increasing numbers of people are affected. While PD and LBD are primarily characterized by the accumulation of α-synuclein in Lewy bodies, evidence shows that smaller, oligomeric aggregates are likely the most toxic form of the protein. Moreover, we have found that oligomeric α-synuclein coexists with tau protein in disease in a possible toxic synergy, implicating tau oligomers as a therapeutic target for synucleinopathies. Here, we have evaluated the efficacy of a tau oligomer-specific antibody (TOMA) in a synucleinopathy mouse model. We treated seven-month-old mice overexpressing mutated α-synuclein (A53T mice) intravenously with either TOMA, Tau-13 for all forms of tau, or a control IgG and injected wild-type mice with saline. After two weeks, mice were evaluated on a battery of behavioral tasks assessing cognitive and motor function. Following testing, half of the mice in each group were sacrificed and tissue was collected for biochemical and immunohistochemical analysis. Remaining mice were aged to 12 months and tested a second time. We found that A53T mice treated with TOMA were protected from cognitive and motor deficits, while treating with an antibody for all forms of tau, Tau-13, appeared to exacerbate the phenotype on multiple measures. We found decreased levels of toxic tau oligomers in the brains of TOMA-treated mice. We also show that levels of dopamine were elevated in TOMA-treated mice, as well as levels of the synaptic protein, Synapsin 1. Our results indicate that targeting tau oligomers is beneficial for a mouse model of synucleinopathy and may be a viable therapeutic strategy for treating diseases in which tau and α-synuclein have a synergistic toxicity.

Disclosures: J. Gerson: None. **D.L. Castillo-Carranza:** None. **U. Sengupta:** None. **N. Henson:** None. **A. Nilson:** None. **R. Kayed:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Has patent applications on the compositions and methods related to tau oligomers and antibodies.

Nanosymposium

463. Therapeutics of Parkinson's Disease: Preclinical Studies

Location: N230

Time: Tuesday, October 20, 2015, 8:00 AM - 10:15 AM

Presentation Number: 463.08

Topic: C.03. Parkinson's Disease

Support: Mercy Health Saint Mary's

Morris K. Udall Center for Excellence in Parkinson's Disease Research

Title: Using rAAV to interrogate the ability of Nurr1 to reverse levodopa-induced dyskinesia in Parkinsonian rats

Authors: *R. C. SELLNOW[1,2], K. STEECE-COLLIER[1], N. M. KANAAN[1], C. E. SORTWELL[1], T. J. COLLIER[1], A. COLE-STRAUSS[1], J. W. LIPTON[1], F. P. MANFREDSSON[1];
[1]Translational Sci. & Mol. Med., Michigan State Univ., Grand Rapids, MI; [2]Cell and Mol. Biol., Michigan State Univ., East Lansing, MI

Abstract: Primary motor symptoms in Parkinson's disease (PD) arise due to the loss of dopamine signaling from the substantia nigra to the striatum. These motor symptoms can be alleviated with levodopa (L-DOPA) treatment, a catecholamine replacement therapy that reverses dopamine depletion in the brain. Unfortunately, chronic L-DOPA treatment inevitably leads to the development of L-DOPA-induced dyskinesias (LIDs) in the majority of PD patients. LIDs are involuntary motor symptoms that include chorea, dystonias, and limb hyperkinesia that are distinct from parkinsonian motor symptoms. Since the molecular etiology of LIDs has yet to be fully elucidated, we sought to determine transcriptional differences between parkinsonian rats that developed dyskinesias and those that did not. We found the transcript for Nurr1, a nuclear orphan receptor involved in dopaminergic neuronal development and health, to be significantly upregulated in the striatum of dyskinetic animals. Preliminary studies utilized recombinant adeno-associated virus (rAAV) to modulate striatal Nurr1 expression prior to L-DOPA treatment in 6-hydroxydopamine unilaterally lesioned rats. These studies have shown that overexpression of Nurr1 exacerbates dyskinesias, while silencing Nurr1 with a targeted shRNA cassette attenuates LIDs suggesting that ectopic Nurr1 expression in the striatum may be an important mediator of LID development. Ongoing studies aim to investigate Nurr1's ability to affect LIDs in animals that have been primed with L-DOPA. In these studies, we plan to deliver Nurr1-modulating rAAV after L-DOPA treatment, instead of before as in the previous study. The goal is to determine if 1) delivering rAAV-Nurr1 to an L-DOPA primed animal that has not developed LIDs will induce dyskinesias, and if 2) delivering rAAV-Nurr1-shRNA to an animal with established LIDs will reverse the dyskinetic symptoms in the presence of L-DOPA. We will establish the LID model by chronically dosing both Sprague-Dawley and Fischer rats following unilateral lesions with 6-hydroxydopamine. We expect to see a typical proportion of dyskinetic and non-dyskinetic animals following L-DOPA (roughly 70% animals developing dyskinesias).

After dyskinesias have been established, we will stereotactically inject either rAAV overexpressing Nurr1 into nondyskinetic animals, or rAAV carrying the Nurr1 shRNA cassette into dyskinetic animals. These ongoing experiments will show whether 1) Nurr1 striatal expression can induce dyskinesias in a previously LID 'resistant' animal and whether 2) LIDs can be attenuated by silencing Nurr1, thus indicating Nurr1 as a potential interventional target for dyskinesia.

Disclosures: R.C. Sellnow: None. **K. Steece-Collier:** None. **N.M. Kanaan:** None. **C.E. Sortwell:** None. **T.J. Collier:** None. **A. Cole-Strauss:** None. **J.W. Lipton:** None. **F.P. Manfredsson:** None.

Nanosymposium

463. Therapeutics of Parkinson's Disease: Preclinical Studies

Location: N230

Time: Tuesday, October 20, 2015, 8:00 AM - 10:15 AM

Presentation Number: 463.09

Topic: C.03. Parkinson's Disease

Title: Sleep alterations as a biomarker of Parkinson's disease

Authors: *A. RACHALSKI[1], A. BOGSTEDT[1], S. TAI[1], D. CAUDAL[2], A. BJÖRKLUND[3], P. SVENNINGSSON[2], E. ÅBERG[1];
[1]Personalized Healthcare Biomarker, Astrazeneca Translational Sci. Ctr., Solna, Sweden; [2]Dept. of Clin. Neuroscience, Karolinska Institutet, Karolinska Univ. Hosp. Solna, Lab. of Translational Neuropharmacology, Ctr. for Mol. Medicine/Translational Neuropharm., Solna, Sweden; [3]Dept. of Exptl. Med. Sci., Wallenberg Neurosci. Center, Lund Univ., Lund, Sweden

Abstract: Background: Sleep is a major complain from Parkinson's Disease (PD) patients with up to 90% of them reporting insomnia, restless legs syndrome, excessive daytime sleepiness (EDS), rapid eye movement sleep disorder (RBD; Schulte and Winkelmann, 2011). Some can be the consequence of the motor symptoms (as nocturnal dyskinesia or tremor) or treatment (as insomnia) but EDS and RBD are reported to occur 5 to 10 years before diagnostic of alpha-synucleinopathies (Claasen and Kutscher, 2011), leaving an open window for early detection. It has been proposed that the alpha-synuclein (ASyn) accumulation in pontine regions important for sleep regulation during presymptomatic stages (Braak et al, 2004) is responsible for these alterations but the mechanisms of how alpha-synuclein affect sleep and may lead to RBD are unknown. This study aims to characterize the sleep alterations in an animal model of PD and to correlate them to the accumulation of ASyn. Methodology: Rats were injected bilaterally with AAV-human ASyn (AAV-ASyn) in Substantia Nigra and compared to AAV-GFP control

animals (Lundblad et al, 2012). Both groups were implanted with electroencephalographic (EEG) and electromyographic (EMG) electrodes. Sleep architecture and spectral profile of the vigilance states were analyzed over 24h. After the recording, animals were euthanized, brains removed and dissected. Human ASyn expression was assessed by immunostaining in AAV-ASyn animals and ASyn levels were measured in plasma and different brain regions by WB and ELISA in both groups. Results: Eight weeks after injection, the AAV-ASyn rats presented a fragmented sleep pattern compared to the AAV-GFP littermates with disruption of the spectral profiles. Moreover, these animals have an important increase of muscle tone during their sleep. We have also confirmed the presence of the human ASyn only in the brain and plasma of AAV-ASyn group. Interestingly, AAV-ASyn animals present increased total ASyn in Brainstem but not in Prefrontal Cortex. Conclusion: Together, our results demonstrate that AAV-ASyn rats have similar alterations of their sleep pattern as PD patients and confirm the model as translationally relevant for PD. Moreover, these changes are concomitant of an increased ASyn level in sleep regulating regions, suggesting ASyn implication in these alterations. This model will then be used to characterize the development of sleep disturbances as an early marker of disease in correlation with ASyn accumulation. In addition, our data highlight the importance of sleep alteration in PD and validate the potential of EEG/sleep characteristics to provide a valuable animal-clinical interface in PD.

Disclosures: **A. Rachalski:** A. Employment/Salary (full or part-time); AstraZeneca. **A. Bogstedt:** A. Employment/Salary (full or part-time); AstraZeneca. **S. Tai:** A. Employment/Salary (full or part-time); AstraZeneca. **D. Caudal:** None. **A. Björklund:** None. **P. Svenningsson:** None. **E. Åberg:** A. Employment/Salary (full or part-time); AstraZeneca.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.01

Topic: C.08. Ischemia

Support: NIH Grant NS085272

AHA Grant 12SDG11780023

NIH Grant NS24617

CCTS Grant UL1RR025755

Title: Targeting glutamate metabolism by glutamate oxaloacetate transaminase in the ischemic penumbra for protection against stroke injury

Authors: *S. KHANNA, S. GNYAWALI, R. STEWART, S. ROY, C. K. SEN, C. RINK; Surgery, Ohio State Univ., Columbus, OH

Abstract: The ischemic penumbra represents a region of impaired, but salvageable tissue, where glucose and oxygen delivery to stroke-affected brain is compromised. During ischemic stroke injury, extracellular glutamate levels in the ischemic penumbra increase and are known to contribute to neurotoxicity. The current work builds upon our observation that glutamate oxaloacetate transaminase (GOT), a glutamate metabolizing enzyme in the brain, can protect brain tissue during ischemic stroke. We previously reported that correction of stroke-induced hypoxia by supplemental oxygen (oxygenated hypoglycemia, OH) induced GOT expression and lowered glutamate levels in stroke-affected brain. Here, we test the hypothesis that induction of GOT increases glutamate metabolism in the ischemic penumbra and protects against stroke-induced injury. In C57/BL6 mice subjected to middle cerebral artery occlusion (MCAO), correction of hypoxia during stroke increased ischemic penumbra volume as quantified by magnetic resonance diffusion-perfusion mismatch. *In vivo* proton magnetic resonance spectroscopy (1H MRS) was used to spatially resolve glutamate levels in the stroke-affected brain. In the ischemic penumbra of OH-treated mice, glutamate levels were significantly lower compared to normoxia controls. Furthermore, induction of GOT in stroke-affected brain increased anaplerosis of TCA cycle intermediates suggesting glutamate metabolism by GOT through a truncated TCA cycle. Targeted over-expression of GOT in somatosensory cortex attenuated stroke-induced injury and improved post-stroke sensorimotor function. Taken together, these key observations pave the way for a new paradigm that GOT orchestrates a functional switch for glutamate in the ischemic penumbra from neurotoxin to survival factor.

Disclosures: S. Khanna: None. **S. Gnyawali:** None. **R. Stewart:** None. **S. Roy:** None. **C.K. Sen:** None. **C. Rink:** None.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.02

Topic: C.08. Ischemia

Support: MINECO (reference BIO2013-49006-C2-2-R)

Junta de Castilla y León fellowship (EDU/346/2013) for Diego Pérez-Rodríguez

Title: The enhancement of the Unfolded Protein Response (UPR)-PERK pathway provides neuroprotection against global cerebral ischemia by increasing autophagy

Authors: *D. PEREZ-RODRIGUEZ[1], B. ANUNCIBAY-SOTO[1], E. GERACE[2], M. SANTOS GALDIANO[1], D. PELLEGRINI-GIAMPIETRO[2], A. FERNÁNDEZ-LÓPEZ[1];
[1]Area de Biologia Celular, Univ. de Leon, Inst. de Biomedicina, Leon, Spain; [2]Dept. of Hlth. Sciences, Section of Clin. Pharmacol. and Oncology, Univ. degli studi di Firenze, Firenze, Italy

Abstract: Introduction: Global ischemia disrupts brain homeostasis leading the cells to the so-called endoplasmic reticulum (ER) stress. Neurons counteract this stress through the autophagy and the ubiquitin-proteasome system (UPS). In this regard, salubrinal, a selective inhibitor of p-eIF2α phosphatases that enhances the unfolded protein response (UPR) through the PERK pathway, have been reported to be neuroprotective when administered before focal ischemia. Aims: To analyze the neuroprotective effect of salubrinal in brain structures with different ischemic vulnerability when administered after the ischemic insult. In addition, we analyze its effect on the autophagy response to global cerebral ischemia. Methods: Autophagy response to global cerebral ischemia was analyzed both in rat organotypic hippocampal cultures exposed to 30 min of oxygen and glucose deprivation (OGD) and in *in vivo* adult rats subjected to 15 minutes of bilateral carotid occlusion. Phagophore formation and autophagy flux markers, including BECLIN1, LC3B, P62/SQSTM1, as well as protein aggregates positive for ubiquitin, were analyzed by PCR, Western blot and immunofluorescence assays. Moreover, propidium iodide and Nissl staining were used to estimate cell damage and cell demise. Results: Global ischemia elicited an autophagic response different in the hippocampal subfields CA1 and CA3 and diametric between the *in vivo* and the organotypic hippocampal cultured models. A subpopulation of CA1 pyramidal neurons showed a great accumulation of polyubiquitin aggregates that colocalized with P62 but did not colocalize with any autophagosome marker. Treatment with salubrinal abolished this accumulation and increased the cell survival in injured CA1 in both experimental models. This neuroprotective effect is linked to an increase in the autophagy flux able to eliminate the misfolded protein aggregates observed in CA1 pyramidal neurons. Conclusions: The enhancement of UPR-PERK pathway improves CA1 outcome after global ischemia by increasing the autophagy flux, which allows the clearance of misfolded protein aggregates. Support: This study was supported by MINECO (reference BIO2013-49006-C2-2-R) who also supports Berta Anuncibay-Soto and María Santos-Galdiano. Diego Pérez Rodríguez is granted by European Social Fund and Junta de Castilla y León (EDU/346/2013)

Disclosures: D. Perez-Rodriguez: None. **B. Anuncibay-Soto:** None. **E. Gerace:** None. **M. Santos Galdiano:** None. **D. Pellegrini-Giampietro:** None. **A. Fernández-López:** None.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.03

Topic: C.08. Ischemia

Support: NIH R01 NS046741

Title: A PAF-receptor antagonist plus docosanoids leads to remarkable neuroprotection in experimental stroke

Authors: *N. G. BAZAN[1], S.-H. HONG[1], L. KHOUTOROVA[1], A. OBENAUS[2], N. A. PETASIS[3], L. BELAYEV[1];
[1]Neurosci. Ctr., LSU Hlth. New Orleans, New Orleans, LA; [2]Pediatrics, Loma Linda Univ., Loma Linda, CA; [3]USC, Los Angeles, CA

Abstract: Acute ischemic stroke triggers complex neurovascular, neuroinflammatory and synaptic alterations. The aim of our study was to test the prediction that blocking pro-inflammatory platelet-activating factor -receptors (PAFR) plus administering selected docosanoids after middle cerebral artery occlusion (MCAo) would lead to sustained neurological recovery. Two different types of bioactive small molecules were investigated. The first was LAU-0901, an antagonist of PAFR that blocks activated pro-inflammatory signaling and has been shown to have promising efficacy in a stroke model (Belayev et al, 2012). The second was products of DHA, a novel synthetic docosanoids (Aspirin-triggered neuroprotectin D1 methyl-ester; AT-NPD1-ME), which activates cell-survival pathways and has potent anti-inflammatory and neuroprotective activity in the brain (Bazan et al, 2012). Sprague-Dawley rats were anesthetized with isoflurane/nitrous oxide and received 2h MCAo by intraluminal suture. Neurological status was evaluated at 3h and 4h, and on days 1, 2 and 3; a grading scale of 0-12 was employed. Animals were treated with LAU-0901 (i.p. 60mg/kg, 2h after onset of stroke), AT-NPD1-ME (i.v. 333mg/kg, 3h after onset of stroke) and vehicles (cyclodextran and saline). There were four groups: LAU-0901+AT-NPD1; LAU-0901+saline; Cyclodextran+AT-NPD1; and cyclodextran+saline. On day 3, *ex vivo* MRI of the brains was conducted using 11.7 T MRI. LAU-0901 and AT-NPD1 treatments alone improved behavioral scores compared to vehicle groups by 22-32%. Using the LAU-0901+AT-NPD1 combination, the neuroprotective effect was enhanced, resulting in improved behavioral score up to 50% on day 3. Total lesion volumes, computed using T2WI, were significantly reduced by 80% with LAU-0901+AT-NPD1 treatment compared to vehicle-treated groups. We concluded that combination treatment of the PAFR antagonist LAU-0901 plus AT-NPD1-ME affords synergistic neuroprotection in the post-

ischemic brain and might provide the basis for future therapeutics in patients suffering ischemic stroke. We are currently exploring the molecular mechanisms involved.

Disclosures: **N.G. Bazan:** None. **S. Hong:** None. **L. Khoutorova:** None. **A. Obenaus:** None. **N.A. Petasis:** None. **L. Belayev:** None.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.04

Topic: C.08. Ischemia

Support: National AHA-13SDG1395001413

American Stroke Association-14BFSC17690007

Evelyn F. McKnight Brain Institute

NIH-NINDS 5R01NS073779-03

NIH-NINDS R01NS056072

Title: Neuroprotective effects of sympathetic attenuation in the ischemic brain

Authors: *R. H.-C. LEE[1], A. COUTO E SILVA[1], C. WILKINS[2], S. VALIDO[1], D. KLEIN[1], C. WU[3], D. DELLA MORTE[1,4], H. LIN[1];
[1]Dept. of Neurol., Univ. of Miami, Miami, FL; [2]Florida Intl. Univ. Herbert Wertheim Col. of Med., Miami, FL; [3]Inst. of Pharmacol. & Toxicology, Tzu Chi Univ., Hualien, Taiwan; [4]Dept. of Systems Med., Univ. of Rome Tor Vergata, Rome, Italy

Abstract: Cardiopulmonary arrest (CA, a form of global cerebral ischemia) is a major cause of death/disability in the US affecting up to 325,000 people/year with only a 10% survival rate that can lead to brain injury resulting in neurological deficits. Circulating norepinephrine levels are significantly increased after CA, which is indicative of enhanced sympathetic nervous system (SNS) activity. However, the pathophysiological function of the SNS in the ischemic brain is unclear. We used a rat model of global cerebral ischemia (asphyxial cardiac arrest, ACA) to investigate the effects of surgical attenuation of the SNS in the brain via decentralization (preganglionic lesion) of the superior cervical ganglion (SCG, the last and major ganglia in the SNS innervating cerebral arteries and the brain). Decentralization of the SCG (DEC)-treated rats

can alleviate ACA-induced hypoperfusion (via cortical cerebral blood flow studies in intra-vital two-photon laser scanning microscopy), which has been shown to play a crucial role in the progression of neuronal cell death and learning/memory deficits after ischemia. Interestingly, DEC-treated rats 5 days prior to ACA inhibited neuronal cell death in the CA1 region of the hippocampus. In support of these basic findings, we performed a retrospective study on ischemic stroke (focal ischemia) patients with atenolol (β1-adrenoceptor antagonist and sympathoplegic agent). Patients on atenolol (at the time of admission) presented with better outcomes (measured by the NIHSS scale) after discharge as compared to patients without β-blocker treatment. Here, we show that ACA-induced activation of the SNS in the brain is one of the major contributors to cerebral hypoperfusion resulting in neuronal injury and neurological deficits following cerebral ischemia. Attenuation of SNS activity is actually beneficial to counteract the detrimental effects of ischemia.

Disclosures: **R.H. Lee:** None. **A. Couto e Silva:** None. **C. Wilkins:** None. **S. Valido:** None. **D. Klein:** None. **C. Wu:** None. **D. Della Morte:** None. **H. Lin:** None.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.05

Topic: C.08. Ischemia

Title: Quality and quantity mononuclear cells protect neuronal cell death in stroke mice

Authors: *T. NAKAYAMA[1], E. NAGATA[1], H. MASUDA[2], S. KOHARA[1], H. YUZAWA[1], Y. TAKAHARI[3], T. ASAHARA[2], S. TAKIZAWA[1];
[2]Regenerative Med. Sci., [3]Support Ctr. for Med. Res. and Educ., [1]Tokai Univ., Isehara, Japan

Abstract: Background: Endothelial Progenitor Cell (EPC) was reported to enhance repairing and regenerating neurovascular units. So far many papers have reported repairing and regenerating experiments using EPCs derived from bone marrow, spleen, or peripheral blood. However, the results were not always satisfied. Recently, we succeeded to get higher grade quality EPCs using a novel colony assay system which we have developed (Masuda H, et al, 2011). In the present study, we used this novel EPC colony assay system, and evaluated EPC effects on ischemic stroke model in mice. Materials and methods: We made 69 ischemic stroke model mice (10 weeks male C57BL/6 mice) with permanent middle cerebral artery occlusion (MCAO). We injected PBS as control (n=23), MNCs from peripheral blood (n=22), or cultured MNCs (n=24) into external carotid artery at each 1 day, 3 days, 5 days, and 7 days after MCAO. At 3 weeks

after MCAO, we took the brains and investigated time-lapse physiological parameters including cerebral blood flow and immunohistochemistry against some anti-vasculogenetic factor antibodies. We made another 15 MCAO mice for injecting PBS (n=5), MNCs from peripheral blood (n=5), and cultured MNCs (n=5) at next day of MCAO. At 3 weeks after MCAO, we operated perfusion fixation with carbon mixed latex and evaluated collateral circulations on those mice. Results: In the stroke model mice at 1 day and 3 days MNCs injections after MCAO, the stroke volume was decreased; however, the positive cells were increased with immunochemistry of IL10. The cerebral blood blow tended to increase on all stroke mice models. Conclusions: Those results indicate that the mice's MNCs including EPCs could promote repairing and regenerating neurovascular units after ischemic stroke, and the better MNCs injection timings might be 1 day and 3 days after MCAO.

Disclosures: T. Nakayama: None. **E. Nagata:** None. **H. Masuda:** None. **S. Kohara:** None. **H. Yuzawa:** None. **Y. Takahari:** None. **T. Asahara:** None. **S. Takizawa:** None.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.06

Topic: C.08. Ischemia

Title: Coenzyme Q10 supplementation during atorvastatin treatment modifies cellular oxidative state following focal cerebral ischemia

Authors: *S. NASOOHI[1,2], L. SIMANI[3], N. NADERI[2], M. FAIZI[2], F. KHODAGHOLI[3]; [1]Shahid Beheshti Univ. of Med. Sci., Tehran, Iran, Islamic Republic of; [2]Dept. of Pharmacol. and Toxicology, Sch. of Pharmacy, Shahid Beheshti Univ. of Med. Sci., Tehran, Iran, Islamic Republic of; [3]Neurobio. Res. Center, Shahid Beheshti Univ. of Med. Sci., Tehran, Iran, Islamic Republic of

Abstract: **Background**: Atorvastatin (At) is frequently advised for secondary prevention in stroke patients Coenzyme Q10 (CoQ10) the lipophilic endogenous antioxidant may be of critical importance considering inevitably sever oxidative stress in stroke brains subjected to subsequent thrombolysis either spontaneously or following thrombolytic therapy. Regarding the evidenced CoQ10 depletion following prolonged statins therapy, this may be highly suggestive At and CoQ10 co-administration may improve stroke outcomes. Our preliminarily experiments examines whether pretreatment with At and / or CoQ10 combination may alter penumbral oxidative state following ischemic stroke in experimental stroke. **Methods:** transient middle

cerebral occlusion (tMCAO) (60 min) was used to induce ischemic / reperfusion injury in rats received oral At (10 mg/kg/day) and / or CoQ10 (200 mg/kg/day) for one month. Animals' neurological function was evaluated 24h after reperfusion and then penumbral cortices were subjected to oxidative assays. Superoxide dismutase (SOD), glutathione peroxidase (GSH) and the lipid peroxidation product Malondialdehyde (MDA) content were selected as oxidative stress markers. **Results:** The oxidative stress markers data obtained in penumbral samples did not show any consistency. MDA content was not affected by the included treatments; SOD activity was reserved by At but abrogated by CoQ10 co-administration. Alternatively GSH activity was not improved by At pretreatment but diminished in samples subjected to At plus CoQ10. This was in quite disagreement with Animals neurological scores indicating a substantial improvement in animals received At plus CoQ10 rather than At alone. The rarity of pre-clinical investigations on prolonged statins therapy, may somehow explain the marked escalating impact of At treatment here we found on neurological function. **Conclusion:** These primary data suggesting CoQ10 improves At effects on stroke neurological outcomes, highlights the probable escalating effect of CoQ10 on cellular oxidative state. Notably applying CoQ10 in daily high doses may explain the observed pro-oxidant activity. However the alternate mechanisms underlying the functional improvement brought by CoQ10 addition to At regimen should be thought of.

Disclosures: S. Nasoohi: None. **L. Simani:** None. **N. Naderi:** None. **M. Faizi:** None. **F. Khodagholi:** None.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.07

Topic: C.08. Ischemia

Support: This work was supported by Platform for Drug Discovery, Informatics, and Structural Life Science and in part by Grants-in-Aid for Scientific Research (to H.U., B: 13470490 and B: 15390028) on Priority Areas-Research on Pathomechanisms of Brain Disord

Title: Prothymosin-alpha concerns TLR4-TRIF signaling in the protection of ischemic retina

Authors: *S. K. HALDER, H. UEDA;
Pharmacol. and Therapeut. Innovation, Nagasaki Univ., Nagasaki, Japan

Abstract: Toll-like receptor (TLR4) is one of the most-studied components in the field of neurobiology due to its both detrimental and beneficial roles in ischemia through two

downstream pathways, myeloid differentiation primary response gene 88 (MyD88) and Toll/interleukin-1 receptor (TIR)-domain-containing adapter-inducing interferon-beta (TRIF). TLR4 generally contributes to ischemic damages in the central nervous system including brain and retina, whereas a brief episode of ischemic stress or pretreatment with lipopolysaccharide prior to lethal ischemia provides TLR4-mediated neuroprotection. Prothymosin-alpha, a nuclear protein, is involved in multitudinous functions inside and outside of cells including its protective roles against brain and retinal ischemia/starving stress. Although TLR4 mediates exogenous prothymosin-alpha-induced immunopotentiation against viral infection in cultured murine macrophage, the beneficial effects of prothymosin-alpha-TLR4 signaling against ischemia remain to be elucidated. In the present study, preconditioning treatment with prothymosin-alpha 48 h before retinal ischemia prevented the cellular damages estimated by histology and immunohistochemical analyses, and functional deficits of retina evaluated by electroretinography. Prothymosin-alpha preconditioning prevented the ischemia-induced loss of ganglion, bipolar and photoreceptor cells, but not amacrine cells in retina. Prothymosin-alpha treatment in the absence of ischemia caused the mild activation, proliferation and migration of retinal microglia, whereas the ischemia-induced microglia activation was inhibited by prothymosin-alpha preconditioning. All of these preventive actions by prothymosin-alpha preconditioning against ischemia were abolished in TLR4 knock-out mice, and by pretreatments with anti-TLR4 antibodies or minocycline, a microglial inhibitor, which themselves had no effects on the ischemia-induced damages or microglia activation. In transcriptional analyses, ProTα preconditioning inhibited the ischemia-induced marked up-regulation of TLR4-related injury genes, while did increase in TLR4-related protective genes. Furthermore, ProTα preconditioning prevented the retinal ischemia-induced cellular and functional damages in MyD88 knock-out mice, but not in TRIF knock-out mice. Taken together, the present study revealed that ProTα preconditioning implicates selective TLR4-TRIF signaling through microglia for the prevention of ischemic damages in retina.

Disclosures: **S.K. Halder:** A. Employment/Salary (full or part-time); Postdoctoral Fellow, Department Of Pharmacology And Therapeutic Innovation, Nagasaki University Graduate School Of Biomedical Sciences, 1-14 Bunkyo-Machi, Nagasaki 852-8521, Japan. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This work was supported by Platform for Drug Discovery, Informatics, and Structural Life Science and in part by Grants-in-Aid for Scientific Research (to H.U., B: 13470490 and B: 15390028) on Priority. **H. Ueda:** A. Employment/Salary (full or part-time); Professor, Department Of Pharmacology And Therapeutic Innovation, Nagasaki University Graduate School Of Biomedical Sciences, 1-14 Bunkyo-Machi, Nagasaki 852-8521, Japan. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This work was

supported by Platform for Drug Discovery, Informatics, and Structural Life Science and in part by Grants-in-Aid for Scientific Research (to H.U., B: 13470490 and B: 15390028) on Priority.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.08

Topic: C.08. Ischemia

Title: Modulation of mitochondrial function with specific infrared light wavelengths: a novel approach to reduce cerebral reperfusion injury in the adult and neonatal brain

Authors: *M. BUKOWSKI[1], C. REYNOLDS[2], J. WIDER[2], E. GRULEY[1], K. PRZYKLENK[3], M. HUTTEMANN[4], T. SANDERSON[1];
[1]Emergency Med., [2]Physiol., [3]Cardiovasc. Res. Inst., [4]Ctr. for Mol. Med. and Genet., Wayne State Univ., Detroit, MI

Abstract: Insufficient oxygen delivery to the brain can promote significant brain damage in the adult or infant brain. While prompt re-oxygenation is critical in the management of affected patients, the reintroduction of oxygen can potentiate injury by promoting reactive oxygen species (ROS) generation within the mitochondria. While mitigating ROS damage may serve as a common therapeutic avenue for cerebral reperfusion injury, traditional attempts to scavenge ROS have failed. This failure is thought to be due to inherent difficulties in delivery to the brain and sub-cellular targets within the early minutes of reflow. Accordingly, we developed a non-pharmacologic therapy that targets cytochrome c oxidase (CcO) using infrared light (IRL) that circumvents these delivery barriers. We discovered 2 specific IRL wavelengths that penetrate the brain and reversibly reduce the activity of CcO. We proposed that these wavelengths will inhibit ROS by stabilizing the αΨm during reperfusion. Our current aim was to investigate whether IRL could provide broad neuroprotection in multiple models of brain ischemia-reperfusion injury. We tested this hypothesis in cell culture, neonatal rat, and adult rat models. All IRL wavelengths that reduce CcO activity reduced neuronal death following oxygen-glucose deprivation (OGD) in cell culture ($n = 7$, $p<0.05$). IRL also directly modulated mitochondrial respiratory rate, reduced αΨm in a switch-like manner, and blocked mitochondrial ROS, providing preliminary insight into the mechanism of action. Next, the 2 wavelengths that reduce CcO activity were evaluated for neuroprotection in an adult rat model of global brain ischemia using a randomized and blinded study design ($n = 8$-12/group). After 14 days, animals subjected to ischemia demonstrated an 88% loss of neurons. Strikingly, for the IRL-treated groups, loss of neurons ranged from only

16% with the best treatment to 35% with the least efficacious regimen ($p<0.05$). IRL treated rats also had preservation of neurologic function, as demonstrated by a 40% improvement in the radial arm maze ($n = 10$, $p<0.05$). We next tested IRL in a neonatal hypoxia model in 7-day-old rat pups via unilateral common carotid ligation followed by 180 min of hypoxia (8% O2). Pups were randomly enrolled into IRL treatment groups (n=14-17), initiated immediately upon relief of hypoxia. Mean infarct volume was reduced with IRL treatment (31.6%) when compared with sham-controls (45.2%; $p<0.05$). These data demonstrate the neuroprotective effect of non-invasive reduction of CcO activity with specific IRL wavelengths and may provide a novel strategy for the treatment of global brain ischemia in the adult and infant brain.

Disclosures: M. Bukowski: None. **C. Reynolds:** None. **J. Wider:** None. **E. Gruley:** None. **K. Przyklenk:** None. **M. Huttemann:** None. **T. Sanderson:** None.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.09

Topic: C.08. Ischemia

Support: NIH R01 NS065786

Title: Docosahexaenoic acid therapy protects the ischemic penumbra after experimental stroke in female rats

Authors: *L. S. BELAYEV[1], L. KHOUTOROVA[1], A. OBENAUS[2], S.-H. HONG[1], N. G. BAZAN[1];
[1]Neurosci. Ctr., LSUHSC, New Orleans, LA; [2]Pediatrics, Loma Linda Univ., Loma Linda, CA

Abstract: Sex and gonadal hormone exposure have considerable independent impact on stroke outcome. Recently, we have shown that docosahexaenoic acid (DHA) therapy is neuroprotective in male rats, but whether a similar effect occurs in female rats is unknown. Isoflurane/nitrous oxide-anesthetized normothermic (brain temperature 36-36.5^{o}C) female Sprague-Dawley rats received 2h middle cerebral artery occlusion (MCAo) by poly-L-lysine-coated intraluminal suture. The agent (DHA, 5 mg/kg; n=6) or vehicle (saline; n=8) was administered i.v. at 3h after onset of MCAo. The composite neuroscore comprises two different neurological tests, the postural reflex test and the forelimb placing test, to measure visual, tactile, and proprioceptive stimuli, which were evaluated on days 1, 2, 3 and 7 (normal score=0; maximal score=12). High resolution *ex vivo* MRI using an 11.7T Bruker was performed on day 7. The core and penumbra

were automatically identified using the Hierarchical Region Splitting method for penumbra identification. Treatment with DHA improved behavioral score as compared to treatment with vehicle on days 1 (by 33%), 2 (by 38%), 3 and 7 (by 39-40%). DHA treatment reduced penumbral (by 80%) and total lesion volumes (by 40%) computed from T2WI, compared to the saline group. We concluded that DHA therapy accelerates recovery of motor function and rescues the ischemic penumbra following focal cerebral ischemia in female rats. DHA has potential for the treatment of male and female patients after ischemic stroke.

Disclosures: L.S. Belayev: None. **L. Khoutorova:** None. **A. Obenaus:** None. **S. Hong:** None. **N.G. Bazan:** None.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.10

Topic: C.08. Ischemia

Title: Exploring MKK7 role in excitotoxicity and cerebral ischemia: design novel pharmacological strategy against brain injury

Authors: *A. E. VERCELLI[1], A. SCLIP[2], S. BIGGI[2], I. E. REPETTO[1], S. CIMINI[2], F. FALLERONI[2], S. TOMASI[1], R. MONTI[1], N. TONNA[3], F. MORELLI[2], V. GRANDE[2], O. MARIN[4], F. BIANCO[3], D. DI MARINO[5], T. BORSELLO[2];
[1]Neurosci. Inst. Cavalieri Ottolenghi, Orbassano, Italy; [2]IRCCS -Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy; [3]Sanipedia S.r.l., Milano, Italy; [4]Dept. of Biomed. Sci., Padua, Italy; [5]Dept. of Physics, Sapienza Univ. of Rome, Rome, Italy

Abstract: Excitotoxicity following cerebral ischemia elicits a molecular cascade, which leads neurons to death. One key molecule of this pathway is c-Jun-N-terminal kinase (JNK), a MAP kinase, which plays both physiological and pathological roles in neurons. We have previously shown that JNK blockade by specific cell permeable peptide inhibitors significantly reduces infarct size and neuronal death. On the other hand, JNK inhibition may have detrimental side effects due to blockade of its physiological function. Here we have designed a new inhibitor, which blocks MKK7, a upstream activator of JNK, which mediates its pathological activation. This inhibitor was designed taking advantage of the growth arrest and DNA damage inducible 45β (GADD45β) ability to bind MKK7, optimizing the essential domain of GADD45β and linking it with a spacer to TAT peptide sequence to penetrate cells. This inhibitor significantly reduces neuronal death in two *in vitro* models of excitotoxic cell death, one induced by NMDA

exposure and the other by oxygen glucose deprivation. We tested the MKK7 inhibitor *in vivo*, in two models of permanent ischemia, the one obtained by electrocoagulation, and the other by thromboembolic occlusion of the Middle Cerebral Artery. In both models, it blocked MKK7 activation and provided significant protection, reducing the infarct size (by 47% and 50% respectively) when injected 30' before the lesion. In the electrocoagulation model, we also tested the efficacy of the peptide when injected 6h after lesion, obtaining similar protection. Therefore, we showed that it is possible to prevent JNK activation in excitotoxicity by specific inhibition of MKK7, preserving the physiological role of JNK driven by MKK4. Targeting MKK7 could represent a new therapeutic strategy for several diseases involving JNK activation. Moreover, this new inhibitor can be useful to further investigate the roles of the single JNK pathway in the developing and in the pathological brain.

Disclosures: **A.E. Vercelli:** None. **A. Sclip:** None. **S. Biggi:** None. **I.E. Repetto:** None. **S. Cimini:** None. **F. Falleroni:** None. **S. Tomasi:** None. **R. Monti:** None. **N. Tonna:** None. **F. Morelli:** None. **V. Grande:** None. **O. Marin:** None. **F. Bianco:** None. **D. Di Marino:** None. **T. Borsello:** None.

Nanosymposium

464. Neuroprotection: *In vivo* Studies

Location: N426A

Time: Tuesday, October 20, 2015, 8:00 AM - 10:45 AM

Presentation Number: 464.11

Topic: C.08. Ischemia

Support: LW was supported by the by Grant from Science and Technology Commission of Shanghai Municipality (No. 13441902600) and Clinical Medical Research Grant of Chinese medical Association (No. 09010180173)

.TA was supported by grants from the Japan Society for the Promotion of Science (Grant-in-Aid for Young Scientists, Type B, No. 20791025 and Grant-in-Aid for Scientific Research C, General, No. 24592157

Title: Neuroprotective effect of neuroserpin in non-tPA-induced intracerebral hemorrhage mouse models

Authors: *L. WANG[1,2], W. LI[1], T. ASAKAWA[3];
[1]Neurol., Huashan Hosp., Shanghai, China; [2]Huashan Hosp. Fudan Uiversity, Inst. of Neurol., Shanghai, China; [3]Dept. of Neurosurg., Hamamatsu Univ. Sch. of Med., Hamamatsu-city, Shizuoka, Japan

Abstract: Aims: to verify the neuroprotection of NSP in ICH mice and to explore the related mechanisms. Methods: C57BL/6J male mice (n = 180) were involved in this study. ICH models were established with infusion of autologous blood into the brain parenchyma. NSP expression in ICH brains by morphological methods and western blotting analysis were detected. The brain water content and blood-brain barrier (BBB) permeability were dected to verify the neuroprotective effects of NSP. To explore the potential mechanisms of NSP, the distribution patterns of occludin-expressing cells associated to NSP administration and the total expression of occludin protein in the ICH and ICH + NSP groups were measured. Results: NSP protein expression was upregulated in ICH models, with a peak at 48 h after ICH induction. NSP local administration reduced the brain edema and the BBB permeability in ICH models. Thus, the neuroprotection of NSP in ICH state was confirmed. The expression of total occludin was unchanged by ICH and subsequent NSP administration; however, the distribution pattern of occludin-expressing cells was obviously changed by the ICH procedure but partly recovered after NSP administration. Conclusion: Protecting and/or repairing the injured vascular endothelial cells may be a potential mechanism involved in NSP neuroprotection, which needs further verification. NSP may be considered as a new potential therapy for ICH for the neuroprotective effects including amelioration of the edema.

Disclosures: **L. Wang:** None. **W. Li:** None. **T. Asakawa:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.01

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Psi Chi Summer Research Grant

Bradley University Department of Psychology O'Grady Award

Title: Behavioral characterization of a modified single prolonged stress model of PTSD in rats: Developmental and longitudinal effects

Authors: A. L. GARRISON[1], C. E. UKPABY[1], E. N. WALSH[1], J. M. SMITH[1], *T. E. KOELTZOW[2];
[1]Psychology Dept., [2]Psychology Dept, Bradley Univ., Peoria, IL

Abstract: New diagnostic criteria for Posttraumatic Stress Disorder (PTSD) in children and adolescents highlight the need to better understand the neurophysiological adaptations that trauma might elicit during development. The single prolonged stress (SPS) rat model of PTSD reliably produces an enhanced fear response to traumatic cues and disrupted cortisol regulation similar to that typically observed in humans with PTSD (Wang et al., 2008; Knox et al., 2012). In addition, SPS has been shown to influence to response of rats to cocaine (Eagle et al., 2015), a finding that is relevant to reports of co-morbidity of PTSD with substance abuse disorders (Jacobsen et al., 2001). The current study seeks to investigate the possible long-term effects of exposure to a modification of the SPS model (two hours of restraint stress followed by 20 minutes of forced swim) during adolescent development. Dependent variables include spontaneous locomotor activity and responses to the elevated plus maze, a black/white chamber, and an open field. Preliminary data indicate that exposure to SPS in young adult rats results in a statistically significant increase in spontaneous locomotor activity ($t(9) = 1.80$, $p < 0.05$; effect size $r = 0.49$) and decreased exploration of the center of the open field ($t(9) = 2.38$, $p < 0.05$; effect size $r = 0.62$) among SPS rats compared to non-stressed controls when measured two weeks after the SPS exposure. Analysis of plasma coricosterone levels and sensitivity to cocaine are in progress.

Disclosures: A.L. Garrison: None. **C.E. Ukpaby:** None. **E.N. Walsh:** None. **J.M. Smith:** None. **T.E. Koeltzow:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.02

Topic: F.03. Motivation and Emotion

Support: European Research Council starting grant (ERC-StG 312511) Vicarious Brain of the European Commission to CK.

Title: Stress reduces affective sensitivity to the distress of conspecifics in rats

Authors: *Y. HAN[1], M. CARRILLO[2], M. HEINEMANS[3], I. PRUIS[5], C. KEYSERS[2,4]; [1]Social Brain Lab. (Keysers Group), Netherlands Inst. For Neurosci., Amsterdam Zuidoost, Netherlands; [2]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [3]Inst. of Interdisciplinary sciences, [4]Fac. of Social and Behavioral Sci., Univ. of Amsterdam, Amsterdam, Netherlands; [5]Earth and Life Sci., VU Univ. Amsterdam, Amsterdam, Netherlands

Abstract: An increasing number of studies have demonstrated the capability of rodents to share the affective state of their social partners. In rodents, this affective sensitivity to the distress of a conspecific appears to be modulated by stress. To further investigate the role of stress, we used an emotional contagion paradigm previously developed in our laboratory. In this paradigm, observer rats exhibit vicarious freezing after witnessing other socially related rats (demonstrators) experience repetitive painful foot-shocks. Vicarious freezing exhibited by the observer animal is used as a behavioral indicator of emotional contagion for the demonstrator's distress. In the current study, pairs of male Long Evans rats were assigned the role of observer or demonstrator and were randonly assigned to one of four conditions: 1) first control condition-no interventions, 2) stressor condition through handling, 3) stressor through handling + metyrapone (anti-stress drug) and 4) second control: Metyrapone without the stressor. In the stressor condition (2&3), the observer was hand-restrained for 15 minutes before emotional contagion test. Metyrapone, a corticosterone synthesis inhibitor (25 mg/kg metyrapone) was subcutaneously administered to the observer animals 30 minutes prior to stressor (3 & 4). Results showed that stressing the observers through a handling procedure (condition 1) prior to test produces a reduction in the vicarious freezing compared to non-stressed controls (both control conditions). In contrast, stressed observers that were pretreated with metyrapone (condition 3) exhibited similar amount of vicarious freezing as control observers (condition 1). This result indicates that stress induced by hand-restrain reduces vicarious freezing in rats which can be counteracted by reducing stress levels through inhibition of corticosterone synthesis. Combined with results from other studies, it suggests that stress plays an important role in modulating emotional contagion in rodents.

Disclosures: **Y. Han:** None. **M. Carrillo:** None. **M. Heinemans:** None. **I. Pruis:** None. **C. Keysers:** A. Employment/Salary (full or part-time); Faculty of Social and Behavioral Sciences, University of Amsterdam.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.03

Topic: F.03. Motivation and Emotion

Support: Grant from Switzerland through the Swiss Contribution to the enlarged European Union PSPB- 210/2010

National Science Centre (Poland) Grant 2013/11/B/NZ3/01560

Title: Central amygdala circuits underlying socially induced anxiety

Authors: *E. A. KNAPSKA[1], K. ROKOSZ[1], A. HAMED[2];
[1]Nencki Inst. of Exptl. Biol. PAS, Warsaw, Poland; [2]Inst. of Psychiatry and Neurol., Warsaw, Poland

Abstract: Human empathy emerges over phylogeny from various behavioral precursors. One of the simplest is emotional contagion, i.e. sharing emotional states between individuals, which can be modelled in rodents. In our model of socially transferred fear we showed that a brief social interaction with a fearful cage mate (demonstrator) promotes aversive learning in an otherwise naïve rat (observer) and activates the amygdala of the observers, especially its central part (CeA). To elucidate the role of neuronal circuits in the central amygdala of the observers, we used two methods of functional mapping: transgenic rats expressing, in behaviorally activated neurons, a PSD-95:Venus fusion protein and injected with anterograde tracer and a combination of retrograde tracing with c-Fos ISH. We have identified several afferent and efferent CeA projections active during socially transferred fear. We discovered strong activation especially in the periaqueductal gray (PAG) and dorsal raphe nuclei (DRN); these structures receive dense projections from the CeA and are implicated in fear and anxiety disorders. To test whether the activated circuits are similar for the socially and non-socially induced emotions, we used double immunodetection for a PSD-95:Venus construct and endogenous c-Fos. About 70% of neurons were activated by both social interaction with fear conditioned partner and subsequent fear conditioning. Moreover, using optogenetics, we showed that specific activation of CeA neurons involved during interaction with emotionally aroused partner results in a decrease of social and non-social exploratory behaviors and inhibition of ultravocalization. These findings suggest that there exists a group of neurons in the central amygdala that are involved in integrating information about a threat, activated during socially transferred fear and subsequently recruited by learning of fear responses. A fraction of these cells is probably specifically involved in socially induced anxiety.

Disclosures: E.A. Knapska: None. **K. Rokosz:** None. **A. Hamed:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.04

Topic: F.03. Motivation and Emotion

Title: Plasticity related changes in response to stress in rats

Authors: *W. M. VANDERHEYDEN[1], L. KOCH[1], M. KEHOE[1], G. R. POE[2];
[2]Anesthesiol., [1]Univ. of Michigan, Ann Arbor, MI

Abstract: Physical fitness may imbue resilience to the acquisition of posttraumatic stress disorder (PTSD). We hypothesized that rats responsive to physical training might display more robust molecular and anatomical markers of fear-associated memory regulation. To test this hypothesis, we assessed fear learning and contextual fear extinction recall as well as plasticity marker changes in response to stress in rats selectively bred for their response to physical exercise. Rats were bred together who responded to treadmill running with either an appropriate cardiovascular fitness response (high response to training, HRT) or a deficient response (low response to training, LRT). 10 HRT and 10 LRT rats were exposed to a fear conditioning paradigm in which five, 1 mA shocks were paired with the cessation of a 10-s long 80 dB tone (60 s Inter-tone interval) in context A (one set of visual and olfactory cues). 24 h after fear conditioning, fear was extinguished in context B (visual and olfactory cues unique from context A) to thirty, 80 dB tones with an inter-tone interval of 60 s. 24 h after extinction, fear recall was assessed in context B with the presentation of ten, 80 dB tones with a 60 s inter-tone interval. Then we exposed a subset of 4 HRT and 4 LRT animals to 2 hours of physical restraint and assessed extracellular signal-regulated kinase (ERK) and brain-derived neurotrophic factor (BDNF) levels using Western Blot. Compared to LRT animals, HRT animals showed a significantly increased fear response (increased freezing) during both the extinction training and extinction recall days (*t*-test, p value < 0.05). HRT animals also showed a significantly higher phosphorylation state of ERK in response to restraint stress compared to similarly stressed LRT animals (Students *t*-test, p value < 0.05). However, BDNF levels were not significantly different between the HRT and LRT animals in response to acute physical restraint (*t*-test, p value > 0.05). Learning such as extinction learning, depends on changes in plasticity-regulated molecules such as ERK and BDNF . Interpretation of these results in light of extinction recall memory processing is limited by the fact that we assessed ERK and BDNF after a simple stressor rather than after extinction training or recall and the absence of results from the background strain. However, these results do suggest that ERK phosphorylation levels may differentiate stress regulation fitness in this rodent model of physical fitness. Additionally, because of its role in epigenetic regulation of gene expression, ERK activation may identify more unique targets and further our understanding of the molecular mechanisms underlying stress and resilience.

Disclosures: W.M. Vanderheyden: None. **L. Koch:** None. **M. Kehoe:** None. **G.R. Poe:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.05

Topic: F.03. Motivation and Emotion

Title: Learned helplessness behavior in rat is associated with monocyte dysregulation

Authors: *N. C. DERECKI[1], L. FOURGEAUD[1], J. SHOBLOCK[2], B. ECKERT[2], G. CHEN[2], T. LOVENBERG[2], A. BHATTACHARYA[2];
[1]Neurosci., [2]Janssen Res. and Develop., San Diego, CA

Abstract: It has been suggested for some time that a relationship exists between inflammation, stress, and mood disorders; however, the precise mechanisms and directionality of the interactions have remained elusive. In several lines of inquiry, circulating serum factors, including IL-6, IFN-alpha, TNF-alpha and IL-1 beta, have been identified in association with mood disorders; thus, several groups have directed efforts at elucidating the direct effects of cytokines as primary initiators of mood disorder. Much less well-understood, however, is the effect of repeated stressors on a subsequent "integrated dysregulation" of the immune system and CNS; we hypothesize that immune dysfunction as potentiated by stress may be a key link between stress and disorders of mood. As such, we examined immune response in peripheral blood, CNS-adjacent meningeal tissues, and brain, in rats subjected to a "learned helplessness" protocol involving foot-shock stressors. Behavioral endpoints were measured including failure to escape foot shocks during a probe trial when given a viable escape route (learned helplessness). Pro-inflammatory monocyte percentages were significantly increased in peripheral blood of helpless rats; intriguingly, however, rats that had undergone foot-shocks but were behaviorally resistant were not significantly different from naïve rats, indicating that the response is linked to the behavior of being "helpless." Contrary to this phenotype in the blood, in meningeal tissues we observed more anti-inflammatory monocytes. Likewise, immunofluorescent labeling of CNS astrocytes and microglia revealed specific region-dependent changes in glial cell morphology and reactivity. Overall, our results suggest that while stress potentiates an initial acute pro-inflammatory response by the immune system, further layers of CNS regulation may serve to shape the overall response to a complex pro- or anti-inflammatory polarization depending upon brain region and cell type.

Disclosures: **N.C. Derecki:** A. Employment/Salary (full or part-time); Janssen Research and Development. **L. Fourgeaud:** None. **J. Shoblock:** None. **B. Eckert:** None. **G. Chen:** None. **T. Lovenberg:** None. **A. Bhattacharya:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.06

Topic: F.03. Motivation and Emotion

Support: Howard Hughes Medical Institute

NIH Grat MH085082

NIH Grant MH070053

Jane Coffin Childs Memorial Fund

National Science Foundation

Simon Foundation

Title: Ventromedlal hypothalamic neurons control defensive behaviors

Authors: *P. S. KUNWAR, M. ZELIKOWSKY, R. REMEDIOS, H. CAI, M. YILMAZ, M. MEISTER, D. ANDERSON;
Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: When threatened, animals exhibit appropriate defensive behaviors that are critical for their survival. The hypothalamus plays a role in such behaviors, but prevailing views depict it as a relay for an upstream defense center, the amygdala, rather than having a central role in control of these behaviors. We showed that optogenetic activation of the ventromedial hypothalamus (VMH)-specific SF1+ neurons is sufficient to produce defensive behaviors of freezing and flight that exhibit properties of scalability, persistence, dominance and negative valence. Furthermore, stimulation of SF1+ neurons triggers avoidance conditioning, refuting the long-held view that the hypothalamus cannot support defensive conditioning. Finally, to assess whether the VMH is necessary for defensive behaviors in diverse contexts, we ablated SF1+ cells and found that these mice failed to demonstrate appropriate predator avoidance, conditioned defense and anxiety behaviors. Collectively, these data suggest that the hypothalamus is not simply a passive relay site but rather plays a central role in the control of defensive behaviors.

Disclosures: P.S. Kunwar: None. **M. Zelikowsky:** None. **R. Remedios:** None. **H. Cai:** None. **M. Yilmaz:** None. **M. Meister:** None. **D. Anderson:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.07

Topic: F.03. Motivation and Emotion

Support: NARSAD Young Investigator Grant 2014, #22434

R21 MH101492-01

Title: Amygdala-dependent molecular mechanisms of the Tac2 pathway in fear learning

Authors: R. ANDERO GALI[1], S. DANIEL[2], J. GUO[2], *D. G. RAINNIE[3], K. RESSLER[2]; [1]McLean Hospital, Harvard Med. Sch., Belmont, MA; [2]Emory Univ., Atlanta, GA; [3]Emory Univiversity, Atlanta, GA

Abstract: Recently we reported that activation of the Tachykinin 2 (Tac2) pathway in the central amygdala (CeA) is necessary and sufficient for the modulation of fear memories. The Tac2 pathway includes the Tac2 gene, which encodes the neuropeptide Neurokinin B (NkB) and its corresponding receptor Neurokinin 3 receptor (NK3R). In this study, we screened Tac2 pathway-related gene variants in patients with PTSD and explore the action mechanisms of Tac2 pathway in fear memory by combination of optogenetics, pharmacology, immunohistochemistry, qRT-PCR, and electrophysiology in wild-type, Tac2-Cre, and Tac2-GFP mice. In a sample of 3070 individuals with post-traumatic stress disorder (PTSD), we have identified two gene variants of the Tac2 pathway that are significantly associated with PTSD diagnosis. Hence, delineating the Tac2 pathway may be necessary to understand and treat fear disorders such as PTSD. In transgenic mice that express ChR2 solely in Tac2 neurons, *in vivo* optogenetic stimulation of CeA Tac2-expressing neurons during fear acquisition enhances fear memory consolidation and drives action potential firing *in vitro*. Notably, Tac2-CeA neurons were found to project to the medial reticular nucleus and periaqueductal grey, areas known to play a role in fear memory formation. In addition, Tac2-CeA neurons were shown to co-express striatal-enriched protein tyrosine phosphatase (STEP), which might play an important role in the regulating Nk3R signaling. Taken together, this study extend previous animal studies to clinical investigation, suggesting that the Tac2 pathway may play a role in PTSD, and we provided data that helps to understand the action mechanisms of the Tac2 pathway.

Disclosures: R. Andero Gali: None. **S. Daniel:** None. **J. Guo:** None. **D.G. Rainnie:** None. **K. Ressler:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.08

Topic: F.03. Motivation and Emotion

Title: Anxiety-like behaviour in approach-avoidance conflict is instrumental, not pavlovian

Authors: *D. R. BACH;
Univ. of Zurich, Zurich, Switzerland

Abstract: Anxiety-like behaviour in rodents and humans is often modelled in approach-avoidance conflict tasks such as operant conflict, elevated plus maze, or open field. Building on Bayesian Decision Theory (BDT), we have recently shown that behavioural inhibition in such tasks is normative under plausible priors on reward-threat correlations. Specifically, approach delays reduce predation probability. Our model predicted that approach delay should depend on expected threat, which was experimentally confirmed in humans. In terms of its neural implementation, threat-dependent approach delay could reflect Pavlovian inhibition to approach a threat, which conforms to BDT predictions under circumstances common in the wild. On the other hand, it could also reflect instrumental (goal-directed) behaviour, computed online. Here, we sought to disambiguate these possibilities experimentally. We identified two conditions for instrumental behaviour. First, Pavlovian behaviour is evoked by stimulus characteristics while instrumental behaviour takes into account action consequences. Secondly, approach delay in the BDT model emanates from reward-threat priors. If such priors exist in neural circuits, their representation must be independent from a particular task. To test the first condition, we modify a human operant conflict task such that behavioural inhibition increases threat probability and thus ceases to be instrumental. Humans show threat-dependent approach invigoration rather than delay, indicating that they take into account action consequences. The second condition is tested by tasking humans to approach a virtual "sleeping predator" in order to reveal its status. Rather than uniformly distributing their approach actions across time, or minimising opportunity costs of time, humans prefer to approach the predator shortly after unobtainable rewards have been displayed. This is again normative under priors encoding reward-threat correlations. In summary, both tests for instrumental behaviour are passed. Our findings indicate that humans use online cost minimisation according to BDT to control anxiety-like behaviour, and contradict a purely Pavlovian account of behavioural inhibition. This crucially constrains the search for a neural implementation of anxiety-like behaviour in humans and other animals.

Disclosures: D.R. Bach: None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.09

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIH Grant K01DA031745

Pennsylvania Department of Health

Title: Fear extinction recall deficits in female rats with low estradiol are normalized by antagonism of angiotensin II type I receptors

Authors: *J. N. PARRISH[1,2], S. Y. LAM[1], M. M. TORREGROSSA[2];
[2]Psychiatry, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Studies have found that low levels of estrogens (estradiol) during fear extinction result in impaired consolidation of extinction and increased fear expression during extinction recall in women and female rats. However, the mechanism by which this occurs has not been identified. Estrogen has been found to modulate the renin angiotensin system (RAS) by downregulating the hypertensive components (including angiotensin II type I receptors (AT1R)) and upregulating the antihypertensive components. Interestingly, the AT1R antagonist losartan has been found to enhance consolidation of extinction and reduce freezing during extinction recall following systemic administration prior to a fear extinction session in male mice. In this study, we investigated whether systemic administration of losartan prior to a fear extinction session could enhance extinction consolidation in female rats with low estradiol levels. Adult female Sprague-Dawley rats received 0.5mg/kg injection of levonorgestrel (a commonly used hormonal contraceptive that lowers circulating estradiol) or vehicle daily for 4 days prior to behavioral testing and throughout the behavioral testing period. Behavioral testing consisted of a classical fear conditioning paradigm, where rats received 5 tone-shock pairings. Rats underwent extinction 24 hours after fear conditioning, where they were presented with 30 tones without shock. Immediately prior to the extinction session, rats received an i.p. injection of 3mg/kg losartan, 10mg/kg losartan, or vehicle. Rats were tested for extinction recall 24 hours after extinction, where 30 tones were presented in the absence of shock. Fear expression was measured by recording the amount of time the rat spent freezing during tone presentations. A repeated measures ANOVA revealed that levonorgestrel treatment significantly impaired extinction recall ($p < 0.05$) relative to high estradiol females, and that both doses of losartan improved extinction recall in the levonorgestrel group to levels similar to high estradiol females. In conclusion, losartan treatment enhances consolidation of extinction and thus reduces fear expression during extinction recall in female rats with low estradiol levels. These findings indicate that treatment with a low dose of losartan (that has little to no effect on blood pressure)

may be effective at enhancing the consolidation of fear extinction in women suffering from anxiety disorders like PTSD who are taking hormonal contraceptives. Current studies are investigating how site-specific infusions of losartan in the brain affect behavior in female rats with low levels of estradiol.

Disclosures: **J.N. Parrish:** None. **S.Y. Lam:** None. **M.M. Torregrossa:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.10

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIH R01MH104261

ONR N00014-12-1-0366

Pritzker Neuropsychiatric Research Consortium

Hope for Depression Research Foundation

Title: FGF2 treatment differentially impacts GAD65 and GAD67 mRNA expression in the forebrain of selectively bred high-responder and low-responder rats

Authors: ***M. WASELUS**, D. M. KROLEWSKI, S. SCHRADE, R. A. ILAGAN, J. HUH, J. PEREZ, H. AKIL, S. J. WATSON, Jr;
Molec. and Behav. Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: The selectively bred lines of high-responder (bHR) and low-responder (bLR) rats, which display robust differences in anxiety-like behaviors, have previously been used in our laboratory to demonstrate the anxiolytic effect of systemic fibroblast growth factor 2 (FGF2) treatment (Perez et al., 2009). The effect of FGF2 administration on brain GABA-ergic function is largely unknown and of particular interest given the role of GABA in both anxiety and depression. Thus, we sought to examine the potential effects of FGF2 administration on GABA-synthesizing enzyme isoforms glutamate decarboxylase 65 (GAD65) and GAD67 in the brains of bHR and bLR rats. Adult male bHR and bLR Sprague-Dawley rats received single daily injections of either vehicle or FGF2 (5ng/g, i.p.) for 21-days. On the day after the last injection, rats were behaviorally assessed for anxiety-like behaviors and the brain was subsequently removed. Thin (10 μm) sections taken through the forebrain of each rat were used to examine the

expression of GAD65 and GAD67 mRNA using radiolabeled *in situ* hybridization with cRNA probes. The effects of phenotype (bHR vs. bLR) and treatment (vehicle vs. FGF2) as well as the interaction between the two were statistically evaluated using a 2-way ANOVA with Tukey's post-hoc tests for multiple comparisons when appropriate. Irrespective of treatment, bHR-bLR differences in GAD65 expression were observed in the prelimbic and infralimbic cortices as well as the core and shell subregions of the nucleus accumbens with bLRs having lower GAD65 expression compared to bHRs in all regions. Examination of GAD67 expression revealed that in the prelimbic and infralimbic cortices, bHR-bLR differences were limited to vehicle-treated rats and eliminated following FGF2 treatment. Moreover, FGF2-induced decreases in GAD67 expression in these regions, as well as the sensorimotor cortex, occurred selectively in bHR, but not bLR, rats. In summary, the reduced expression of GAD65 in bLRs relative to bHRs supports the previously proposed association between decreased GABA function and anxiety-like behaviors. However, the failure of FGF2 treatment to augment GAD65 or GAD67 mRNA in bLRs suggests that the anxiolytic effects of FGF2 in the bLR line may not be related to changes is GABA function in the regions selected for analysis. Future studies will further examine GAD65 and GAD67 expression in other brain regions including the hippocampus which is known to play a role in anxiety and mood disorders.

Disclosures: **M. Waselus:** None. **D.M. Krolewski:** None. **S. Schrade:** None. **R.A. Ilagan:** None. **J. Huh:** None. **J. Perez:** None. **H. Akil:** None. **S.J. Watson:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.11

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIMH Grant R01-MH087583

NIMH Grant RO1-MH099085

Title: Estrous cycle surpasses sex differences' regulation of the medial prefrontal cortex transcriptome in rats and reveals an important underlying role of early growth response 1 (Egr1)

Authors: *F. DUCLOT, M. KABBAJ;
Biomed. Sci., Florida State Univ., Tallahassee, FL

Abstract: Despite clear sex differences in the prevalence of anxiety disorders, the underlying molecular mechanisms remain elusive. While women are twice as likely as men to be diagnosed with anxiety disorders and generally present with higher anxiety scores, this phenotype varies with ovarian hormones fluctuations observed throughout a woman's reproductive life and menstrual cycle. It is therefore critical to further our understanding of the mechanisms underlying the higher vulnerability and prevalence of anxiety disorders in females and their interaction with the ovarian cycle. Notably, such gender differences are also observed in laboratory animals, where female rats exhibit lower levels of social interaction than males, denoting higher social anxiety. We recently showed that this sexually biased phenotype was controlled by the expression levels of the immediate early-gene and transcription factor early growth response 1 (Egr1, also known as Zif268, NGFI-A, Krox-24, or Zenk) in the medial prefrontal cortex (mPFC). Here, we undertook a large-scale characterization of sex differences in the mPFC transcriptome of males, proestrus and diestrus female rats by RNA-sequencing to investigate the influence of hormonal fluctuations (high in proestrus, low in diestrus). Surprisingly, while sex differences in gene expression in the rat mPFC were relatively small, they were substantially affected by the estrous cycle and proestrus and diestrus females presented with distinct and partly opposite sexually-biased transcriptomes. Moreover, the extent of differential gene expression and splicing within females vastly exceeded those between males and females, revealing a profound reorganization of the mPFC transcriptome throughout the estrous cycle. Interestingly, these variations affect genes related to the regulation of synaptic function at multiple levels and thus suggest a widespread modulation of neurotransmission across the estrous cycle. In order to investigate the specific involvement of Egr1 in these regulations, we sought to discover the specific genes under the direct transcriptional control of Egr1 by chromatin immunoprecipitation followed by sequencing (ChIP-seq). Combined to our RNA-seq analysis, this approach revealed substantial differential binding of Egr1 to synaptic plasticity-related genes which varied within females' estrus cycles. In addition to demonstrating the importance of accounting for the estrous cycle, our data thus suggest a particular involvement of Egr1 in controlling the sex- and estrous cycle-dependent transcriptomic reorganization in the rat mPFC.

Disclosures: **F. Duclot:** None. **M. Kabbaj:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.12

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIH Grant NS073899

Title: A cell-based screen identifies compounds that attenuate FKBP51 repression of glucocorticoid receptor activity

Authors: *J. J. SABBAGH, M. R. JONES, S. N. FONTAINE, C. A. DICKEY;
Mol. Med., Univ. of South Florida, Tampa, FL

Abstract: FK506 binding protein 51 (FKBP51), encoded by the FKBP5 gene, is an Hsp90 co-chaperone implicated in multiple psychiatric diseases, including depression and post-traumatic stress disorder (PTSD). FKBP51 levels increase with age due to reduced FKBP5 methylation, leading to vulnerability to stress and altered glucocorticoid signaling. Furthermore, single nucleotide polymorphisms (SNPs) in FKBP5 are associated with increased risk for developing depression and PTSD, suggesting targeted inhibition of FKBP51 may be beneficial in neuropsychiatric diseases. Using FKBP51 knockout mice, we have confirmed that FKBP51 does inhibit glucocorticoid receptor (GR) activity in the brain as expected. Therefore, we designed a screening platform to identify compounds that could attenuate FKBP51-mediated suppression of GR activity. Using cell-based luciferase assays, we screened more than 1000 pharmacologically active compounds and identified several lead molecules that abrogated the suppressive effect of FKBP51 on GR activity. Follow-up screens highlighted two compounds in particular that did not independently affect GR activity. One of these compounds was previously shown to impact depression, but it was thought to do so through a different mechanism, while the other compound has been used to treat other psychological disorders, but not depression. We have discovered that these compounds most likely work by directly disrupting GR-FKBP51 binding. These compounds also rescue the FKBP51-mediated decrease in GR nuclear translocation. Lastly, immobility time in the tail suspension test is reduced by these compounds, suggesting they exhibit anti-depressant efficacy. These findings provide new molecular probes to interrogate FKBP51 function at the GR complex and highlight that FKBP51 is a potentially druggable target for depression and PTSD.

Disclosures: J.J. Sabbagh: None. **M.R. Jones:** None. **S.N. Fontaine:** None. **C.A. Dickey:** None.

Nanosymposium

465. Stress and Anxiety: Animal Models

Location: S102

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 465.13

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NARSAD Young Investigator Grant

Title: Intergenerational transmission of trauma exposure through fkbp5 dna methylation in rhesus macaques

Authors: *T. KLENGEL[1], D. GUZMAN[1], B. HOWELL[1], Z. JOHNSON[1], E. B. BINDER[2], K. J. RESSLER[1], M. SANCHEZ[1];
[1]Yerkes Natl. Primate Res. Ctr., Emory Univ., Atlanta, GA; [2]Max Planck Inst. of Psychiatry, Munich, Germany

Abstract: In human, exposure to severe stress in early life significantly contributes to the pathophysiology of psychiatric disorders in adulthood. While stressful and even traumatic events are common in childhood, only a minority of exposed individuals later develops a disorder, which is presumably modulated by genetic predisposition through gene by environment interactions (GxE). Many studies including from our group characterized the GxE of FKBP5 (FK506 binding protein 5) and childhood trauma on the risk for post-traumatic stress disorder (PTSD) and other phenotypes. We recently identified allele-specific demethylation as a mechanism inducing life-long epigenetic changes in FKBP5 contributing to the deregulation of the HPA axis and thus leading to an increased risk to develop PTSD (Klengel et al., Nat Neurosci., 2013). Although highly controversial, exposure to environmental factors may lead to the transmission of information through the gametes to subsequent generation possibly influencing disease risk not only in the exposed generation. Here we extend our findings on a non-human primate model of childhood trauma in rhesus macaques using a cross-fostering paradigm to investigate the effect of ancestral childhood maltreatment on rheFKBP5 DNA methylation across generations. We find strong effects of ancestral maltreatment in cross-fostered offspring in FKBP5 DNA methylation at the very same region that is relevant in human. We thus present for the first time data showing the ancestral environment influencing the offspring epigenetic imprint at the FKBP5 locus.

Disclosures: T. Klengel: None. **D. Guzman:** None. **B. Howell:** None. **Z. Johnson:** None. **E.B. Binder:** None. **K.J. Ressler:** None. **M. Sanchez:** None.

Nanosymposium

466. Auditory Processing: Cortical Encoding of Complex Sounds

Location: S402

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 466.01

Topic: D.02. Auditory System

Support: HBP Grant

FWO Grant

IUAP Grant

PF Grant

Title: Homology and specificity of natural sound-encoding in human and monkey auditory cortex

Authors: *J. ERB[1,2], M. ARMENDARIZ[3], F. DE MARTINO[1,2], W. VANDUFFEL[3,4,5], E. FORMISANO[1,2];
[1]Dept. of Cognitive Neurosci., Fac. of Psychology and Neuroscience, Maastricht, Maastricht, Netherlands; [2]Maastricht Brain Imaging Ctr. (MBIC), Maastricht, Netherlands; [3]Lab. voor Neuro- en Psychofysiologie, KU Leuven, Leuven, Belgium; [4]MGH Martinos Ctr., Charlestown, MA; [5]Harvard Med. Sch., Boston, MA

Abstract: How does the neural representation of natural sounds compare between human and non-human primate species? We used contrast-agent enhanced fMRI (Vanduffel et al., 2001) in awake macaque monkeys (0.7 mm isotropic voxel, using implanted phased-array coils, Janssens et al., 2012) to investigate the cortical encoding of natural sounds. We modelled fMRI responses in the auditory cortex as a function of the sounds' spectro-temporal content (fMRI encoding), and derived single- and multi-voxel modulation transfer functions as well as topographic maps of sensitivity to frequency, spectral and temporal modulations. Results are compared to human 7T fMRI data collected using identical stimuli and analyzed with the same modelling approach (Santoro et al., 2014). Topographic cortical maps of acoustic features in the macaque are similarly organized as in humans: Tonotopic maps showed typical alternating high-low frequency gradients across the primary core and surrounding belt areas (Moerel et al., 2014; Joly et al. 2014). Consistent with human results (Santoro et al., 2014), fast temporal and coarse spectral acoustic information was preferably encoded in posterior auditory regions, as opposed to slow temporal and fine spectral information in anterior-lateral auditory regions. As an important difference, however, the macaques' temporal modulation function showed a preference for faster modulation rates, with a peak at approximately 60 Hz, whereas the humans' preferred modulation rate was centered at 3-4 Hz. The latter modulation rate has been linked to the processing of syllables in speech (Luo and Poeppel, 2007). Supporting this hypothesis, sound representations in humans maximized the fine-grained discrimination of speech and other human vocal sounds, but not of sounds from other categories (Santoro et al., submitted). No such effect, however, could be observed in the macaque although identical sounds and methods were used. These findings suggest that tuning of the human auditory cortex to the syllabic rate is unique and might constitute a product of the evolution of speech and language.

Disclosures: **J. Erb:** None. **M. Armendariz:** None. **F. De Martino:** None. **W. Vanduffel:** None. **E. Formisano:** None.

Nanosymposium

466. Auditory Processing: Cortical Encoding of Complex Sounds

Location: S402

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 466.02

Topic: D.02. Auditory System

Support: NWO Grant 446-12-010

NWO Grant 864-13-012

NWO Grant 453-12-002

NIH Grant P41 EB015894

NIH Grant P30 NS076408

NIH Grant S10 RR26783

WM KECK Foundation

Title: Cortical depth-dependent processing of natural sound features in human auditory cortex

Authors: ***M. MOEREL**[1], F. DE MARTINO[2], K. UGURBIL[1], E. YACOUB[1], E. FORMISANO[2];
[1]Ctr. for Magnetic Resonance Res., Univ. of Minnesota, Minneapolis, MN; [2]Maastricht Univ., Maastricht, Netherlands

Abstract: Throughout the human auditory cortex, neurons with similar feature preference cluster together creating large-scale maps (e.g. tonotopy) [1]. Invasive animal studies suggest that another spatial organization is implemented orthogonal to the cortical sheet. That is, neuronal preference for frequency and spectrotemporal modulations may be stable throughout cortical columns [2,3]. Here we examine cortical depth-dependent feature preference in the human primary auditory cortex (PAC) based on its responses to natural sounds as measured with high field functional MRI (7 Tesla). We acquired high-resolution anatomical (0.6 mm isotropic) and functional data (0.8 mm isotropic), while volunteers (N = 6) listened to 144 natural sounds. Cortical responses were analyzed with an encoding model that defined the voxels' responses by their frequency-specific spectrotemporal modulation preference [4]. The trained model predicted

responses to novel sounds significantly above chance (mean prediction accuracy [SEM] = 0.69 [0.02]; chance = 0.5; $p < 0.001$). Large-scale feature maps, created by color-coding voxels according to the frequency, temporal (rate) or spectral modulations (scale) with the highest model weight, were in accordance with previous findings [1,4]. Next, we quantified the cortical depth-dependent stability of feature preference (i.e., "columnarity") as the ratio between the topographic maps' local gradient parallel and orthogonal to the cortical sheet. For frequency and rate, we observed regions of consistent preference across cortical depths (i.e., columnar regions; $p < 0.05$ [permutation testing]). In line with results from recordings in cat PAC [3], scale preference was less stable across depths (significant difference to 'rate'; $p < 0.05$ [paired t-test]). Specifically, compared to deep cortical depths, superficial depths preferred lower scales ($p < 0.05$ [paired t-test]). We observed both overlapping and distinct columnar regions across feature maps, suggesting a columnar coding strategy in which tuning to some features is kept stable while tuning to another feature varies systematically. These preliminary findings show the feasibility of studying neuronal population tuning to acoustic features at submillimeter resolution using high field fMRI. Future analyses will evaluate the performance of different computational models across cortical depths to explore intracolumnar computations in the human PAC. 1. Formisano et al. (2003) Neuron. 2. Schreiner (2009) Spectral processing in auditory cortex. In: The Auditory Cortex (Winer and Schreiner, eds). 3. Atencio, Schreiner (2010) J. Neurophysiol. 4. Santoro et al. (2014) PLoS Comput Biol.

Disclosures: M. Moerel: None. **F. De Martino:** None. **K. Ugurbil:** None. **E. Yacoub:** None. **E. Formisano:** None.

Nanosymposium

466. Auditory Processing: Cortical Encoding of Complex Sounds

Location: S402

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 466.03

Topic: D.02. Auditory System

Support: McDonnell Scholar Award

NEC Research Award

Title: fMRI responses to natural and model-matched synthetic sounds reveal a hierarchy of auditory cortical computation

Authors: S. NORMAN-HAIGNERE[1], *J. MCDERMOTT[2];
[2]Brain and Cognitive Sci., [1]MIT, Cambridge, MA

Abstract: A central goal of auditory neuroscience is to understand the neural representation of natural sounds. One approach is to use “encoding models” to predict neural responses from stimulus features. However, there is no guarantee that features that predict neural responses are those that actually drive them, because distinct features are often correlated across natural stimuli. Here we introduce an alternative approach utilizing “model-matched stimuli” synthesized to evoke the same response as a natural sound in a model of neural computation. If the model provides a good description of the neural response, then the neural response to natural sounds and matched synthetic sounds should be similar even though the sounds may differ in many other respects. We used this approach to explore the sensitivity of different regions in human auditory cortex to standard acoustic features hypothesized to underlie their response. Using fMRI, we measured cortical responses to natural and synthetic sounds that were matched in average spectrotemporal modulation power, using a variant of existing texture synthesis methods. Crucially, the synthetic sounds were constrained only by their modulation power statistics, and as such were perceptually distinct from the natural sounds they were matched to (which exhibit additional higher-order statistical dependencies not made explicit by the spectrotemporal modulation model, and thus not replicated in the synthetic matches). Despite these perceptual differences, the natural and model-matched synthetic sounds produced nearly equivalent voxel responses in primary auditory cortex, suggesting that modulation power accounts for much of the neural response there. In contrast, voxel responses in non-primary regions differed markedly to the two sound sets, with many voxels producing little to no response for the synthetic sounds. This functional difference was much less pronounced using encoding models: modulation statistics were effective predictors of voxel responses in both primary and non-primary regions, presumably because they are correlated with higher-order features to which non-primary regions are tuned. Our approach reveals an increase in selectivity in non-primary regions of human auditory cortex and illustrates the use of model-matched stimuli in testing theories of cortical computation.

Disclosures: **S. Norman-Haignere:** None. **J. McDermott:** None.

Nanosymposium

466. Auditory Processing: Cortical Encoding of Complex Sounds

Location: S402

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 466.04

Topic: D.02. Auditory System

Support: DOE Computational Science Graduate Fellowship to AK

NSF Graduate Research Fellowship to SNH

NEC award to JHM

McDonnell Scholar Award to JHM

Title: Functional organization of auditory cortex revealed by neural networks optimized for auditory tasks

Authors: *A. J. KELL, D. L. K. YAMINS, S. V. NORMAN-HAIGNERE, J. H. MCDERMOTT;
Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Despite many proposals, there is little consensus on the functional organization of non-primary auditory cortex. Here we probe functional organization by developing models that perform difficult auditory tasks at near-human levels and then comparing the model representations with responses measured in human auditory cortex. If the set of solutions to difficult auditory tasks is small, the models could plausibly converge on representations similar to those in the brain. Models that perform well on ecologically relevant tasks thus provide candidate hypotheses of auditory cortical computation. As a first step in this research program, we trained a hierarchical convolutional neural network (CNN) to recognize words in high levels of complex background noise. We used millions of examples of speech from labeled corpora, explicitly optimized network architecture (Yamins, Hong, et al., 2014), and trained filters with standard back-propagation. Crucially, the CNN was optimized only for the speech task; it was not optimized to predict neural responses of any sort. With training complete, we measured fMRI responses to 165 natural sounds (e.g., outdoor sounds, mechanical sounds, animal vocalizations, speech, music, etc.) in the auditory cortex of eight humans, and tested whether different layers of the speech-trained CNN could predict the voxel responses. We computed the response of each unit in the CNN to the 165 sounds, and measured the representational similarity between the neural and model responses using linear regression. Specifically, we modeled each voxel as a linear mixture of model units from a particular CNN layer, and predicted the response to left-out stimuli. We have three key findings. First, the CNN predicts neural responses better than a standard spectrotemporal filter model, and better than an untrained CNN with the same architecture (and thus same number of model units). Second, the CNN suggests a computational distinction between primary and non-primary auditory cortex: shallow and deep CNN layers both predict primary auditory responses well, but deep CNN layers predict responses in non-primary cortex substantially better than shallow layers. Third, within speech-selective cortex, the predictive advantage of deeper layers of the CNN increases along the medial-to-lateral axis, potentially suggesting a previously unreported hierarchical organization within speech-selective cortex. Overall, our results suggest that task-optimized models can both clarify known properties of auditory cortex and reveal previously unknown aspects of cortical organization.

Disclosures: **A.J. Kell:** None. **D.L.K. Yamins:** None. **S.V. Norman-Haignere:** None. **J.H. McDermott:** None.

Nanosymposium

466. Auditory Processing: Cortical Encoding of Complex Sounds

Location: S402

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 466.05

Topic: D.02. Auditory System

Support: CIHR Grant R5312A04

Title: Neural adaptation depends on temporal context in younger and older listeners

Authors: ***B. HERRMANN**[1,2], J. OBLESER[3,2], M. J. HENRY[1,2], I. S. JOHNSRUDE[1]; [1]Dept. of Psychology, The Univ. of Western Ontario, London, ON, Canada; [2]Max Planck Res. Group "Auditory Cognition", Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany; [3]Univ. of Luebeck, Luebeck, Germany

Abstract: Neural adaptation refers to the reduction of neural response magnitude following sound repetition. In human electroencephalography, effects of neural adaptation are particularly pronounced for the N1 auditory cortex response. Traditionally, N1 adaptation has been thought to be solely a function of the duration of the interval between successive sounds. Here we investigated the effects of the extended temporal history on neural adaptation and asked whether such temporal context effects change with aging. Electroencephalograms were recorded from younger (N=21, 24.6 years) and older participants (N=18, 61.7 years) listening to sequences of tones in which the interstimulus interval (ISI) changed in a regular way (becoming steadily shorter or longer), or in which the same ISIs were randomly presented. We compared neural responses to tones preceded by identical intervals in both sequence types, so any amplitude differences between regular and irregular contexts must arise from the extended temporal stimulation history. N1 amplitudes increased as a function of preceding interval duration. However, this amplitude increase was larger for older than younger participants, indicating that older participants have a larger dynamic range of neural responses. Critically, the degree to which N1 amplitude was modulated by the duration of the preceding interval was smaller in irregular than regular sequences. The data show that neural adaptation is not only influenced by the immediately preceding temporal interval, but by the overall temporal context in which tones are embedded. Within temporally regular sequences, the N1 response was larger when the tone presentation rate sped up compared to when it slowed down. This difference was reduced for older participants. Conversely, evoked gamma band responses (35-75 Hz; preceding the N1)

were larger for speeding up than for slowing down contexts in older but not in younger participants. In sum, the current data show (1) that neural adaptation depends on the temporal context in which sounds are presented, and that this adaptation changes with age; (2) that N1 auditory cortex responses in older participants are less sensitive to temporal regularities, although their dynamic response range is larger; and (3) that evoked gamma band responses show (potentially compensatory) context sensitivity in older participants.

Disclosures: B. Herrmann: None. **J. Obleser:** None. **M.J. Henry:** None. **I.S. Johnsrude:** None.

Nanosymposium

466. Auditory Processing: Cortical Encoding of Complex Sounds

Location: S402

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 466.06

Topic: D.02. Auditory System

Support: NIDCD 2 R01 05660

NIDCD 5F32DC011985

Title: A new framework to investigate hemispheric asymmetries in speech

Authors: *A. FLINKER, D. POEPPEL;
Psychology, New York Univ., New York, NY

Abstract: The left and right hemispheres have been argued to have different sensitivities to temporal and spectral auditory information, but the underlying cortical mechanisms remain unknown. Two related models posit that asymmetries arise from a relative difference in temporal integration windows (i.e. AST, Poeppel 2003) or a difference in spectral versus temporal resolution (i.e. Zatorre et al. 2002). Here we examine a unifying scheme based on the modulation power spectrum (MPS) of speech, providing a novel framework to parametrically manipulate speech stimuli and test psychophysical and neurophysiological responses. In contrast with a spectrogram, which represents the signal's amplitude across time and frequency, the MPS is a second order representation that assesses how the time-frequency power is modulated across the spectral and temporal axes. We propose that the two hemispheres integrate different ranges of spectral and temporal modulations. In order to address this hypothesis, we implemented a new filtering technique and varied the degree of spectral and temporal modulations in the signal to produce new sentences materials. We characterized the modulation space as a function of

intelligibility as well as pitch (here: gender) identification. Neurophysiological responses (MEG power 0.1-8 Hz) across sensors correlated significantly with the temporal and spectral modulation space. The spatial distribution of sensors was more left lateralized for the temporal modulation axis and more right lateralized for the spectral modulation axis. Behaviorally, the fine-graded parametric steps reveal a sharp intelligibility cutoff, a right ear dichotic advantage as well as an influence of spectral modulation on pitch perception.

Disclosures: A. Flinker: None. **D. Poeppel:** None.

Nanosymposium

466. Auditory Processing: Cortical Encoding of Complex Sounds

Location: S402

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 466.07

Topic: D.02. Auditory System

Support: NIH, R01 DC009823

Title: Melody discrimination task reveals functional activation deficits in a left posterior inferior frontal region in tone-deaf compared to typically developing individuals

Authors: *L. ROGENMOSER[1,2,3], P. LOUI[4], K. SCHULZE[5], S. MARCHINA[1], H. LI[1], G. SCHLAUG[1];
[1]Beth Israel Deaconess Med. Ctr., Harvard Med. Sch., Boston, MA; [2]Div. Neuropsychology, Inst. of Psychology, Univ. of Zurich, Zurich, Switzerland; [3]3.Neuroscience Ctr. Zurich, Univ. of Zurich and ETH Zurich, Zurich, Switzerland; [4]Program in Neurosci. and Behavior, Dept. of Psychology, Wesleyan Univ., Middletown, CT; [5]Inst. of Child Health, Univ. Col. London, London, United Kingdom

Abstract: Tone-deafness (TD) is frequently defined by performance in a pitch and melody discrimination test. Phenotypically, TD individuals are usually characterized by an inability to sing in tune or to use their auditory feedback to make corrections to their vocal output. TD has been related to structural alterations in non-primary auditory regions in the temporal lobe as well as auditory-motor integration and motor-programming regions in the frontal brain and the major fiber tract (arcuate fasciculus) connecting these brain regions (see Loui et al., 2009; Mandell et al., 2007; Hyde et al., 2007). The question arises here is whether subjects with TD show functional impairment in addition in brain regions previously shown to have structural differences compared to typically developing individuals. To address this question, we compared the functional activation pattern of a melody and a rhythm discrimination task in TD and

typically developing control subject. A group of TD subjects (n=11), using the cutoff suggested by the Montreal Battery for Evaluation of Amusia (MBEA; Peretz et al., 2003), and a control group (n=13) performed melody and rhythm discrimination tasks (for more details, see Overy et al., 2005) while they underwent a functional magnetic resonance imaging (fMRI) scanning session using a sparse temporal design fMRI design (for more details, see Gaab et al., 2003). TD subjects performed significantly poorer than controls on the melody subtests (but not on the rhythm ones) of the MBEA. Similarly, their melody discrimination performance in the fMRI experiment was significantly below that of a control group, which was not seen in the rhythm discrimination test. In line with this, the fMRI analysis revealed activation deficits during the melody discrimination task mainly in fronto-temporal regions (especially the left inferior frontal gyrus and right middle temporal gyrus) in comparison to that of non-TD control subjects. No such between group differences were seen for the rhythm discrimination task. These functional activation deficits are most likely a reflection of the underlying anatomical abnormalities in amusic brains, since these findings partly overlap with the regions that showed structural alterations in previous voxel-based morphometric studies in TD (Mandell et al., 2007; Hyde et al., 2007).

Disclosures: **L. Rogenmoser:** None. **P. Loui:** None. **K. Schulze:** None. **S. Marchina:** None. **H. Li:** None. **G. Schlaug:** None.

Nanosymposium

466. Auditory Processing: Cortical Encoding of Complex Sounds

Location: S402

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 466.08

Topic: D.02. Auditory System

Support: Lithuanian Research Council Grant MIP-009/2014

Title: Phase-Locking Index of 40Hz Auditory Steady-State Response is not related to major personality trait dimensions

Authors: ***M. KOROSTENSKAJA**[1,2,3], O. RUKSENAS[4], I. GRISKOVA-BULANOVA[4]; [1]Functional Brain Mapping and BCI Lab, Florida Hosp. For Children, Orlando, FL; [2]MEG Lab, Florida Hosp. for Children, Orlando, FL; [3]Comprehensive Pediatric Epilepsy Center, Florida Hosp. for Children, Orlando, FL; [4]Dept. of Neurobio. and Biophysics, Vilnius Univ., Vilnius, Lithuania

Abstract: Background: Although a number of studies have demonstrated state-related auditory steady-state response (ASSR) dependence, the investigations assessing trait-related ASSR changes are limited. Five consistently identified major trait dimensions, also referred to as "big five" (Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness), are considered to account for virtually all personality variance in both healthy people and those with psychiatric disorders. The purpose of the present study was, for the first time, to establish the link between 40Hz ASSR and "big five" major personality trait dimensions in healthy young people. Methods: 94 young healthy volunteers participated (38 males and 52 females; mean age±SD 22.180± 2.75). The 40 Hz clicks were presented for each subject thirty times in a pseudo-randomized order with an inter-train interval of 1-1.5 s. The EEG responses were recorded from F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 locations according to 10/20 electrode placement system. Phase-locking index (PLI) was calculated and decomposed through non-negative multi-way factorization (NMWF), indicating the activity that is the most common across subjects. For assessing "big five" peronality traits NEO Personality Inventory Revised (NEO-PI-R) was used. Results and conclusions: No significant correlation between 40Hz ASSR PLI and "big five" personality traits was observed. Our results indicate that there is no dependency between 40Hz ASSR entrainment and personality traits. These results suggest low 40 Hz ASSR variability among the healthy population that makes it a valuable asset when utilized as a selective marker for neuropsychiatric disorders.

Disclosures: **M. Korostenskaja:** None. **O. Ruksenas:** None. **I. Griskova-Bulanova:** None.

Nanosymposium

467. Visual-Motor Processing: Prediction and Adaptation

Location: S401

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 467.01

Topic: D.05. Visual Sensory-motor Processing

Support: Ministero dell'Università e della Ricerca (MIUR) by Futuro in Ricerca

Fondazione del Monte di Bologna e Ravenna (Italy)

DFG 15 LA952-6

Title: Saccade adaptation and perceived size after trans-saccadic manipulation of object size

Authors: ***A. BOSCO**[1], M. LAPPE[2], P. FATTORI[1];
[1]Univ. of Bologna, Bologna, Italy; [2]Univ. of Munster, Munster, Germany

Abstract: We usually explore a visual scene by saccadic eye movements. When saccadic eye movements consistently fail to land on the intended target, saccade accuracy is restored by gradually adapting the amplitude of successive saccades to the same target. Such saccadic adaptation can be artificially induced by systematically displacing a small visual target during the execution of the saccade. However, saccades are normally performed to objects that present a surface. In the present study, we investigated changes in saccade amplitude and in visual perception when the size of a target object was systematically changed during a saccade. Two groups of participants were tested in two experiments: shortening and lengthening paradigms. In the shortening experiment, participants made saccades to targets of 10 different sizes located at 14.3 deg on the right of the initial fixation target which were each shortened during saccade execution. In the lengthening experiment, the targets were lengthened during the saccades. During saccade execution, the bar was changed by 30% of its original length. In both experiments, during a pre- and post-adaptation phase, subjects were instructed to manually indicate the horizontal size of each target by grip aperture (index and thumb extension). In both experiments, we evaluated the effect of change in visual perception on saccade and hand grip parameters. We observed first that saccadic adaptation can be induced by modifying target object size and secondly that this gradual change in saccade amplitude in the direction of the object size change evokes a concomitant change in the perception of initial object size. These findings show that size is a relevant signal for saccadic system and its trans-saccadic manipulation entails considerable changes at multiple levels of sensorimotor performance. In fact, the substantial transfer of size visual misperception to grip aperture is compatible with the view that object features such as size are better processed when the eyes capture the target with the fovea. In such view, we can argue that the distortion of grip aperture following the saccadic adaptation is strongly based on foveal vision. In fact, grasping and manipulation of objects require a representation of the central part of visual field that is critical to collect visual information for the interaction between hand and object.

Disclosures: **A. Bosco:** None. **M. Lappe:** None. **P. Fattori:** None.

Nanosymposium

467. Visual-Motor Processing: Prediction and Adaptation

Location: S401

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 467.02

Topic: D.05. Visual Sensory-motor Processing

Support: ERC-2012-StG_312227

James MacDonnell Foundation award

ANR-10-LABX-0087 IEC

Title: Spike-frequency adaptation optimizes the tradeoff between efficiency and accuracy in a predictive coding model

Authors: *G. J. GUTIERREZ, S. DENEVE;
Group for Neural Theory, Ecole Normale Superieure, Paris, France

Abstract: Networks of neurons are often tasked with representing and performing computations on their inputs, and relaying this information to downstream networks. However, they don't have unlimited resources with which to operate. Using a top-down approach, we build a neural code that seeks to minimize its representation error and its metabolic costs [1]. In doing so, we construct a neural network that is E/I balanced and whose neurons are subject to spike-frequency adaptation. This framework allows one to investigate and make predictions about the structure of neural networks as well as the roles that specific biophysical mechanisms may have in neural computation. We use this approach to investigate encoding and decoding in a model of orientation discrimination. While spike-frequency adaptation leads to efficient and biologically realistic spiking activity, it also produces a variable population code that is dependent on recent spiking history. This can lead to drastic changes in the neural tuning curves depending on the statistics of the stimuli. Despite those changes, an accurate representation can still be obtained without having to adjust the decoder because the global network activity adjusts itself through it's balanced, recurrent connectivity. These results predict that population code variability isn't simply due to noise, rather, it is a consequence of the cost/accuracy tradeoff inherent in the neural code. [1] M. Boerlin, C.K. Machens, and S. Deneve, PLoS Comput Biol. 9(11): e1003258 (2013).

Disclosures: G.J. Gutierrez: None. **S. Deneve:** None.

Nanosymposium

467. Visual-Motor Processing: Prediction and Adaptation

Location: S401

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

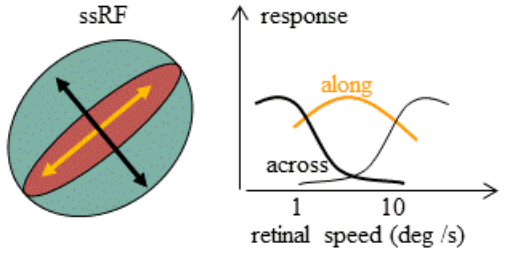
Presentation Number: 467.03

Topic: D.05. Visual Sensory-motor Processing

Title: The trajectory of fixational eye movements can be encoded at high resolution by cortical simple cells: A Hypothesis

Authors: *E. AHISSAR, A. ARIELI;
Weizmann Inst. Sci., Rehovot, Israel

Abstract: Eye Movements (eyeM) are an essential component of visual perception. Stationary scenes are sampled and scanned by eyeM at various spatial scales, primarily at the scene level via saccades and at the local level via fixational eyeM (FeyeM). Given the constant motion of visual images on the retina, a crucial factor in resolving spatial ambiguities is the exact trajectory of eyeM. We show here that the trajectory of eyeM can be encoded at high resolution by symmetrical simple retinal RFs (ssRFs). The inhibitory flanks of ssRFs produce an isolated "corridor" through which, at certain retinal velocities, image details are encoded in only one direction - along the elongated axis of the RF (left panel, orange arrow). With retinal speeds inducing a delay of a few ms between the inhibitory and excitatory zones of the RF orthogonally-moving stimuli (black arrow) would be inhibited. For foveal ssRFs these velocities are estimated around 1-10 deg/s, typical fixational drift speeds. The sensitivity of ssRFs to moving bars should thus depend on the speed of retinal motion - stronger for bars moving "along" (orange) at drift-like speeds and for bars moving "across" (black) at lower or higher speeds (right panel). At drift speeds retinal proprioception is thus conveyed by a labeled-line code. Each ssRF is 'labeled' with a direction of eyeM; it will be activated only if the concurrent eyeM includes a motion component in its orientation. Thus, cortical simple cells encode eyeM as follows: their activation indicates the direction, the rate of their spikes indicates the retinal speed and the number of spikes indicates the retinal distance (in # of retinal RFs) of the concurrent eyeM. With sparse scenes, complex cells would be more reliable coders of eyeM trajectory due to their integration of several simple cells of the same orientation. This encoding can account for motion illusions such as the Ouchi illusion. Encoding of motion projections along horizontal and vertical ssRFs entails a kind of Cartesian decomposition of the 2D image into two 1D projections.



Disclosures: E. Ahissar: None. **A. Arieli:** None.

Nanosymposium

467. Visual-Motor Processing: Prediction and Adaptation

Location: S401

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 467.04

Topic: D.05. Visual Sensory-motor Processing

Support: Swedish Research Council grant VR-M-K2013-62X-03026

Swedish Research Council grant VR-NT 621-2007-6049

Human Brain Project

Karolinska Institute Research Funds

Title: Inhibition normalises multisensory integration on gaze controlling neurons in the optic tectum

Authors: *A. A. KARDAMAKIS, J. PEREZ-FERNANDEZ, S. GRILLNER;
Karolinska Inst., Stockholm, Sweden

Abstract: Movements towards and away from sensory stimuli in the environment are critical for survival. Neurons in the deep layers of the optic tectum (superior colliculus in mammals) that command gaze movements rely on the synaptic integration of diverse sensory inputs. These multisensory cells form a canonical circuit with afferent sensory input targeting the superficial and intermediate tectal layers. Although studies have shown that multiple sensory modalities can modulate their neural activity, the synaptic underpinnings of this multisensory integration have not been investigated. Recently, we have shown that the GABAergic system within the optic tectum can generate visual stimulus selection through a process of competitive inhibition in the lamprey - a conserved vertebrate system. This is effectively carried out through long-range inhibitory connections across the tectal map of space that generate local excitation and global suppression onto gaze controlling neurons in the deep layer mediating orienting or avoidance movements. We now show that synaptic inhibition is not only critical for generating stimulus selection but also essential for multisensory integration. Here, we studied the mechanisms underlying cross-modal integration of visual and electrosensory signals onto gaze controlling neurons. Using whole-cell recordings in a midbrain preparation, we report that unimodal inputs generated direct excitation that was quickly followed by inhibition from local GABAergic interneurons. Notably, their distinctive intrinsic properties supported the temporal integration of excitatory and inhibitory synaptic currents during co-activation of both sensory afferent pathways, which resulted in a continuous scaling of their net excitatory responses. In particular, sensory-induced excitatory currents had a greater impact on their membrane depolarisation, when they did not temporarily overlap with feedforward inhibition, while synaptic depression during sustained activation ensured balanced activity in these neurons. This is was further corroborated in the intact animal where we demonstrate that deep layer neural activity, during local visual and electrosensory activation, increases sublinearly throughout a wide range of

stimulus intensities. Pharmacological blockade of local GABAergic inhibition amplified responses with rigorous discharge of action potentials during unimodal and crossmodal stimulation, thus, cancelling any additive effects onto gaze controlling neurons. These results suggest that modality-dependent recruitment of inhibition provides an evolutionary strategy for generating robust multisensory normalisation.

Disclosures: A.A. Kardamakis: None. **J. Perez-Fernandez:** None. **S. Grillner:** None.

Nanosymposium

467. Visual-Motor Processing: Prediction and Adaptation

Location: S401

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 467.05

Topic: D.05. Visual Sensory-motor Processing

Support: NIH Grant R01NS065065

NINDS Diversity Supplement 3R01NS065065-01A2S1

Title: Eye-centered tuning is weak in dorsal premotor cortex when monkeys are not trained to fixate

Authors: *B. ALEMAYEHU[1], N. PAVLOVSKY[1], J. CHIOU[1], E. TYLER-KABARA[1], N. HATSOPOULOS[2], S. CHASE[3], A. BATISTA[1];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Univ. of Chicago, Chicago, IL; [3]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The dorsal aspect of the premotor cortex (PMd) is a key node in the cortical pathway for visually-guided reaching. There is debate about where in the eye-to-arm reference frame transformation PMd sits. One issue in this debate is whether or not the task that the animal is trained to perform may affect the tuning properties of PMd neurons. To address this we recorded from PMd of two Rhesus monkeys while they performed a delayed reaching task. The animals were not trained to fixate. We found that tuning in PMd for reach target location relative to the direction of gaze was quite weak. We recorded neural activity using a 96-channel Blackrock microelectrode array. Ten sessions with 45 +/- 10 well-isolated neurons per session were analyzed. We first used a standard linear regression to determine neural tuning. We found that tuning to the location of the target relative to the hand (target-hand reference frame; TH) was strong (79% of cells in Monkey L, 96% in Monkey I). We also found tuning to the location of the target relative to the eye (target-eye reference frame, TE; 59% of cells in Monkey L, 95% in

Monkey I). However, we recognized that this measurement of TE could be an overestimate. We found that the animals exhibited consistent gaze behavior patterns during the task, and we reasoned that this could induce apparent TE tuning, even if none were present. We used two analysis techniques to control for the influence on neural tuning of behavioral coupling. We used a partial regression analysis to first remove the tuning due to one reference frame so we could investigate whether the residual variance was tuned in the other reference frame. When the effect of TH was removed, only one-fourth of our cells exhibited significant tuning to TE. In our second analysis, we simulated cells whose tuning were entirely determined by TH tuning. We built a simulated neural population with TH tuning measured from the real data, but no TE tuning. When those simulated neurons were analyzed like the real data, we found they exhibited TE tuning. The amount of TE tuning recovered from the simulation was comparable to the amount of TE tuning measured in the real data (Monkey L: 59% for the real data, and 49% in the simulated data; Monkey I: 96% for the real data, and 94% for the simulated data.) Thus, our simulations show that even when no TE tuning is present, TH tuning and behavioral coupling can produce spurious TE tuning. Our results suggest that neural tuning to the target location relative to gaze is inherently quite weak, but may arise in PMd once animals are trained and instructed to fixate.

Disclosures: **B. Alemayehu:** None. **N. Pavlovsky:** None. **J. Chiou:** None. **E. Tyler-Kabara:** None. **N. Hatsopoulos:** None. **S. Chase:** None. **A. Batista:** None.

Nanosymposium

467. Visual-Motor Processing: Prediction and Adaptation

Location: S401

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 467.06

Topic: D.05. Visual Sensory-motor Processing

Support: NIH Grant EY014924

Title: Changes in local field potential-derived receptive fields within the frontal eye field before eye movements

Authors: *X. CHEN[1,2], M. ZIRNSAK[1,2], T. MOORE[1,2];
[1]Dept. of Neurobio., Stanford Univ., Stanford, CA; [2]Howard Hughes Med. Institute, Stanford Univ. of Med., Stanford, CA

Abstract: Receptive fields (RFs) of neurons within the primate visual system have been reported to shift prior to saccadic eye movements. It has been widely assumed that these presaccadic RF

shifts anticipate the actual retinal displacements caused by eye movements in order to stabilize vision. In contrast to this predictive remapping of RFs we recently demonstrated that RFs based on the spiking activity of frontal eye field (FEF) neurons of the macaque monkey converge massively toward the saccadic end point. Here, we investigate the presaccadic RFs derived from simultaneously recorded local field potentials (LFPs) within the FEF. LFPs reflect multiple neuronal processes including extracellular voltage fluctuations due to synaptic inputs and thus carry additional information over that of spiking activity. We quantified LFP RFs in four different frequency bands, alpha (8-12 Hz), beta (16-30 Hz), gamma (30-80 Hz), and high gamma (80-150 Hz). With the exception of gamma, we obtained clear RFs in each of the remaining frequency bands during fixation and prior to saccades. Similar to the RFs derived from spiking activity, LFP RFs were retinocentric during periods of fixation; that is, they remained fixed relative to the fovea across different eye positions. However, shortly before eye movements, LFP RFs in the alpha, beta and high gamma band shifted substantially. Similar to the spiking RFs, the global pattern of the LFP RF shifts consisted of a convergence toward the saccadic end point. Next, we compared the time at which the visual probe stimulus used to map the RFs could be reliably encoded from low frequency band LFPs and corresponding spiking activities. The results of this comparison thus far show that during fixation, the latency of information about probe location was comparable for spiking activity and LFPs, whereas the amount of information was 1.5-fold higher for the LFPs. In contrast, during the presaccadic period, probe-location information was encoded earlier by the spiking activity (-27 ms) than by the LFPs. Furthermore, the amount of information about the probe was 2-fold greater in the spiking activity than in the LFPs. This pattern of results suggests that RF shifts might occur earlier in the FEF than in posterior visual areas, which provide the major source of visual inputs.

Disclosures: **X. Chen:** None. **M. Zirnsak:** None. **T. Moore:** None.

Nanosymposium

467. Visual-Motor Processing: Prediction and Adaptation

Location: S401

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 467.07

Topic: D.05. Visual Sensory-motor Processing

Support: CIHR Grant MOP-130444

Ontario Gradual Scholarship

Title: Spatiotemporal transformations between sensory, memory, and movement responses in the primate frontal eye field

Authors: *A. SAJAD, M. SADEH, X. YAN, H. WANG, J. D. CRAWFORD;
Ctr. for Vision Res., York Univ., Toronto, ON, Canada

Abstract: During a memory-guided gaze shift task neurons in the Frontal Eye Field (FEF), one of the key nodes in sensorimotor transformation, often show activity related to visual presentation, movement generation, and working memory which forms a linking bridge between the visual and movement responses. Previously, we showed that in a classic memory-guided gaze task (in head-unrestrained conditions), where subjects need to make delayed gaze shifts to remembered location of visual stimuli, visual and movement responses in the FEF encode visual target location (T) and final gaze position (G), respectively. This differential code between visual and movement responses suggested that spatial sensorimotor transformation occurs within the FEF and its interconnected network (Sajad et al. 2014). However what is unknown is how this spatial transformation occurs as activity evolves from visual to memory, throughout memory, and from memory to movement. In order to investigate this we analyzed the spatiotemporal evolution of 74 neurons from the FEF of two monkeys through the entire visual-memory-motor extent of their response. Using a spatial model-fitting method described previously (Keith et al. 2009) we constructed spatial models based on sensory- and motor-related parameters and identified the model that provided the best fit to the data. In addition to spatial models based on T (i.e., sensory parameter), and G (i.e., movement parameter), we considered a continuum of models along the T-G axis between (and beyond) T and G (Sajad et al. 2014) which allowed us to consider possibility for intermediary spatial codes. Our analysis showed that overall the population of FEF neurons showed a gradual drift from T towards G; but different neuronal subpopulations contributed differently to this trend. Visual responses of Visual (V, n = 10) and Visuomovement (VM, n = 42) neurons contained a spatial code very closely described by T. The memory activity which was most prominent in VM neurons and a subpopulation of Movement neurons (DM, n = 12) showed a gradual shift from T only partially towards G, and this intermediary spatial code was even present at the time of gaze onset. This contrasts to movement-only neurons with no delay activity (M, n = 10) which contained a spatial code described very closely by G in their movement response. These results show that at least two spatial transformations occur within the FEF (and its interconnected network) in the simple memory-guided gaze task: Transformation within an imperfect goal-memory circuit, followed by a memory-to-motor transformation downstream of the working memory network.

Disclosures: A. Sajad: None. **M. Sadeh:** None. **X. Yan:** None. **H. Wang:** None. **J.D. Crawford:** None.

Nanosymposium

467. Visual-Motor Processing: Prediction and Adaptation

Location: S401

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 467.08

Topic: D.05. Visual Sensory-motor Processing

Support: NWO-EW 612.066.826

NWO Brain and Cognition 433-09-208

ERC advanced 339490

Title: A learning rule explaining how rewards teach attentional signals in frontal cortex

Authors: *P. R. ROELFSEMA[1], S. M. BOHTE[2], J. MARTINEZ-TRUJILLO[3], J. ROMBOUTS[2];
[1]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [2]Centrum Wiskunde & Informatica, Amsterdam, Netherlands; [3]McGill Univ., Montreal, QC, Canada

Abstract: Many theories propose that top-down attentional signals in frontal cortex control processing in sensory cortices by modulating neural activity. But who controls the controller? Here we investigate how a biologically plausible neural reinforcement learning scheme can create higher order representations and top-down attentional signals. The learning scheme trains neural networks using two factors that gate Hebbian plasticity: (1) an attentional feedback signal from the response-selection stage to earlier processing levels and (2) a globally available neuromodulator that encodes the reward prediction error. We demonstrate how the neural network learns to direct attention to one of two colored stimuli that are arranged in a rank-order (Lennert & Martinez-Trujillo, 2011). Like humans and animals, the model made more errors if it had to compare stimuli that were "close" in rank. Like monkeys trained on this task, the network developed units that are tuned to the rank-order of the colors and it generalized the newly learned rule to previously unseen color combinations. Specifically, the model exhibited transitive inference. If it had learnt that A was lower in rank than B and that B was lower in rank than C, the model inferred that A was also lower in rank than C. The model thereby provides new insight into how individuals learn order relationships and also how they learn to control attention as a function of reward contingency. Reference Lennert, T., & Martinez-Trujillo, J. (2011). Strength of response suppression to distracter stimuli determines attentional-filtering performance in primate prefrontal neurons. Neuron, 70(1), 141-152.

Disclosures: P.R. Roelfsema: None. **S.M. Bohte:** None. **J. Martinez-Trujillo:** None. **J. Rombouts:** None.

Nanosymposium

468. Hormones, Neurotransmitters and Social Behavior

Location: S405

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 468.01

Topic: F.03. Motivation and Emotion

Support: AR110109

MH086708

GM097632

MH064489

Voelcker Research Foundation

Title: Uptake 2 transporter blockade ameliorates deficits in sociability in two mouse models

Authors: *G. G. GOULD[1], C. M. SMOLIK[1], C. MOTEN[1], M. A. JAVORS[2], W. KOEK[1], J. G. HENSLER[3], L. C. DAWS[1];
[1]Physiol., [2]Psychiatry, [3]Pharmacol., UT Hlth. Sci. Ctr, SA, San Antonio, TX

Abstract: Impaired social behavior is a persistent, treatment-resistant core symptom of autism. While selective 5-HT reuptake inhibitors (SSRIs) such as Prozac (fluoxetine) enhance sociability in limited subpopulations, their efficacy is diminished when 5-HT transporter (SERT) function is compromised. Aside from SERT, ancillary central transporters of 5-HT include organic cation transporters (OCTs) and plasma membrane monoamine transporters (PMAT), collectively known as "uptake 2". Uptake 2 typically has lower affinity for 5-HT, but removes it from extracellular fluid with greater capacity than SERT. The study hypothesis was that uptake 2 blockade would enhance social behavior via greater 5-HT neurotransmission. Effects of uptake 2 blockade on the social behavior were compared in two socially-deficient mouse lines: BTBRT+Itpr3tf/J and SERT knock-out. Decynium-22 (D-22) was administered via acute injection or sub-chronic osmotic minipump delivery. Mouse behavior was assessed in three-chamber sociability tests. *In vitro* [3H] 5-HT uptake or [3H] citalopram competition with D-22 compared its blockade capacity and affinity to fluoxetine. D-22 pharmacokinetics in serum and brain were assessed by HPLC. Acute D-22 (0.1 - 0.01 mg/kg) injections enhanced social interaction preference in both BTBR and SERT -/-, by sniffing and chamber dwelling. Social novelty preference was undiminished by D-22 in BTBR. Furthermore, 2 week D-22 administration improved interaction preference in both lines, with no apparent adverse effects. D-22 blocks 5-HT uptake in mouse brain *in vitro* with Km = 90 ± 10 nM, and has little affinity for SERT (Ki > 3000 nM). D-22 also appears to cross the blood-brain barrier. Overall, uptake 2 transporter blockade may be an effective strategy for enhancing otherwise impaired social behavior in mice.

Disclosures: **G.G. Gould:** None. **C.M. Smolik:** None. **C. Moten:** None. **M.A. Javors:** None. **W. Koek:** None. **J.G. Hensler:** None. **L.C. Daws:** None.

Nanosymposium

468. Hormones, Neurotransmitters and Social Behavior

Location: S405

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 468.02

Topic: F.03. Motivation and Emotion

Support: JSPS KAKENHI Grant Number 25293254

Title: Influence of early social experience on sociability and brain serotonin function in common marmosets

Authors: ***C. YOKOYAMA**, A. KAWASAKI, C. TAKEDA, H. ONOE;
RIKEN Ctr. For Life Sci. Technologies (CLST), Kobe, Japan

Abstract: Postnatal environmental factors influence the physiological and psychological state through life. Here we studied effects of social risk during early development on social behavior and brain serotonin function in common marmosets, a non-human primate species known to have human-like social activity. Early social risk condition, which was induced by a nursery rearing (NR) procedure, was compared to normal parental-reared (PR) condition. NR animals were further conducted to two groups in terms of later social environment after six months of the age, NRLA who continuously lived alone and NRLP who lived in pairs. These animals were compared to PR animals who continuously lived in pairs (PRLP). Social behavior was tested by behavioral response to the age-matched unfamiliar conspecific. Brain serotonergic function was measured by positron emission tomography (PET) with [11C]DASB, a specific PET tracer for serotonin transporters (SERT). In childhood (three and six months of the age), NR animals displayed low sociability such as social withdrawal in vocal and behavioral responses to an unfamiliar conspecific, and significant reduction in SERT binding in the midline brain structures including the posterior cingulate and medial prefrontal cortices, and also in the hypothalamus, thalamus, the hippocampus, and midbrain as compared to PR. In adulthood (two-three years of the age), NRLA showed social withdrawal in behavioral response to the unfamiliar conspecific, while NRLP showed no less sociability than PRLP. NRLA showed tendency of lower SERT binding in the posterior cingulate and medial prefrontal cortices and midbrain, where SERT binding activity was correlated with behavioral sociability. NRLP showed tendency of higher SERT binding in the piriform and inferior temporal cortices. These results suggest that the early

social deprivation causes long-lasting but restorable social withdrawal, which may be linked to serotonergic dysfunction in the specific brain areas.

Disclosures: **C. Yokoyama:** None. **A. Kawasaki:** None. **C. Takeda:** None. **H. Onoe:** None.

Nanosymposium

468. Hormones, Neurotransmitters and Social Behavior

Location: S405

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 468.03

Topic: E.03. Behavioral Neuroendocrinology

Support: FAPESP 2013/10069-8 to DFF

FAPESP 2010/18066-0 to DFF

NIMHR01-058616 to ZXW

Title: Changes in social context induce extinction of amphetamine-seeking behavior in female prairie voles

Authors: *D. F. FUKUSHIRO[1,2], R. FRUSSA-FILHO[2], M. L. ANDERSEN[2], Y. LIU[1], Z. X. WANG[1];
[1]Florida State Univ., Tallahassee, FL; [2]Federal Univ. of Sao Paulo, Sao Paulo, Brazil

Abstract: There is ample evidence of the protective effects of prosocial interactions on vulnerability to drug use and abuse, but little is known about their role on already established addiction-like behaviors. Using the female prairie vole (Microtus ochrogaster), a socially monogamous rodent species that forms pair bonds after mating, we investigated the effects of social interactions during adulthood on extinction of acquired amphetamine (Amph) conditioned place preference (CPP), a model of drug-seeking behavior triggered by environmental cues surrounding drug use. Experiment 1 was designed to test the effects of social stimuli on extinction of Amph-induced CPP. Adult female voles were subjected to the CPP procedure with 0.5 mg/kg Amph or saline (Sal). A pre-test established the initial cage preferences and then 40-min conditioning sessions were performed twice daily (6 h apart) for 4 days, administering Amph in the non-preferred cage. After showing Amph-induced CPP, Sal or Amph conditioned females were housed continuously with their familiar female cagemates (Sal-FF and Amph-FF) which had received the same drug treatment during the CPP conditioning, or were housed with a novel drug-naïve female (Amph-NF) or vasectomized male (Amph-NM). Two days later, 4 extinction sessions were performed at 48-intervals using the similar CPP paradigm. Our data

indicate that females that cohabited with a novel conspecific, but not the familiar cagemate, showed extinction of Amph-induced CPP and this effect was independent of the sex of the conspecific. Experiment 2 was designed to test the specific role of social bonding for the induction of extinction of Amph-induced CPP. Adult females were treated with Sal or 0.5 mg/kg Amph for 4 days in their home cages. Twenty-four hours later, subjects were paired with a vasectomized male (defined as the partner), with which they cohabitated for 8 days. Preference for the male partner versus a male stranger was examined by 4 3-h partner preference tests (PP), performed every other day, with the first one being held 48 h after the female-male pairing. Our data demonstrated that Amph-treated females showed sustained impairment in PP even after long-term mating/cohabitation with a male partner, suggesting that the induced extinction of Amph CPP was not due to pair bond formation. Together, our data indicate that changes in the social environment may have profound beneficial effects on facilitating the extinction of Amph-seeking behaviors.

Disclosures: D.F. Fukushiro: None. **R. Frussa-Filho:** None. **M.L. Andersen:** None. **Y. Liu:** None. **Z.X. Wang:** None.

Nanosymposium

468. Hormones, Neurotransmitters and Social Behavior

Location: S405

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 468.04

Topic: E.03. Behavioral Neuroendocrinology

Support: NNSF of China Grant #: 31471113

Start fund of Harbin Medical University

Title: Supraoptic oxytocin-secreting system involves a switch of sexually-associated social behavior elicited by intranasal oxytocin

Authors: X.-Y. LIU, D. CUI, D. HOU, J.-L. CHANG, Y. ZHANG, H. ZHU, *Y.-F. WANG; Harbin Med. Univ., Heilongjiang, China

Abstract: Oxytocin is a hypothalamic neuropeptide and can regulate many social behaviors including sexual interest toward conspecifics. Intra-nasal administration of oxytocin has been used extensively in studying the pro-social behavioral effects of oxytocin; however, it remains a question whether the effect of exogenous oxytocin is correlated with the activity of intrinsic oxytocin-producing cells in the brain. The supraoptic nucleus is a major source of brain oxytocin

that directly modulates activities of brain areas that control sexually-associated social behaviors. Thus, in the present study, we tested the hypothesis that intranasally-applied oxytocin can alter sexual interest of adult male rats toward sexually-different conspecifics through activation of supraoptic oxytocin neurons. We put individual adult male rats in the center of an eight-arm radial maze device, and observed the frequency and duration of their approaching adult estrous female, non-estrous (diestrus and metestrus) female or male rats. The result showed that these males exhibited significantly more times and longer duration of approaching estrous females. Intranasal application of oxytocin significantly changed the pattern of this sexually-associated behavior. That is, the males became less interested in the estrous females but the non-estrous females and the stranger males. This oxytocin-evoked switching of sexual interest was associated with normal functions of the supraoptic nucleus. Mechanically disturbing the activity of this nucleus by intra-supraoptic injection of vehicle or L-aminoadipic acid (a gliotoxin) solution reduced the frequency and duration of the male rats that approached to the estrous females. Administration of L-aminoadipic acid but not the vehicle blocked intranasal oxytocin-evoked switching of this social behavior pattern. Mechanistically, intranasally-applied oxytocin can activate oxytocin neurons by activating oxytocin receptors in the olfactory epithelium and/or olfactory bulbs since low dose of nasal oxytocin receptor antagonist or a locally-applied anesthetic blocked oxytocin-evoked activation of oxytocin neurons in the supraoptic nucleus. These findings reveal for the first time that intranasal oxytocin can change sexually-associated social behaviors and that the hypothalamic oxytocin-secreting system can mediate this effect, at least partially. This work highlights that the effect of intranasally-applied oxytocin is likely mediated by a nose-olfactory bulb-supraoptic nucleus-social brain pathway.

Disclosures: **X. Liu:** None. **D. Cui:** None. **D. Hou:** None. **J. Chang:** None. **Y. Zhang:** None. **H. Zhu:** None. **Y. Wang:** None.

Nanosymposium

468. Hormones, Neurotransmitters and Social Behavior

Location: S405

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 468.05

Topic: F.03. Motivation and Emotion

Support: Case Western Reserve University Institutional support OPR695900

Title: Central oxytocin regulates olfactory communication, scent marking, that involves affiliative signals between male mice

Authors: *H. ARAKAWA;
Dept. of Res. Admin., Case Western Reserve Univ., Cleveland, OH

Abstract: Growing evidence supports that central oxytocin (OT), neuropeptide, play a key role in regulating social communication. Present study aimed to demonstrate how social signaling including olfactory cues and scent marking, a prominent mode of olfactory communication in rodents, is regulated by central OT. In social approach test, male C57BL/6 mice were allowed to investigate wire-mesh bins in one of which OT or vehicle-infused stimulus mice (nasal administration, 40 min prior test) were placed. Exposure of those OT-infused mice via a wire-mesh remarkably increased approaches and sniffing and also decreased scent marking deposited by intact male mice. These results suggest that OT may change (olfactory) social cues released from OT-infused mice which, in turn, suppress territorial (aggressive) behavior and induce approach/social contacts in social cue receivers. As such, in scent marking paradigm, central infusion of OT reduced territorial marking toward male conspecifics, and thus, in turn, reduced the scent marking of untreated males which were confronted with OT infused mice. Buspirone, a partial agonist at 5-HT1A receptors, induced release of central OT, also decreased scent marking in male mice. Nasal infusion of OT antagonist into these Buspirone-infused mice prevented the decreased scent marks, while those into saline-infused mice had no change in scent marking. These data indicated a sensitivity of scent marking in OT availability and suggest that 5-HT1A receptors would be involved in OT-regulation of olfactory communication between male mice.

Disclosures: H. Arakawa: None.

Nanosymposium

468. Hormones, Neurotransmitters and Social Behavior

Location: S405

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 468.06

Topic: F.01. Human Cognition and Behavior

Title: Oxytocin and Religious Brain

Authors: *J. R. KORENBERG[1], L. DAI[2], J. S. ANDERSON[3], J. B. KING[4], M. A. FERGUSON[4], J. A. NIELSON[5], D. GIANGRASSO[4], C. S. CARTER[6], H. P. NAZARLOO[6];
[1]Brain Institute, Pediatrics, Univ. of Utah, Salt Lake Cty, UT; [2]Pediatrics, [3]Radiology, [4]Neurosci. Grad. Student, Univ. of Utah, Salt Lake City, UT; [5]Psychiatry and Psychology, Harvard Univ. & Massachusetts Gen. Hosp., Salt Lake City, UT; [6]The Kinsey Inst., Indiana University, Bloomington, Bloomington, IN

Abstract: The molecular and neural mechanisms regulating human social behaviors are fundamentally important but largely unknown. Religious experience is one of the most powerful transformative factors in the lives of individuals and cultures, and provocative evidence showed that religion influences social behaviors in different and even controversy ways. It has been suggested that religious priming serves to enhance pro-sociality for in-group members, while increasing aggression towards out-group. It is interesting that social peptide hormone oxytocin, has been implicated to play a role in cooperation and competition within and between groups. In addition, recent study showed that religion priming and an oxytocin receptor gene polymorphism interact to affect self-control in a social context. We therefor hypothesized that religious priming will result in an increase in pro-sociality as measured by observer ratings of social stimuli, plasma serum levels of oxytocin, and functional connectivity in social brain regions. In this study, we report the plasma oxytocin levels before and after a thirty-minute period of religious experience in a cohort of eleven returned Mormon missionaries. Our preliminary results showed that the plasma oxytocin and vasopressin levels are highly associated. This is the first time to study the *in vivo* relationship of peptide hormones in regulating religious belief and will enhance our understanding of neurobiology of the effects of religious experience on social behaviors.

Disclosures: J.R. Korenberg: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Site PI for Roche Pharma drug study. **L. Dai:** None. **J.S. Anderson:** None. **J.B. King:** None. **M.A. Ferguson:** None. **J.A. Nielson:** None. **D. Giangrasso:** None. **C.S. Carter:** None. **H.P. Nazarloo:** None.

Nanosymposium

468. Hormones, Neurotransmitters and Social Behavior

Location: S405

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 468.07

Topic: E.03. Behavioral Neuroendocrinology

Support: NSERC RGPIN 312458 (DAM)

CIHR JNM-116637 (DAM)

NSERC CGS-NSERC (ASG)

Title: Non-neural androgen receptors affect sexual differentiation of brain and behavior

Authors: *A. B. SWIFT-GALLANT[1,2], L. A. COOME[2,1], F. RAMZAN[2,1], D. MONKS[1,2,3]; [1]Psychology, Univ. of Toronto Mississauga, Mississauga, ON, Canada; [2]Psychology, [3]Cells and systems biology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Testosterone is the major endocrine mechanism promoting sexual differentiation of the mammalian nervous system and behavior, but we have an incomplete knowledge of which cells and tissues mediate these androgenic effects. To distinguish between neural and non-neural actions of androgens in sexual differentiation of brain and behavior, we generated a loxP-based transgenic mouse, which overexpresses androgen receptors (AR) only when activated by Cre. We used this transgene to overexpress AR globally in all tissues using a CMV-Cre driver (CMV-AR), and we used a Nestin-Cre driver to overexpress AR only in neural tissue (Nes-AR). We then examined whether neural or global AR overexpression can affect socio-sexual behaviors using a resident-intruder paradigm. We found that both neural and global AR overexpression resulted in decreased aggressive behaviors and increased social behaviors, supporting a role for a neural site of action for these effects. Global, but not neural, AR overexpression in males led to an increase in same-sex anogenital investigation. Copulatory behaviors were differentially affected by neural and global overexpression of AR. Neural-only increases in AR led to an overall reduction in thrusting, whereas global overexpression of AR resulted in increased thrusting following sexual experience. Together, these results suggest novel roles for non-neural AR in sexual differentiation of mice, and indicate that excess AR can lead to a paradoxical loss of AR function.

Disclosures: A.B. Swift-Gallant: None. **L.A. Coome:** None. **F. Ramzan:** None. **D. Monks:** None.

Nanosymposium

468. Hormones, Neurotransmitters and Social Behavior

Location: S405

Time: Tuesday, October 20, 2015, 8:00 AM - 10:00 AM

Presentation Number: 468.08

Topic: E.03. Behavioral Neuroendocrinology

Support: NIH Grant R24OD011180

NICHD DIR

Title: Cortisol in mother's milk in the neonatal period predicts later cognitive performance and social behavior in infant rhesus monkeys (*Macaca mulatta*)

Authors: *A. M. DETTMER[1], A. M. MURPHY[1], E. SLONECKER[1], D. GUITARRA[1], K. L. ROSENBERG[2], S. J. SUOMI[1], J. S. MEYER[2];
[1]Lab. of Comparative Ethology, NICHD/NIH, Poolesville, MD; [2]Psychological and Brain Sci., Univ. of Massachusetts Amherst, Amherst, MA

Abstract: Mother's milk is known to contain constituents that are crucial to infant development, yet the role of hormones in early mother's milk on later infant cognitive and social behavior remains unexplored. Recent research has focused on "lactational programming," whereby hormones in milk, namely cortisol, act to program infant growth and temperament. We studied N=26 rhesus monkey (*Macaca mulatta*) mother-infant dyads born and reared in large social groups from birth through weaning at 8 months. We sought to determine the role of cortisol in mother's milk in the neonatal period on cognitive performance on an inhibition task, and on social behavior with peers later in development. We collected milk twice in the first 30 postnatal days and analyzed the samples for cortisol content. Beginning at 6 months of age, a subset of infants (n=8) was given a cognitive task five days per week to assess impulsivity/response inhibition. From 4-8 months of age, a larger subset of infants (n=24) was observed twice weekly for 10mins each to record the occurrence of social behaviors (i.e., play, grooming, mounting), both initiated and received. Regression analysis revealed that average cortisol in mother's milk in the first 30 days of life negatively predicted "balk" rates (i.e., % trials the infant refused to participate; R^2=0.43, p=0.045) and "bonk" rates (i.e., % trials the infant responded with an impulsive response; R^2=0.67, p=0.026) on the cognitive task. Moreover, average milk cortisol also negatively predicted the frequency of initiated social behaviors, but for males only (R^2=0.37, p=0.043). These findings support the "lactational programming" hypothesis and supplement previous findings in humans and monkey infants that cortisol in mother's milk predicts negative affect/cautious temperament (Grey et al., 2013; Hinde et al., 2014). Collectively, our results point to a role for hormones in mother's milk, beginning at birth, in subsequent infant neurological and behavioral development. Future studies will be able to draw upon these results to determine the mechanisms for this type of programming.

Disclosures: A.M. Dettmer: None. **A.M. Murphy:** None. **E. Slonecker:** None. **D. Guitarra:** None. **K.L. Rosenberg:** None. **S.J. Suomi:** None. **J.S. Meyer:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.01

Topic: F.01. Human Cognition and Behavior

Support: NSFC Grant 31471069

NSFC Grant 91432109

Title: Asymmetric spatial representation within attention filed

Authors: ***Y. ZHOU**[1], L. LIANG[2], M. ZHANG[1];
[1]Beijng Normal Univ., Beijing, China; [2]The First Clin. Col. of Harbin Med. Univ., Harbin, China

Abstract: Spatial attention improves our ability for selecting salient or behaviorally relevant stimuli as well as filtering out the distractor for visual processing, which is evidenced by shortening the reaction time of sensory-motor transformation and decreasing the threshold of visual discrimination within attention field. The covert focusing of spatial attention has traditionally been metaphorically thought as a 'spotlight' or 'zoom lens' on the attended area in visual field, where the contrast gain or response gain of visual stimuli was enhanced symmetrically as a Gaussian shape. However, the clear structure of spatial representation within attention filed has not been tested. Here we reported that, in both top-down and bottom-up spatial attention involved visual discrimination tasks, subjects' manual reaction time and correct ratio were asymmetrically correlated with the location of visual stimuli relative to the center of covert attention. In left-right conditions, subjects responded faster and more accurately in the stimulus-response compatible trials (the visual stimuli appeared in the left side within attention field (stimuli left) and subjects pressed left key (response left); stimuli right and response right) than in incompatible trials (stimuli left but response right; stimuli right but response left). So did in the up-down conditions. Through control experiment, we showed that the behavioral asymmetry highly depended on the participation of covert spatial attention rather than the relative positions (object-centered) of visual stimuli. Those results indicated that the spatial representation within attention field was asymmetrically distributed, which was similar to a contractible visual field. Combining with previous electrophysiology findings of the compression of visual receptive field toward the attended location, we propose that the whole visual spatial representation in higher visual cortex might shift and compress toward the current focus of spatial attention.

Disclosures: **Y. Zhou:** None. **L. Liang:** None. **M. Zhang:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.02

Topic: F.01. Human Cognition and Behavior

Support: Australian Research Council (ARC) Future Fellowship 3251260

Title: Ocular exposure to short wavelength light modulates behavioural and electrophysiological markers of spatial attention bias

Authors: *D. NEWMAN[1], A. C. P. MARTINS[3], R. ABE[4,2], M. T. R. ZORATTI[4,2], M. H. O'NEILL[1], S. W. LOCKLEY[5,2], S. P. KELLY[6], G. M. LOUGHNANE[7], R. G. O'CONNELL[8], M. A. BELLGROVE[1];
[1]Building 17, Clayton Campus, Wellington Road, [2]Sch. of Psychological Sci., Monash Univ., Melbourne, Australia; [3]Fac. of Med., Federal Univ. of Parana, Curitiba, Brazil; [4]Fac. of Medicine,, Federal Univ. of Mato Grosso, Cuiaba, Brazil; [5]Div. of Sleep Med., Harvard Med. Sch., Boston, MA; [6]Sch. of Electrical, Electronic and Comms Engin., Univ. Col. Dublin, Dublin, Ireland; [7]Sch. of Engin. and Trinity Ctr. for Bioengineering, [8]Trinity Col. Inst. of Neurosci. and Sch. of Psychology, Trinity Col. Dublin, Dublin, Ireland

Abstract: Introduction: Alert healthy subjects typically exhibit a subtle bias of spatial attention favouring left space. This bias is attenuated, or shifted rightwards, under conditions of decreased alertness. This is consistent with theoretical models proposing that a right-hemisphere-lateralised ventral 'alertness' network regulates inter-hemispheric rivalry in the bilateral dorsal orienting network. Ocular exposure to short wavelength blue enriched white light (λmax ~480nm) can result in increased alertness and overt behavioural improvements during cognitive tasks. Here we tested the hypothesis that prior exposure to higher, relative to lower, intensities of blue enriched white light would promote the direction of attention to left space, as measured by behavioral and electrophysiological indices. **Methods:** Healthy participants (N=24) were exposed to three blue enriched light intensities (low/medium/high- 50/350/1400 lux, respectively) in a counterbalanced repeated-measures design over 54 separate sessions. Sessions began 13.5 hours after waking and comprised 10 min dark adaptation, then 1 hour of light exposure followed by a ~36 min spatial attention task. Behavioral and EEG indices of spatial attention were derived. Arousal was indexed via pre-target pupil diameter during the spatial attention task, independent of the prior light exposure manipulation. **Results**: Participants were faster to detect targets in the left, as compared to right hemi-field, an effect that was maximal after high intensity light exposure. Pre-target pupil diameter increased as a function of light intensity, indicative of increased arousal following high intensity light exposure. EEG markers of spatial orienting, such as the N2pc, varied as a function of light intensity, such that greater amplitudes were observed after high intensity light exposure. **Conclusion:** These data show that prior exposure to blue enriched white light influences behavioral and EEG measures of spatial attentional orienting, potentially via its alerting effects. These data provide the tantalizing prospect that blue enriched white light might have rehabilitative value in disorders of spatial attention such as unilateral spatial neglect and ADHD.

Disclosures: **D. Newman:** None. **A.C.P. Martins:** None. **R. Abe:** None. **M.T.R. Zoratti:** None. **M.H. O'Neill:** None. **S.W. Lockley:** None. **S.P. Kelly:** None. **G.M. Loughnane:** None. **R.G. O'Connell:** None. **M.A. Bellgrove:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.03

Topic: F.01. Human Cognition and Behavior

Title: Attention modulates reliability of neural responses to natural narrative stimuli

Authors: *J. KI;
City Col. of New York, Bronx, NY

Abstract: Attentional engagement is a major determinant in how effectively we gather information through our senses. Its variation within individuals indicates motivational states and personal interests. Unfortunately, the controlled measurement of attentional engagement in the laboratory typically bears little resemblance to the conditions under which we absorb information in the real world. Here, we use electro-encephalography to measure fast neural responses to natural narrative stimuli while we manipulate attentional state: participants were instructed to either attend normally, or to silently count backwards during presentation of auditory or audiovisual stimuli. We hypothesized that engagement of attention will promote reliable neural responses. As predicted, we observed that the neural responses correlated across subjects most strongly during the attentive state, in particular for audio-visual stimuli. Stories with a cohesive narrative elicited correlated responses along several dimensions, while stimuli with little or no narrative were dominated by a single component, regardless of modality. The modulation of reliability was strong enough to perfectly differentiate between attentive and inattentive states for the audiovisual stimulus with suspenseful narrative. From these results we conclude that the reliability of fast brain responses is closely tied to levels of attentional engagement, which is strongest for audio-visual narrative stimuli.

Disclosures: **J. Ki:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.04

Topic: F.01. Human Cognition and Behavior

Support: NSF BCS-1230377-0

Title: Expectancies about target-similar distractors impact target selection

Authors: J. LEE[1], C. LEONARD[1], S. J. LUCK[1,2], *J. J. GENG[2,1];
[1]Ctr. for Mind and Brain, [2]Psychology, Univ. of California Davis, Davis, CA

Abstract: Successful achievement of any task requires the ability to select goal-relevant information and suppress distractors. Previous research has demonstrated that attentional enhancement operates by increasing the gain of sensory neurons encoding target-relevant features while decreasing that of other features. However, it remains unclear how attentional selection and suppression operate simultaneously when they come into conflict (i.e. when distractors are similar to the target). We investigated this issue with event-related potentials, focusing on the N2pc and Pd components, which are indices of attentional selection and suppression, respectively. A visual search task was used in which the target was defined by color and shape. The frequency of a target-colored distractor was manipulated over blocks to have a 75% probability of occurring in high-frequency blocks and a 25% probability in low-frequency blocks. We hypothesized that the need to limit distraction by the target-colored distractors in the high-frequency block would also result in reduced attentional enhancement for the target. The results were consistent with our hypothesis. Reaction times were longer to targets in the high-frequency block, compared to the low-frequency block, when the target-colored distractor was absent, but shorter when a target-colored distractor was present. This suggests that feature-based gain enhancement was weaker when target-colored distractors were more likely to occur. Consistent with the behavioral data (n=16), the mean amplitude of the N2pc in response to targets (without a target-colored distractor) was smaller, and the Pd larger, in high-frequency blocks compared to low-frequency blocks. Thus, even though the manipulation was entirely in distractor probability, attentional selection of the target was weaker, even on trials when no target-colored distractors were present. These results indicate that expectancies about target-similar distractors not only impact the ability to suppress them but also affect the ability to select the target. Attentional selection of the target was modulated based on the frequency of a target-colored distractor, suggesting that feature-based attentional gain was adjusted to maximize the balance between the need to suppress distractors and to select targets.

Disclosures: J. Lee: None. **C. Leonard:** None. **S.J. Luck:** None. **J.J. Geng:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.05

Topic: F.01. Human Cognition and Behavior

Title: Time course of activation of the posterior intraparietal sulcus during spatial attention: a single pulse TMS experiment

Authors: *V. NEYENS[1,2], N. CASPARI[1,2], M. SCHROOTEN[1,2,3], R. VANDENBERGHE[1,2,3]; [1]Kuleuven, Leuven, Belgium; [2]Lab. for Cognitive Neurol., Leuven, Belgium; [3]UZ Leuven, Leuven, Belgium

Abstract: According to previous studies, posterior intraparietal sulcus (pIPS) enhances processing of visual stimuli in the contralateral hemifield in attentionally demanding conditions (Vandenberghe et al. 2005, Gillebert et al. 2011). By means of single pulse transcranial magnetic stimulation (TMS) of pIPS we aimed to examine whether its major role is in the delay or the test phase of a classic attentional paradigm. We predicted that pIPS, as a visually responsive area, is crucial in the test phase but not in the delay phase. We applied single pulse TMS on pIPS in 28 healthy subjects during a spatial cueing task. All subjects completed 2 sessions consisting of 6 runs of 120 trials. A trial started with a central spatial arrow cue pointing either leftwards or rightwards, followed by a delay of 200 ms during which only a fixation point was shown. After the delay a peripheral grating was added in the cued hemifield. In 50% of the trials the target grating appeared on its own ('single trials'), in the remaining 50% a task-irrelevant grating was added in the uncued hemifield ('double trials'). Subjects had to discriminate by button-press the orientation of the target grating: clockwise or anticlockwise with respect to a reference orientation of 45°. In 40% of the trials we applied a TMS pulse in the delay phase (150 ms before target onset), in 40% a TMS pulse was delivered in the test phase (150 ms after target onset). In the remaining 20% there was no TMS. The TMS site, left versus right pIPS, was counterbalanced between runs. A 2 x 2 x 2 repeated measures ANOVA with target location (ipsi- versus contralateral relative to the TMS site), TMS timing (delay versus test phase) and trial type (single versus double trial) as factors and response accuracy as outcome measure revealed a three-way interaction [$p = 0.0091$, $F(1,27) = 7.948$] and a main effect of trial type [$p = 0.0302$, $F(1,27) = 5.26$]. When TMS was applied in the test phase, there was a significant two-way interaction between trial type and target location [$p = 0.0493$, $F(1,27) = 4.107$]. Accuracies were significantly higher for single than for double trials for ipsilateral targets [$p = 0.0127$, $F(1,27) = 7.168$], but not for contralateral targets. When we delivered TMS in the delay phase, no

significant interaction effects were found. After subtracting accuracies from corresponding trials without TMS as a correction for baseline performance, results were essentially confirmed. These results suggest a critical role for pIPS during selective attention in the test phase dependent on trial type and target location. This is compatible with the behavior of a previously tested stroke patient with a lesion confined to left pIPS (Gillebert et al. 2011).

Disclosures: **V. Neyens:** None. **N. Caspari:** None. **M. Schrooten:** None. **R. Vandenberghe:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.06

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R01-DA013165

Title: Neural basis of learned adjustments in attentional flexibility according to environmental statistical structure

Authors: ***A. W. SALI**[1], S. M. COURTNEY[1,2,3];
[1]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD; [2]Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]F.M. Kirby Res. Ctr. for Functional Brain Imaging, Kennedy Krieger Inst., Baltimore, MD

Abstract: Individuals regularly experience fluctuations in their readiness to update attentional selections. These moment-by-moment changes in attentional flexibility vary based on the statistical structure of the environment (Sali, Anderson, & Yantis, in press). However, the neural systems involved in learned adjustments of preparatory control remain unknown. In the current study, we used functional magnetic resonance imaging to identify the neural systems that respond preferentially for contextually-defined unlikely orienting cue presentations relative to likely presentations. During each trial, participants monitored a rapid serial visual presentation (RSVP) stream of alphanumeric characters for the onset of an attentional orienting cue that signaled to either make a saccadic eye movement to a different RSVP stream or to continuing fixating the same stream. Following each cue presentation, participants made a parity judgment for target stimuli appearing in the cued stream, such that trial-by-trial RT served as an indicator of attentional flexibility. Critically, for half of the participants, shift cues tended to appear following a short temporal interval, while hold cues tended to appear following a long interval.

The remainder of participants experienced the opposite cue probability mapping. The behavioral cost in RT for shift attention trials relative to hold attention trials at each temporal interval varied as a function of the environmental statistical structure, therefore providing evidence of learned preparatory modulations of attentional control. Analysis of the neuroimaging data revealed that cued overt shifts of attention were associated with a greater blood oxygenation level dependent (BOLD) response within bilateral intraparietal sulcus and the right medial superior parietal lobule. However, activity in these regions did not vary according to cue probabilities. Instead, we observed greater activity within the right anterior insula/inferior frontal gyrus, right middle frontal gyrus, and the right supplementary motor area for statistically unlikely cue presentations relative to likely cue presentations. Together, the current results suggest that these ventral attentional control regions may play a role in the detection of statistically improbable orienting cues, even when they appear at a perfectly predictable spatial location.

Disclosures: **A.W. Sali:** None. **S.M. Courtney:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.07

Topic: F.01. Human Cognition and Behavior

Support: ERC grant NeuroConsc

Title: Constraints on temporal attention: Time-resolved decoding of brain activity during the Attentional Blink

Authors: *S. MARTI[1], S. DEHAENE[2];
[1]INSERM / CEA Neurospin, GIF / YVETTE, France; [2]Collège de France, Paris, France

Abstract: The detection of a target item is degraded when subjects are distracted by another task (the Attentional Blink, AB). Recent evidence suggests that temporal attention is diffused and delayed during the AB. In the present study, we tested the hypothesis that during the AB, the weakening of attentional processes leads to intrusion of distractors into consciousness. We asked participants to report two target items embedded in a series of distractors while brain activity was recorded with MEG. Behavioral results revealed a typical AB: the identification of the second target stimulus was degraded when the delay between the two targets was less than half a second. A detailed examination of subjects' reports revealed that, in error trials, the target was often substituted by distractors in the temporal neighborhood. Furthermore, using time-resolved

multivariate pattern analyses, we were able to isolate the brain responses induced by each item in the RSVP. Preliminary results revealed that the sequence of brain patterns induced by each stimulus was similar to the one observed when the same stimulus was presented in isolation. However, while early brain responses (<250 ms) were unaffected during the RSVP, late brain responses (250-400 ms) had shorter durations. Importantly, late brain responses linked to stimuli immediately preceding or following the second target item were strongly attenuated while those induced by the target item were sustained and amplified. These results show that (i) during RSVP, relevant and irrelevant stimuli are processed to the same level, but (ii) the temporal selection of a target stimulus inhibits the processing of nearby distractors and sustain target-related processes. Future analyses will evaluate how these processes are affected by tasks overlap.

Disclosures: S. Marti: None. **S. Dehaene:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.08

Topic: F.01. Human Cognition and Behavior

Support: VIDI grant for the Netherlands Organisation for Scientific Research

Title: A role for the ventral striatum in selective awareness: An intracranial EEG study of the attentional blink

Authors: *H. A. SLAGTER[1], L. C. RETEIG[2], A. MAZAHERI[4], D. DENYS[3];
[2]Dept. of Psychology, [3]Dept. of Psychiatry, [1]Univ. of Amsterdam, Amsterdam, Netherlands;
[4]Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Conscious perception is characterized by a global propagation and integration of brain signals, as reflected by sustained and recurrent interactions between frontal and posterior cortical brain areas. Yet, while cortical regions clearly play a role in conscious perception, they are modulated by “low-level” subcortical structures such as the basal ganglia and thalamus. Previous research has established that dopamine release in the striatum, the input structure of the basal ganglia, releases the tonic inhibition of the thalamus by the output structures of the basal ganglia, resulting in activation of cortex. This raises the intriguing possibility that the striatum through its ability to modulate thalamocortical activity plays a crucial role in controlling which information is selected for global broadcasting and becomes a content we are aware of. To shed light on the

role of the striatum in selective awareness, this study used the unique opportunity to directly record electrophysiological activity from the nucleus accumbens and the anterior limb of the internal capsule in 7 patients having electrode implants for deep-brain-stimulation therapy, while they performed an attentional blink (AB) task. In this task, subjects have to detect two targets (T1 and T2) in a rapid stream of distractors. Notably, subjects often fail to consciously perceive T2 if it occurs within 100-500 ms after T1: the AB effect. Patients displayed a typical AB and often failed to perceive T2 when it followed T1 after 200ms. Analyses of the intracranial EEG data revealed, firstly, that the conscious perception of T2 was associated with an increase in low frequency (theta; 3-5 Hz) power around 300ms after T2 onset. Given that the ventral striatum receives longer-latency input from the hippocampus by means of theta oscillations, we speculate that this increase in theta activity in the ventral striatum to perceived targets likely represents context-dependent gating of prefrontal cortical regions, determining which information enters a state of sustained representation. Second, only in trials in which T2 was not perceived, T1 elicited a short-latency (100ms) increase in alpha power. Recent evidence from animal studies suggests that the striatum may also prioritize processing of salient stimuli, including arousing and behaviorally relevant events, by triggering frontal systems to orient attention within 100ms post-stimulus. The observed short-latency signal to T1 when T2 was not perceived may hence provide support for the idea that the AB is caused by T1-driven attentional capture. Together, these novel findings suggest an important role for the ventral striatum in selective awareness.

Disclosures: **H.A. Slagter:** None. **L.C. Reteig:** None. **A. Mazaheri:** None. **D. Denys:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.09

Topic: F.01. Human Cognition and Behavior

Support: NWO-MaGW VICI Grant 453-09-002

Title: Alpha and gamma oscillations support parallel mechanisms for processing stimulus value associations

Authors: ***T. R. MARSHALL**[1], S. DEN BOER[2], R. COOLS[1], O. JENSEN[1], S. FALLON[3], J. M. ZUMER[4];
[1]Donders Inst., Nijmegen, Netherlands; [2]Philips Res., Eindhoven, Netherlands; [3]Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom; [4]Psychology, Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Attention must be continuously, optimally balanced between maintaining current task goals and being 'captured' by task-irrelevant yet important information. Directing visual spatial attention to one hemifield is known to produce hemisphere-specific, behaviourally relevant modulations of neuronal oscillations; posterior alpha (8-12Hz) increases to block out irrelevant information and gamma (40-100Hz) activity reflects active feed-forward stimulus processing. Attention is also known to be biased by learned associations with stimuli in the visual field, but little is currently known about the interaction between attention, value, and oscillatory activity. Here, we trained participants via a conditioning manipulation to associate a set of novel visual stimuli (Chinese kanji symbols) with different value outcomes. Symbols could be paired with financial rewards, penalties, or with neither. We then measured participants' neural activity with magnetoencephalography (MEG) while they performed a cued spatial (left versus right) attention task where the value-associated stimuli served as targets or distracters. We hypothesised that the value-associated stimuli would bias attention and alpha and gamma oscillations as compared to the neutral stimuli. We found dissociable effects in the alpha and gamma bands, by characterizing hemispheric lateralization of power when considering attention to the left versus right hemifield. Alpha-band lateralisation was determined by stimulus value-salience; salient targets (associated with positive and negative outcomes) decreased alpha power in target-processing regions (contralateral to attention) whereas salient distractors attenuated alpha lateralisation. Furthermore, alpha lateralisation on a single-trial basis predicted participants' response speeds. In contrast, negative - but not positive - distractors altered gamma lateralisation via an increase in gamma ipsilateral to the distractor. Thus, stimulus value impacts neuronal oscillations in a frequency-specific manner. Value-salience biased alpha oscillations in a similar manner to voluntary attention, suggesting that value and attention may be instantiated by similar underlying mechanisms. Given that alpha oscillations are known to be under top-down control of the dorsal attentional network, this same network may also be responsible for biasing attention according to stimulus value-salience. We are currently investigating the role of the basal ganglia in co-ordinating this top-down control. In contrast, gamma-band activity was specifically increased by negative distractors, suggesting a separate mechanism.

Disclosures: **T.R. Marshall:** None. **S. den Boer:** None. **R. Cools:** None. **O. Jensen:** None. **S. Fallon:** None. **J.M. Zumer:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.10

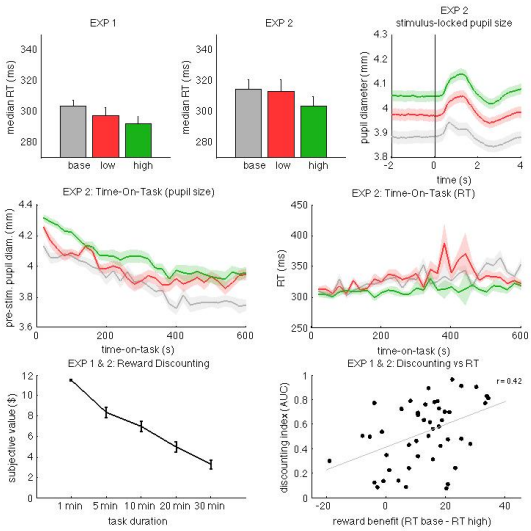
Topic: F.01. Human Cognition and Behavior

Support: NMRC/STaR/015/2013

Title: Rewards boost sustained attention by inducing greater effort

Authors: *S. A. MASSAR, M. W. L. CHEE;
Duke-Nus Grad. Med. Sch., Singapore, Singapore

Abstract: Maintaining vigilance over time in sustained attention tasks is an effortful process. Performance in such tasks is hypothesized to be limited by finite cognitive resources that deplete with sustained performance. Recent theories emphasize the role of motivation in allocation of such resources. It has been proposed that costs of effortful performance are constantly weighed against the benefits of rewards. Here we examined whether a) response times in a sustained attention task improve with increasing reward, b) any improvement is accompanied by objective evidence for increased effort, and c) whether rewards are discounted if participants have to stay on task for a longer time. Participants performed a sustained attention task under three levels of reward (baseline, low and high reward). Following these task blocks a reward-discounting task was performed to measure the extent to which subjects experienced task performance as a cost. The outcome of the discounting task determined how long the participants had to perform the attention task for the remainder of the experiment. Performance improved with increasing reward, as evident from faster reaction times (Exp1, N=25). This effect was replicated in an independent sample (Exp2, N=24), in which higher rewards elicited enhanced effort as indexed by larger pupil diameter during task performance. Regardless of reward however, both behavioral performance and pupil diameter diminished with increasing time-on-task. Discounting curves constructed from the choice task indicated that subjects devalued rewards that came at the cost of staying vigilant for a longer duration. Finally, the extent to which participants discounted rewards in the choice task correlated with their reward-induced performance improvement in the sustained attention task. These data suggest that reward motivation can boost sustained attention performance through increased attentional effort; and that sustained performance is regarded as a cost against which reward value is discounted.



Disclosures: S.A. Massar: None. **M.W.L. Chee:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.11

Topic: F.01. Human Cognition and Behavior

Title: Attentional gain modulation relies on local feature-tuned normalization

Authors: *I. M. BLOEM[1,2], S. LING[1,2];
[1]Psychological and Brain Sci., Boston Univ., Boston, MA; [2]Ctr. for Computat. Neurosci. and Neural Technology, Boston Univ., Boston, MA

Abstract: Attentional feedback has been shown to evoke increases in the gain of early visuocortical responses, but its effects are likely non-uniform, both within and across visual areas. What neural computations give rise to these gain changes? Here, we used fMRI to investigate the hypothesis that gain increases with attention rely on a release from local inhibition. Specifically, we examined whether visuocortical responses that exhibit more strongly weighted inhibitory interactions would also exhibit larger attentional benefits. To do so, we measured the local, voxel-wise magnitude of both orientation-tuned inhibition and attentional modulation within early visual cortex. We assessed orientation-tuned inhibition strength by presenting participants with stimuli composed of two oriented gratings, which were combined in

either a collinear or orthogonal configuration. Consistent with feature-tuned inhibition, collinear stimuli evoked weaker mean BOLD responses than orthogonal stimuli, indicating robust tuned-normalization. Furthermore, the magnitude of local inhibition varied substantially between voxels within a visual area, suggesting heterogeneity in local inhibitory strength across a population. We next explored whether the strength of local inhibition relates to the magnitude of attentional modulation. To do so, participants were shown oriented gratings, and asked to either attend towards the grating (performing a fine orientation discrimination task), or attend away from the grating (performing a demanding task at fixation). We found an increase in BOLD response when attention was directed towards a stimulus, but the voxel-wise strength within a visual area had substantial variability in the amount with which attention boosted stimulus-evoked responses. Leveraging the population-wide heterogeneity in both orientation-tuned inhibition and attentional modulation, we discovered that the strength of tuned inhibition for each individual voxel correlated significantly with the strength of attentional modulation, within striate and extrastriate cortex. Taken together, these results suggest that attentional modulation is not uniform within a visual area, and that the ability of a local neural subpopulation to increase its gain with attention is critically dependent on its weighted normalization strength: local inhibition regulates a population's potential for attentional benefits.

Disclosures: I.M. Bloem: None. **S. Ling:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.12

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant EY018216

Title: Spatial attention reduces noise in the fMRI response

Authors: *W. J. CHANEY[1], J. FISCHER[2], D. WHITNEY[1];
[1]Univ. of California, Berkeley, Berkeley, CA; [2]MIT, Cambridge, MA

Abstract: Spatial attention enhances the representation of relevant stimuli, leading to improved performance in a variety of tasks. The neural mechanisms of spatial attention are manifold, including gain in response amplitudes, sharpened position selectivity, and reduced correlations in the noise of simultaneously observed neurons (Cohen and Maunsell, 2009; Mitchell et.al., 2009). This reduction in correlated noise within attended locations is a potentially powerful mechanism

for boosting the fidelity of a signal carried by a population of cells, but the extent to which reduced noise correlations also manifest at larger scales than single neurons, and can be measured by fMRI in humans, is unknown. Here we tested whether spatial attention reduces the correlated noise in the fMRI BOLD signal between pairs of voxels. We examined the effects of attention on the representation of four Gabor stimuli presented simultaneously, one in each quadrant of the visual field at jittered eccentricities. Subjects attended for contrast decrements in the Gabors in one visual field (either upper or lower in alternating runs) while ignoring the Gabors in the other visual field. After regressing out stimulus driven activity in V1 and V2 in a General Linear Model analysis, we analyzed pairwise correlations of the residual timecourses in voxels representing either the attended or unattended visual fields. We found that attention to either the upper or lower visual field reduces both the correlation and coherence of these timecourses. This reduction cannot be predicted from reduced noise within individual voxels or an increase in stimulus driven activity due to attention, and it cannot be explained by vasculature differences or local scanner artifacts as each region is attended or ignored for an equal number of runs. We further found a potential benefit of decorrelated noise on the precision of spatial information carried by the population activity: voxels exhibiting the greatest decorrelation due to attention also showed the greatest improvement in position selectivity with attention. The reduction in correlated noise within attended locations is an efficient way to increase the precision of the information carried by population activity, and may facilitate readout by higher level processes that pool over information in early visual cortex.

Disclosures: W.J. Chaney: None. **J. Fischer:** None. **D. Whitney:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.13

Topic: F.01. Human Cognition and Behavior

Support: Duke-NUS Grant by Ministry of Health, Singapore

STAR award from NMRC, Singapore

Title: Arousal-associated dynamic functional connectivity patterns predict vigilance performance

Authors: C. WANG, J. ONG, K.-K. NG, M. W. L. CHEE, *J. ZHOU;
Duke-Nus Grad. Med. Sch., Singapore, Singapore

Abstract: Intrinsic connectivity networks (ICNs) detected using task-free fMRI exhibit recurring patterns as distinct connectivity states (CS). Although such dynamic ICNs have been proposed to relate to different conscious states, few studies have directly correlated CS with behavior. Here we used spontaneous eye-closure in the drowsy state as a proxy for sensory processing capacity to identify CSs that correlate with greater and lesser levels of arousal. Young adults underwent two 6-min task-free scans, followed by four task scans measuring response speed to auditory stimuli. Scans were performed in the midafternoon circadian dip (~3pm) after 5h of nocturnal sleep. Eye-video during task-free runs were scored from 1-closed to 9-open. Dynamic ICNs (Yeo et al. 2011) were estimated using 40s wide, sliding-window correlation. K-means clustering was used to estimate the centroids of CS. We then computed distributions of CS occurrences at each eye score interval. CS derived from task fMRI were estimated using an identical approach and were matched to their task-free fMRI counterparts. From the 5 CSs derived from task-free fMRI, we identified 2 extreme CS (fig 1a). At one extreme was a CS corresponding to a state of low arousal with high likelihood of behavioral lapses (eye closures). At the one extreme was a CS corresponding to a state of high arousal (eye openness). The extremes of the 6 task-related fMRI CSs were highly similar in configuration to their task-free fMRI counterparts (fig 1b). Participants who spent more time in high arousal CS performed better in the task, whereas more time in low arousal state CS predicted poor performance (fig 1c). We identified dynamic CS in task-free fMRI associated with high or low level of arousal for a given individual corresponded with CS uncovered from task-regressed fMRI. CS derived thus predicted task performance in the drowsy state. Our findings suggest the feasibility of using dynamic functional connectivity to compliment eye-closure and response time as measures to track vigilance and understand the functional relevance of dynamic functional connectivity.

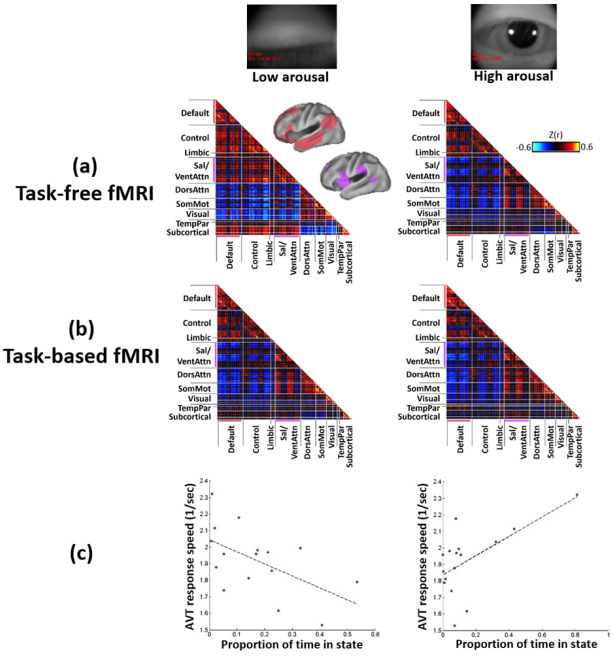


Figure 1. **Row a:** task-free fMRI connectivity states whose occurrence increases the likelihood of low arousal, marked by eye closure (left), or a state of high arousal associated with a wide-eyed state (right). **Row b:** connectivity matrices derived from task-related fMRI that matched to low (left, r = 0.78) and high (right, r=0.91) arousal connectivity states in task-free fMRI. **Row c:** a higher proportion of time spent in a low arousal connectivity state predicted poorer auditory vigilance task performance (right, r = -0.558, p = 0.025), whereas a higher proportion of time in a high arousal connectivity state predicted faster responding (left, r = 0.524, p = 0.037).

Disclosures: **C. Wang:** None. **J. Ong:** None. **K. Ng:** None. **M.W.L. Chee:** None. **J. Zhou:** None.

Nanosymposium

469. Human Cognition and Behavior: Functional Mechanisms of Attention

Location: N228

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 469.14

Topic: F.01. Human Cognition and Behavior

Support: NSF Grant 1157121

Title: Fluctuations of fMRI activation patterns underlie the theta-band rhythmic effects of visual object priming

Authors: ***B. GUO**[1], J. GOOLD[1], H. LUO[2], M. MENG[1];
[1]Dept. of Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [2]Dept. of Psychology, PKU-IDG/McGovern Inst. for Brain Res., Peking Univ., Peking, China

Abstract: In order to efficiently interact with an ever-changing environment, the brain dynamically responds to sensory stimulations. Recent behavioral studies suggest a theta-band rhythm in the effects of priming that underlies how human observers make alternate predictions of a future event based on presented visual input (e.g., Huang, Chen, & Luo, 2015). Here, we hypothesized three possible brain mechanisms that may lead to such rhythmic behavioral priming effects: 1) object representations may be rhythmic in the inferior temporal (IT) cortex; 2) Object representations may be constant, but attentional selection of the representations may be rhythmic; 3) Sensory sampling may be rhythmic as early as the primary visual cortex (Brodmann area 17), therefore all the subsequent processes may also be rhythmic. To test these possibilities, activity corresponding to visual object priming was measured in regions of interest (ROIs) across the whole brain by using fMRI. In addition to the BA17 and the frontoparietal attention network, separate fMRI scans were used to localize object-selective ROIs in the IT cortex including the fusiform face area (FFA) and the parahippocampal place area (PPA). Critically, to examine rhythmic effects, time-resolved measurements of fMRI activation patterns were attained by varying trial-by-trial stimulus onset asynchrony (SOA) between prime and probe in small steps of 20ms, beginning from 200ms and continuing to 1080ms. In each trial, participants were asked to maintain fixation at a cross displayed in the center and to make speeded responses to a probe stimulus (detecting face or house). The prime and probe are either congruent (prime is a face and probe is a face; prime is a house and probe is a house) or incongruent (prime is a face and probe is a house; or vice versa). Our behavioral results replicated previous findings, showing theta-band oscillations in the priming effects of reaction times as a function of SOA. More interestingly, multivariate pattern analysis of the fMRI data also demonstrated theta-band oscillations as a function of SOA and out-of-phase relationship between congruent and incongruent conditions in the FFA and PPA. No such effects were found in the BA17 and frontoparietal attention network. Our study is the first to map theta-band rhythms across the whole human brain using fMRI. Our results suggest that object representation is oscillatory with theta-band rhythms in the IT cortex, providing insights to understanding how the brain dynamically responds to sensory stimulations.

Disclosures: **B. Guo:** None. **J. Goold:** None. **H. Luo:** None. **M. Meng:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.01

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant AG026158

NIH Grant AG038465

Title: Extraversion is associated with lower amyloid deposition in cognitively normal elderly

Authors: *H. OH[1,2], Q. R. RAZLIGHI[1], C. HABECK[1], Y. STERN[1];
[1]Taub Inst., [2]Neurol., Columbia Univ., New York, NY

Abstract: There is great interest in understanding individual differences that influence the vulnerability of individuals to age-related neurodegenerative diseases. Several protective factors, which collectively contribute to "reserve", have been proposed including higher education, more lifetime cognitive activity, and exercise. Little is known about whether and how an individual's personality relates to the risk of age-related neurodegenerative diseases, in particular Alzheimer's disease (AD). In this study, we examined whether extraversion and neuroticism are related to the level of beta-amyloid (Aβ) deposition, a pathological hallmark of AD, in cognitively normal elderly. Using 18F-Florbetaben positron emission tomography (PET), we assessed a level of Aβ deposition of 36 cognitively normal elderly (20 Female, mean age = 64.9, SD = 3.1), who also completed comprehensive neuropsychological tests. Extraversion and neuroticism scores were based on a subset of the Big-Five personality inventory (Goldberg, 1992). Amyloid deposition was determined using standardized uptake value ratio (SUVR) using a gray matter cerebellum reference region. Extraversion (mean = 3.4, SD = 0.7, range: 1.8-4.5) was negatively associated with higher Aβ deposition in the precuneus, accounting for age, sex, and years of education ($\beta = -0.44$, $p < 0.05$). The whole-brain voxel-wise analysis showed a negative association between extraversion and Aβ deposition across frontal, parietal, and temporal cortices. With cognitive composite scores assessing 4 cognitive domains (i.e., reasoning, vocabulary, processing speed, and memory), extraversion was positively associated with memory performance, accounting for age, sex, and years of education ($\beta = 0.47$, $p < 0.05$). Neuroticism, however, was not associated with either Aβ deposition or cognitive performance. This preliminary study suggests that extraversion, possibly through lifestyle factors, correlates with Aβ deposition and memory functions in cognitively normal elderly. Future studies need to address a causal relationship between personality and the vulnerability to AD-related pathology.

Disclosures: H. Oh: None. **Q.R. Razlighi:** None. **C. Habeck:** None. **Y. Stern:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.02

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R01 DK09157

NIH Grant R01 AG25667

NIH Grant R01 AG25032

Title: White matter integrity mediates the relationship between cardiorespiratory fitness and cognitive function in older adults

Authors: *L. E. OBERLIN[1], T. D. VERSTYNEN[3], A. Z. BURZYNSKA[4], M. W. VOSS[5], R. S. PRAKASH[6], S. M. PHILLIPS[7], E. L. MAILEY[8], E. MCAULEY[4], A. F. KRAMER[4], K. I. ERICKSON[2];
[1]Dept. of Psychology, [2]Univ. of Pittsburgh, Pittsburgh, PA; [3]Carnegie Mellon Univ., Pittsburgh, PA; [4]Univ. of Illinois at Urbana-Champaign, Champaign, IL; [5]The Univ. of Iowa, Iowa City, IA; [6]Ohio State Univ., Columbus, OH; [7]Northwestern Univ., Evanston, IL; [8]Kansas State Univ., Manhattan, KS

Abstract: White matter supports higher-order cognitive processes by facilitating signal transmission between cortical regions. The integrity of white matter declines with advancing age, leading to a decline in memory and executive processes in older adulthood. Yet, recent research suggests that higher physical activity and fitness levels may be associated with less white matter degeneration and better cognitive performance. Unfortunately, these prior studies infrequently associate white matter measures to cognitive outcomes, so the behavioral importance of greater white matter integrity with higher fitness levels remains a matter of speculation. Here we tested whether higher cardiorespiratory fitness levels were associated with greater white matter integrity and whether this relationship constituted an indirect pathway between cardiorespiratory fitness and memory in a cognitively healthy older adult sample. Diffusion tensor imaging was used to determine microstructural white matter integrity in a group of 113 (mean age = 66.61) neurologically healthy adults. Measures of cardiorespiratory fitness (VO2max) and spatial working memory performance were also collected. Using a whole-brain voxelwise approach, we found that higher fitness levels were associated with greater white matter integrity in anterior fiber tracts, including the anterior corona radiata, anterior internal capsule, and genu of the corpus callosum. Further, a statistical mediation analysis revealed that white matter integrity within these regions mediated the relationship between fitness and spatial working memory performance. These results suggest that higher levels of aerobic fitness may protect against age-related declines in white matter integrity, which may, in turn, preserve memory performance in older adulthood.

Disclosures: L.E. Oberlin: None. **T.D. Verstynen:** None. **A.Z. Burzynska:** None. **M.W. Voss:** None. **R.S. Prakash:** None. **S.M. Phillips:** None. **E.L. Mailey:** None. **E. McAuley:** None. **A.F. Kramer:** None. **K.I. Erickson:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.03

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R37 AG024102

NIH Grant P01 AG043362

Title: Modifiers of eight-year longitudinal change in frontal lobe cortical thickness

Authors: *P. ROBINSON[1], P. RAST[2], K. KENNEDY[3], K. SCHAIE[1], S. WILLIS[1];
[1]Univ. of Washington, Seattle, WA; [2]Psychology, Univ. of Victoria, Victoria, BC, Canada;
[3]Univ. of Texas, Dallas, Dallas, TX

Abstract: Most longitudinal studies of cortical thickness typically span two to three occasions. Here, we report on eight-year longitudinal change over five occasions at two-year intervals. Cognitively normal subjects were recruited from the Seattle Longitudinal Study (N=190 ;mean age=69.55, range=56-91; %male= 42; %HBP=58; %APOE4=30). High-resolution T1-weighted images were acquired for each subject at each occasion and automatically parcelated using the FreeSurfer analysis suite. For the present analysis we focused on 8 parcels averaged across hemispheres in the frontal lobe that represent association cortex. The frontal lobe is of particular interest in cognitive aging. Parcels were aggregated by weighted average into four regions: Superior Frontal Gyrus (SFG), Middle Frontal Gyrus (MFG), Inferior Frontal Gyrus (IFG), and Medial Frontal Gyrus (mF). We investigated cross-sectional (AGE) and longitudinal (TIME) effects and two salient modifiers of neural and cognitive health: Apolipoprotein E (APOE) haplotype and hypertension (HBP). Significant cross sectional age effects were found for all 4 regions. Significant TIME effects or interactions were also found for all regions. For SFG, MFG and IFG older adults showed accelerated thinning over time (TIMEXAGE). No significant APOE or HBP main effcts or interactions were found. The significant TIME effects suggest broad longitudinal thinning in frontal association cortex with accelerated thinning with age for 3 of 4 regions. These findings highlight the importance of longitudinal design.

Disclosures: P. Robinson: None. **P. Rast:** None. **K. Kennedy:** None. **K. Schaie:** None. **S. Willis:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.04

Topic: F.01. Human Cognition and Behavior

Title: MindCrowd: web-based paired associates learning and reaction time testing demonstrates significant main effects of age, gender, education, and familial history of Alzheimer's disease on performance

Authors: M. J. HUENTELMAN[1,2,3], I. SCHRAUWEN[1,2,3], A. SINIARD[1,2,3], R. RICHHOLT[1,2,4], J. CORNEVEAUX[1,2,3], E. GLISKY[5,2,3], L. RYAN[5,2,3], *M. DE BOTH[1,2,3]; [1]Neurogenomics, Translational Genomics Res. Inst. (TGen), Phoenix, AZ; [2]Arizona Alzheimer's Consortium, Phoenix, AZ; [3]Evelyn F. McKnight Brain Inst. at the Univ. of Arizona, Tucson, AZ; [4]Evelyn F. McKnight Brain Inst. at the Univ. of Arizona, Phoenix, AZ; [5]Univ. of Arizona, Tucson, AZ

Abstract: Variation in cognitive function across individuals is well documented and known to be due to a combination of heritable and non-heritable factors. Most studies performed to date have been largely underpowered to detect the factors influencing cognitive performance, especially when such factors exert a subtle effect. To address this, we created MindCrowd.org, a web-based assessment of simple visual reaction time (RT) and paired associates learning (PAL). Since April 1, 2013, 82,634 visitors started our test, with 52,995 participants completing the entire RT+PAL paradigm and answering 20 lifestyle and demographic questions including age, sex, education, and disease (64.1% completion rate). The RT task consists of a target object (pink sphere) that appears randomly, and the user is asked to respond as quickly as possible. We conduct 5 trials. The PAL task consists of 12 word pairs presented sequentially. During the test, the user is given half of a word pair and must recall the correct paired word. The 12 pairs are repeated over 3 rounds for 36 total tests. From all completed tests, we filter to select a final cohort for analysis by removing duplicate test takers, subjects who didnâ€™t understand the rules, and invalid or duplicate email addresses. While this data pruning approach is likely overly stringent, it still yields a final cohort size of 18,998 (PAL) and 15,990 (RT) subjects. Multiple regression models were fit with the PAL and RT results. Age is the most significant factor influencing both PAL and RT performance ($p < 1.00e-132$, $r = -0.20$ words; $p = 8.13e-132$, $r = 0.30\%$, respectively). At every age, females score better than males on PAL ($p = 3.05e-45$, $r = -1.77$ words). Conversely, males perform better on RT across every age ($p = 3.89e-63$, $r = 5.31\%$). Higher education is associated with better PAL and RT performance ($p = 2.69e-81$, $r = 3.69$ words; $3.02e-4$, $r = 2.31\%$). Lastly, a first degree relative with AD significantly, negatively impacts PAL and RT performance ($p = 2.02e-07$, $r = 0.70$ words; $6.54e-4$, $r = 0.02\%$). To

investigate the familial AD effect, we first note a lengthening in PAL response time (the time taken to input the word pair). Second, there is a significant decrease in the PAL learning curve. Lastly, we identify several health and lifestyle factors that interact with familial AD status and PAL performance, including history of drug abuse, time of day, education, and number of daily prescriptions. This suggests heritable factors associated with first degree AD risk exert an effect on cognitive performance, even in healthy individuals at young adult ages. Our results demonstrate the effectiveness of web-based recruitment for the study of cognition across a diverse cohort.

Disclosures: M.J. Huentelman: None. **I. Schrauwen:** None. **A. Siniard:** None. **R. Richholt:** None. **J. Corneveaux:** None. **E. Glisky:** None. **L. Ryan:** None. **M. De Both:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.05

Topic: F.01. Human Cognition and Behavior

Support: DFG Grant BR 2877/2-2

Title: Attention control ability modulates neurobehavioral effects of episodic prospection on temporal discounting in aging

Authors: *L. K. SASSE, J. PETERS, C. BÜCHEL, S. BRASSEN;
Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Episodic future thinking has been demonstrated to attenuate the neurobehavioral devaluation of future rewards in young adulthood (tag-effect) via functional interaction between the hippocampus and prefrontal areas (Peters and Büchel, 2010). Whether this tag-effect can be similarly evoked in healthy older adults is yet to be determined. It has been suggested that value integration in more complex choice tasks may be impaired in aging due to age-related deficits in fluid cognitive abilities, such as attention control (Samanez-Larkin & Knutson, 2015). The present study addressed these questions and investigated the tag-effect as a function of attention control ability in healthy older adults. Functional magnetic resonance imaging was applied in older adults during a delay discounting task in which they had to choose between a smaller immediate or a variable larger, but delayed reward. The delayed reward was either purely monetary (control condition), or connected to a social event (tag condition). Attentional control ability was assessed with an established paradigm (Sasse et al., 2014) prior to scanning. Our

results indicate that in comparison with younger controls, the group of older adults exhibited a significant reduction in the tag-effect along with diminished activation of the neural episodic prospection network. On the individual level, however, older adults' attention control ability significantly predicted the presence of the tag-effect. Specifically, elderly subjects with high abilities were more likely to exhibit a behavioral tag-effect paralleled by increased hippocampal activation. Moreover, in these high ability subjects, functional coupling between the hippocampus and the ventral striatum was significantly increased during subjective value processing in the episodic compared to the control condition. Our data indicate that beneficial effects of episodic prospection on the valuation of future rewards critically depend on attention control ability in aging. This is further supported by our neural findings, suggesting that only in the face of sufficient attentional resources elderly people can successfully integrate episodic information with neural value computation.

Disclosures: L.K. Sasse: None. **J. Peters:** None. **C. Büchel:** None. **S. Brassen:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.06

Topic: F.01. Human Cognition and Behavior

Title: The effects of age on proactive and reactive control during working memory

Authors: *H. MACPHERSON[1,2], D. WHITE[1], M. HUGHES[1];
[1]Swinburne Univ., Melbourne, Australia; [2]Ctr. for Physical Activity and Nutr. Res., Deakin Univ., Melbourne, Australia

Abstract: Cognitive decline is a feature of the aging process, with working memory particularly susceptible to age-related decline in the later years of the lifespan. Even in the absence of objective memory deficits, increased bilateral neural activation has been observed in older adults during performance of working memory tasks. Age-related alterations to the neural correlates of working memory have been interpreted as compensatory (i.e. beneficial to performance), inefficient (i.e. no benefit to performance) or reflecting a shift in strategy. We used fMRI to investigate the extent to which this functional reorganization reflects changes in strategy utilization in the form of increased reliance on reactive rather than proactive control strategies. Participants were 18 healthy young adults (20 to 34 years) and 18 healthy older adults (55-69 years of age) who were matched for years of education, IQ and working memory digit span. Participants completed an n-back task consisting of 2-back (target) trials and 3 and 4-back (lure)

trials. A second version of the n-back contained cues to indicate which new items would be repeated as lures. The cued task version was designed to promote proactive control strategies and the non-cued version was expected to elicit reactive control strategies. Results indicated response times were faster for the cued condition, however there was no difference in accuracy for the cued and non-cued tasks. There were no significant differential age effects for accuracy or response time for the cued versus non-cued task versions. Similarly for fMRI data, the age x task condition (cued, non-cued) interaction did not reveal differential patterns of activation. Instead, older adults demonstrated increased bilateral inferior and superior temporal activation, left middle frontal gyrus and right cingulate activation, regardless of task condition. Greater activity was also observed in the right inferior temporal gyrus, a region which has previously been implicated in switching between reactive and proactive control modes. Younger adults demonstrated greater activation across left ventrolateral PFC, left insula and bilateral middle temporal gyrus. Findings from this study suggest that in older adults, recruitment of a more extensive network of bilateral brain regions during working memory is not due to age differences in the utilization of proactive and retroactive strategies.

Disclosures: H. Macpherson: None. **D. White:** None. **M. Hughes:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.07

Topic: F.01. Human Cognition and Behavior

Support: NIH grant R00 AG-036818-05

NIH grant R00 AG-036848-05

NIH grant P01 AG-043362

NIH grant R37 AG-024102

Title: Changes in association white matter tract integrity precede thinning of regional gray matter cortex: Four-year findings from the Seattle Longitudinal Study of aging

Authors: *K. M. KENNEDY[1], P. R. A. W. ROBINSON[3], K. M. RODRIGUE[2], P. RAST[6], K. W. SCHAIE[4], S. L. WILLIS[5];
[1]Behavioral & Brain Sci., [2]Behavioral & Brain Sci. Ctr. Vital Longevity, Univ. Texas, Dallas,

Dallas, TX; [3]Dept. of Radiology, [5]Psychiatry and Behavioral Sci., [4]Univ. of Washington, Seattle, WA; [6]Dept. of Psychology, Univ. of Victoria, Victoria, BC

Abstract: Cross-sectional research has demonstrated that aging has strong detrimental effects on both gray matter (GM) and white matter (WM) brain structure. How aging of these two types of tissues are related to each other is unknown. The current longitudinal study sought to address this issue using multiple occasion MRI scan data (MPRAGE for GM, DTI for WM). Participants included 107 individuals from the Seattle Longitudinal Study of aging (M age = 67, 53-85 yrs old) for whom at least three time points of each scan were obtained. We utilized latent growth curve modeling to assess level and 4-year change (i.e., intercept and slopes) between metrics of GM and WM integrity. FSL was used for probabilistic tractography and Freesurfer was used for cortical thickness measurement. We assessed specifically the major association WM bundles (SLF, ILF, uncinate, cingulum, fornix) and their relevant cortical GM counterparts. We hypothesized specifically change in WM with level of GM thickness at last time point (slope-intercept association). Results indicate robust findings for WM change-GM level associations, suggesting that four years of degradation of white matter fibers is predictive of thinner regional association cortices at the end of those four years. We found these relations to be both proximally related (e.g., fornix integrity and thickness of the surrounding temporal cortex) and distally related (e.g., uncinate integrity and frontal and parietal thickness). These longitudinal study findings suggest that changes in white matter integrity underlie or precede gray matter thinning in association cortices during the course of normal aging.

Disclosures: K.M. Kennedy: None. **P.R.A.W. Robinson:** None. **K.M. Rodrigue:** None. **P. Rast:** None. **K.W. Schaie:** None. **S.L. Willis:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.08

Topic: F.01. Human Cognition and Behavior

Support: R01AG044292

F32AG047686

Title: Increased dopamine synthesis capacity in older adults is associated with cognitive inflexibility

Authors: *A. S. BERRY[1], V. D. SHAH[1], S. L. BAKER[1], J. W. VOGEL[2], H. SCHWIMMER[2], S. M. MARKS[2], W. J. JAGUST[1];
[1]Lawrence Berkeley Natl. Lab., Berkeley, CA; [2]UC Berkeley, Berkeley, CA

Abstract: Cognitive flexibility, a measure of executive function, is disrupted in older adults. The present study examines the role of dopamine (DA) in mediating age-related differences in cognitive flexibility using 6[^{18}F]fluoro-L-*m*-tyrosine (FMT) PET. FMT is a measure of DA synthesis capacity similar to FDOPA, and is quantified as net tracer influx (K_i). Previous studies indicate that multiple components of the DA system decline with age. However, there is also evidence for what may be compensatory upregulation of DA synthesis in older adults. Here we measured age differences in DA synthesis capacity in older adults (n = 9; mean age = 75.69) and young adults (n = 12; mean age =23.86) cross-sectionally, and examined relationships between DA synthesis capacity and cognitive flexibility in older adults. Analyses focused on FMT K_i measured in manually traced regions of interest in dorsal caudate, dorsal putamen and ventral striatum, averaged across hemispheres. FMT K_i was partial volume corrected using a region of interest approach (Rousset et al., 1998). While striatal gray matter volume was reduced in older adults, we found DA synthesis capacity was higher in all 3 striatal regions ($F(1,19)$, $p = .005$) relative to young adults. An age by region interaction revealed largest group differences in dorsal caudate K_i ($p < .001$). Next, we assessed cognitive flexibility using a task switching paradigm previously shown to involve dorsal caudate (Stelzel, 2010). Older adults were less cognitively flexible than younger adults, showing greater mixing costs when two task rules were active relative to one (accuracy, $p < .05$; response time $p < .005$). In young adults, higher FMT K_i in dorsal caudate correlated with better performance during mixed runs (smaller switch costs for switch vs repeat trials, $r = -.54$). However, this behavioral benefit for high K_i individuals was not found in the older adult group, and the relationship between K_i and performance trends in the opposite direction ($r = .28$). These results suggest elevated DA synthesis capacity in older adults is not sufficient to maintain cognitive flexibility or may have detrimental effects on performance.

Disclosures: A.S. Berry: None. **V.D. Shah:** None. **S.L. Baker:** None. **J.W. Vogel:** None. **H. Schwimmer:** None. **S.M. Marks:** None. **W.J. Jagust:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.09

Topic: F.01. Human Cognition and Behavior

Support: NIA Grant AG025526

State of Arizona and Arizona DHS

Title: Impact of white matter hyperintensity volume on cortical brain morphology in healthy cognitive aging

Authors: *G. E. ALEXANDER[1,2,3,4], P. K. BHARADWAJ[1,4], K. A. HAWS[1,4], L. A. NGUYEN[1,4], M. C. FITZHUGH[1], T. P. TROUARD[5], G. A. HISHAW[6];
[1]Dept. of Psychology, [2]Neurosci. Grad. Interdisciplinary Programs, [3]Physiological Sci. Grad. Interdisciplinary Programs, [4]Evelyn F. McKnight Brain Inst., [5]Biomed. Engin., [6]Neurol., Univ. of Arizona, Tucson, AZ

Abstract: White matter hyperintensities on T2 FLAIR magnetic resonance imaging (MRI) scans are often observed in healthy aging and to a greater extent in those with cerebrovascular risk factors, like hypertension. We sought to evaluate the effects of WMH lesion volume on cortical brain morphology and cognitive performance in a sample of 79 healthy, community-dwelling adults, 50 to 89 years of age without hypertension to determine whether the presence of white matter lesions in this healthy elderly cohort have an impact on the course of cognitive and brain aging. Participants (33M/46F; mean ±sd age = 65.7 ± 10.0; mean ± sd Mini-Mental State Exam = 29.3 ± 1.0) completed a battery of neuropsychological tests and were medically screened to exclude neurological, psychiatric, and medical illnesses that could affect cognitive function, including any hypertension diagnosis and clinic systolic blood pressures greater than 140 mmHg. Regional patterns of cortical brain thickness and area were assessed using Freesurfer software with T1-weighted 3T volumetric MRI scans (GE Signa Excite system) and logWMH volumes were computed from T1 and T2 FLAIR images using a multispectral, automated lesion segmentation method to produce probability maps with a lesion segmentation toolbox (SPM8 LST). The relations between logWMH and cortical morphology were evaluated using Monte Carlo correction with 10,000 iterations for clusters with $p < 0.05$. The results showed that after controlling for the effects of age in the cohort, greater logWMH volume was associated with greater reductions in cortical thickness in medial frontal and right inferior temporal regions. In contrast, cortical area showed greater increases in lateral orbital and superior frontal and inferior parietal regions in relation to greater logWMH volumes. Greater logWMH volumes were also associated with poorer performance on several measures of executive cognitive functions, assessing aspects of inhibition and set-shifting abilities ($0.016 \leq p \leq 0.041$). Together, these findings suggest that in healthy community-dwelling, normotensive older adults, greater WMH volume leads to diminished cortical thickness, as well as poorer cognitive performance involving brain regions often impacted by cognitive aging, but is also associated with corresponding increases in cortical area. This areal expansion may reflect a compensatory response in these healthy older adults that could serve to enhance brain connectivity when faced with increasing WHM lesion load.

Disclosures: **G.E. Alexander:** None. **P.K. Bharadwaj:** None. **K.A. Haws:** None. **L.A. Nguyen:** None. **M.C. Fitzhugh:** None. **T.P. Trouard:** None. **G.A. Hishaw:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.10

Topic: F.01. Human Cognition and Behavior

Title: Age-related differences in task load, response compatibility and selective attention in task switching: An fMRI study

Authors: ***S. QIN**, K. NASHIRO, M. O'CONNELL, X. CHEN, C. BASAK;
Univ. of Texas At Dallas, DALLAS, TX

Abstract: Across a wide range of cognitive domains, older adults typically recruit additional fronto-parietal brain regions than younger adults. This is argued to be either compensatory, evidenced by nearly equivalent performances between the two age groups, or dedifferentiation, evidenced by lower performance in older adults. The CRUNCH model of aging (Reuter-Lorenz & Cappell, 2008) hypothesizes that task difficulty may play a critical role in interpreting of such age differences in neural recruitment. In the current fMRI study, older and younger adults were subjected to a hybrid-block design task switch paradigm, which consisted of single task blocks, and mixed task blocks where the two tasks alternated randomly (Figure 1). Analyses of imaging data took into account the 3 different levels of task difficulty (single, dual non-switch and dual switch trials) as well as 2 types of finger-mapping compatibility (compatible vs. incompatible). For older adults the simplest task demand yielded increased activation of the task-related regions (Figure 2a). Moreover, individual differences in neural modulation from single to dual tasks in older adults were positively correlated with the dual task accuracy (Figure 2c). These results support the CRUNCH model. Also, over-recruitment of additional parietal areas in older adults was observed, which may be considered compensatory due to equivalent accuracies across the two age groups.

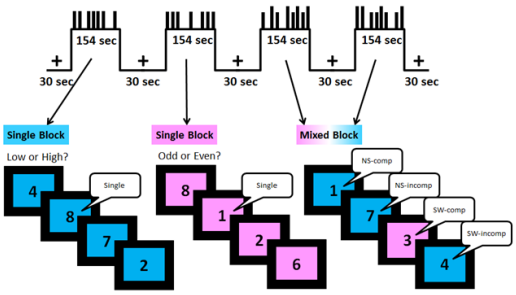


Figure 1. Task switching paradigm. A hybrid blocked and event-related design was used, which consisted of two single blocks and two mixed blocks interspersed by fixation periods. The short bars in the task blocks represent non-switch trials, and the long bars represent switch trials. The blue background indicated to judge whether a digit was lower or higher than five, while the pink background instructed to judge whether a digit was odd or even. There were five trail types as follows in order of task difficulty: Single, NS-comp, NS-incomp, SW-comp and SW-incomp.

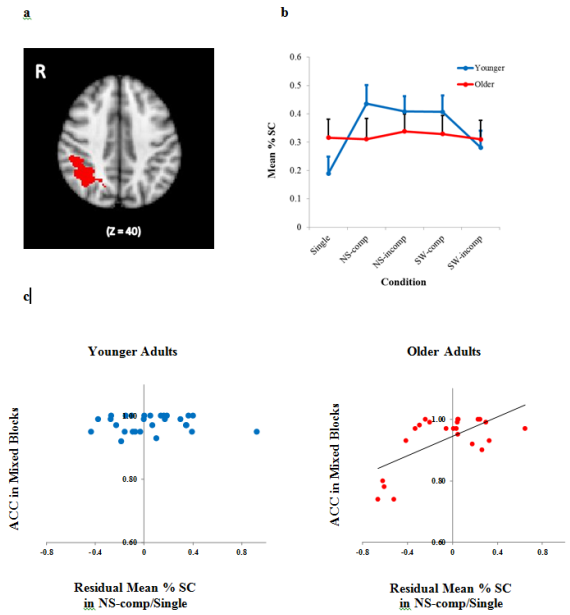


Figure 2. Age-group differences in the right angular gyrus activation (a MC region) as a function of task difficulty and its correlation with accuracy in the mixed blocks.

Disclosures: S. Qin: None. **K. Nashiro:** None. **M. O'Connell:** None. **X. Chen:** None. **C. Basak:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.11

Topic: F.01. Human Cognition and Behavior

Title: Brooding is related to neurobehavioral changes during the construction and elaboration of autobiographical memories in non-depressed elderly

Authors: *S. BRASSEN, S. SCHNEIDER;
Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Introduction: Rumination upon negative previous events is a well-known risk and key factor of depression in midlife. Only little is known about whether such relations also exist in late-life depression. However, as older people tend to review their past, they might carry an increased risk to ruminate upon previous events and decisions (Ingersoll-Dayton et al., Aging and Mental Health, 2010). This risk might be particularly pronounced in the context of impaired autobiographical memory function hindering individuals to adequately retrieve concrete memories (Dalgleish & Werner-Seidler, TiCS, 2014). Methods: In the present study, 23 (17 women, mean age 64.8 +/- 4.7 years) non-depressed older adults with varying degrees of brooding tendency were scanned with functional magnetic resonance imaging while performing the construction and elaboration of autobiographical memories cued by positive and neutral words. Results: Brooding tendency, as measured with the “Brooding” subscale of the Response Style Questionnaire, was associated with longer construction phases and more negatively rated elaborations, especially in response to positive cues. On the neural level, participants with high brooding tendency showed increased activation in the amygdala during the search for specific memories (construction phase) and reduced engagement of the episodic memory network during elaboration. Conclusion: Our findings support the hypothesis that ruminative thinking interferes with the search for specific memories while facilitating the retrieval of negatively biased schemes. Thus, the present results emphasize a critical role of autobiographical memory function for risk of depression in late life. Given the general decline of autobiographical memory function in aging, memory specificity training might be a particularly promising tool to increase resilience against depression in late-life.

Disclosures: S. Brassen: None. **S. Schneider:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.12

Topic: F.01. Human Cognition and Behavior

Support: Velux Stiftung Project No. 369

URPP Dynamics of Healthy Aging

Title: Regional differences in and predictors of age-related cortical thinning: findings from the Longitudinal Healthy Aging Brain (LHAB) database project

Authors: *S. MERILLAT[1], P. RAST[4], F. LIEM[1], P. ROBINSON[5], C. ROECKE[1], S. L. WILLIS[6], M. MARTIN[1,2], L. JANCKE[1,3];
[1]URPP Dynamics of Healthy Aging, [2]Dept. of Gerontopsychology, [3]Dept. of Neuropsychology, Univ. of Zurich, Zurich, Switzerland; [4]Dept. of Psychology, Univ. of Victoria, Victoria, BC, Canada; [5]Dept. of Radiology, Integrated Brain Imaging Ctr., [6]Psychiatry and Behavioral Sciences, Seattle Longitudinal Study, Univ. of Washington, Seattle, WA

Abstract: Age-related cognitive changes are often attributed to changes in brain anatomy and function observed with advancing age. However, while the nature of brain-behavior change associations is complex and far from being understood, we also do not sufficiently understand age-related change trajectories in brain structure, which supposedly underlie changes in cognition. We examined two-year longitudinal change in cortical thickness over 3 yearly measurement occasions in 186 older adults (Mean baseline age = 70.6 range 64.0-85.4). Data were taken from the Longitudinal Healthy Aging Brain (LHAB) database currently being built at the University Research Priority Program (URPP) "Dynamics of Healthy Aging" at the University of Zurich. MRI data were collected on a Philips 3T Ingenia scanner. Cortical thickness estimation was performed with FreeSurfer v5.3. Cortical thickness values for the resulting parcels were extracted for each study participant and measurement occasion and clustered to build four regional composite scores representing frontal, parietal, temporal and cingulum association cortices. Multivariate multilevel models using a stepwise modeling procedure examined longitudinal change in cortical thickness. In a first step we ran baseline models of change in cortical thickness for all four regions jointly. In a second step we included blood pressure, APOE status and years of education to explain individual differences in cortical thickness and thinning rates. Cortical thinning was statistically significant in all four regions (annual change ranged from 0.16% to 0.60% atrophy per year). In the frontal and cingulum regions, cortical thinning was accelerated with advancing age. Hypertension was associated with reduced cortical thickness at study entry (on average 1.9% thinner cortices compared to normals) and also with accelerated cortical thinning in the frontal and temporal lobes (an additional loss of 0.5% per year of cortical thickness). APOE status and education did not explain differences in cortical thickness or thinning. Reliable individual differences in cortical thickness and rate of thinning were observed for all regions. In conclusion, we see a magnitude of cortical thinning in the very healthy and highly educated LHAB sample that is comparable with the very few

previous studies addressing this question on the basis of longitudinal data. Our results indicate that in regions particularly important for cognitive aging (i.e. the frontal association cortex) cortical thinning is accelerated with advancing age and that health factors, such as hypertension, influence both mean level and the trajectory of cortical thinning.

Disclosures: **S. Merillat:** None. **P. Rast:** None. **F. Liem:** None. **P. Robinson:** None. **C. Roecke:** None. **S.L. Willis:** None. **M. Martin:** None. **L. Jancke:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.13

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R37-AG11230

Title: Changes in white matter diffusion properties support the "last-in-first-out" hypothesis of brain aging

Authors: *A. R. BENDER[1], M. C. VOELKLE[2,3], N. RAZ[4,5];
[2]Ctr. for Lifespan Psychology, [1]Max Planck Inst. for Human Develop., Berlin, Germany; [3]Dept. of Psychology, Humboldt Univ., Berlin, Germany; [4]Inst. of Gerontology, [5]Dept. of Psychology, Wayne State Univ., Detroit, MI

Abstract: The limited extant reports of longitudinal white matter (WM) changes in healthy aging, using diffusion tensor imaging (DTI), suggest that such changes differ across brain regions and DTI indices. According to the "last-in-first-out" view, late-developing WM tracts may be particularly vulnerable to pathology or advanced age. Thus, comparison of age-related longitudinal changes in association, commissural and projection WM fiber regions may provide a better understanding of which WM fiber types are most susceptible to the negative effects of aging. In the present study, we used a skeletonized, region of interest DTI approach to assess the effects of age and hypertension, a common age-related vascular risk factor, on longitudinal change in axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA) in healthy middle-aged and older adults (mean age = 65.4, SD = 9.0 years). Using linear mixed effects models, we evaluated the differential influences of age and hypertension at baseline on seven-year changes in association, commissural and projection fiber regions. Separate models were fitted to AD, RD, and FA data. Across models, association fibers showed the most pronounced declines over time. Advanced age was associated with longitudinal changes in RD

and FA, independent of fiber type. In addition, follow up analyses on projection fiber regions showed older age was only associated with longitudinal increases in RD in late-developing but not early-developing projection fibers. Hypertension was marginally associated with higher AD and RD at baseline, but not with change. The present findings demonstrate the increased vulnerability of earlier developing WM regions and are in accord with the "last-in-first-out" hypothesis of the brain aging.

Disclosures: **A.R. Bender:** None. **M.C. Voelkle:** None. **N. Raz:** None.

Nanosymposium

470. Cognitive Changes During Ageing

Location: S404

Time: Tuesday, October 20, 2015, 8:00 AM - 11:30 AM

Presentation Number: 470.14

Topic: F.01. Human Cognition and Behavior

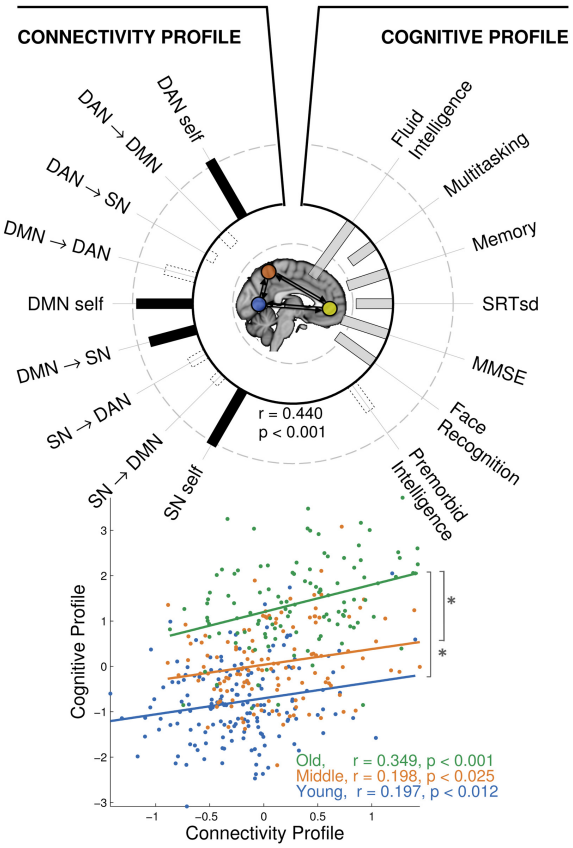
Support: BB/H008217/1

Title: Increased extrinsic and intrinsic connectivity maintains cognition across the lifespan coupled with age-related decay in regional neuronal activity

Authors: ***K. A. TSVETANOV**[1], R. N. A. HENSON[3], L. K. TYLER[1], A. RAZI[4,5], L. GEERLIGS[3], T. HAM[6], .. CAM-CAN[2], J. B. ROWE[3];
[2]Cambridge Ctr. for Ageing and Neurosci., [1]Univ. of Camrbidge, Cambridge, United Kingdom; [3]Med. Res. Council Cognition and Brain Sci. Unit, Cambridge, United Kingdom; [4]The Wellcome Trust Ctr. for Neuroimaging, Univ. Col. London, London, United Kingdom; [5]Dept. of Electronic Engin., NED Univ. of Engin. and Technol., Karachi, Pakistan; [6]Dept. of Clin. Neurosciences, Cambridge Univ., Cambridge, United Kingdom

Abstract: Preservation of cognitive functioning is critical to successful ageing. One factor that might support this preservation is flexibility in the interactions between key functional brain networks. One way to estimate this flexibility is to examine both between-network and within-network (i.e. between-node) connectivity from resting-state functional magnetic resonance imaging (rs-fMRI). However, common correlational methods for testing such interactions are confounded by age-related changes in the neurovascular coupling. In order to estimate causal network interactions at the neuronal rather than vascular level, we inverted dynamic causal models that specified both the neural interactions and neurovascular forward models for each node. The networks' parameters were optimised to explain the spectral dynamics of rs-fMRI. Using on a population-based cohort (n = 635) uniformly sampled across the healthy adult

lifespan (18-88 years), we assessed directed connectivity within and between three key large-scale networks: the salience network, the dorsal attention network and the default mode network. We found that aspects of both within- and between-network connectivity were highly predictive of age, even when allowing for age-related differences in neurovascular coupling. Multivariate canonical correlation analysis revealed that the relationship between network connectivity parameters and cognitive functions ($r = .44$, $p < .001$) was age-dependent: relatively better cognitive performance in older subjects who relied more strongly on neural dynamics (see fig). These effects were in part driven by a common feature of all networks, namely higher inhibitory self-connections, which results in an accelerated decay of information in the absence of external inputs, i.e, reduced stability of neural states. In sum, our findings suggest that the balance between excitatory connectivity within and between networks, and the stability of intrinsic neural representations, vary with age, and that cognitive function of older subjects becomes increasingly dependent on these factors.



Top panel: Heliograph of variate loadings (structural correlations) for the first canonical variate, where the relative size of correlations is indicated by the length of the bars (black is positive, grey is negative; bars with low contribution ($r < .3$) shown with non-continuous outline). The half-maximum strength of correlation is indicated by the rings (outer is $r = +0.5$, inner is $r = -0.5$). ***Bottom panel:*** Corresponding bi-variate canonical correlation for three arbitrary age groups. The relationship between connectivity profile and cognitive profile is higher for older subjects,suggesting that good performance in older adults relies more strongly on connectivity between networks. Asterisk denotes significant.

Disclosures: **K.A. Tsvetanov:** None. **R.N.A. Henson:** None. **L.K. Tyler:** None. **A. Razi:** None. **L. Geerligs:** None. **T. Ham:** None. **.. Cam-CAN:** None. **J.B. Rowe:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.01

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant RC1NS069014

NIH Grant R01NS076774

NIH Grant R01NS086859

NIH Intramural Grant Z01-HD008776

Jane Coffin Childs Foundation

HHMI

Title: Dynamic, multi-color labeling of active synapses *in vivo* in *Drosophila*

Authors: *L. J. MACPHERSON[1], E. E. ZAHARIEVA[2], P. J. KEARNEY[2,3], T.-Y. LIN[4,5], Z. TURAN[1,6], C.-H. LEE[4], M. GALLIO[2];
[1]Biochem. and Mol. Biophysics, Columbia Univ., New York, NY; [2]Dept. of Neurobio., Northwestern Univ., Evanston, IL; [3]Univ. of Massachusetts Med. Sch., Worcester, MA; [4]Section on Neuronal Connectivity, Lab. of Gene Regulation and Development, Eunice Kennedy Shri, NIH, Bethesda, MD; [5]Grad. Inst. of Life Sci., Natl. Def. Med. Ctr., Taipei, Taiwan; [6]Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: Determining the pattern of activity of individual connections within a neural circuit could provide insights into the computational processes that are the basis of brain function. Here, we demonstrate new strategies to label active synapses *in vivo* in *Drosophila*. First, we develop a powerful activity-dependent marker for synapses based on by trans-synaptic interactions. Next, we create color variants, achieving activity-dependent, multi-color tagging of active synapses *in vivo*. Our system allows for the first time retrospective labeling of synapses (rather than whole neurons) based on their activity, in multiple colors, in the same animal. As individual synapses often act as computational units in the brain, our method will promote the design of experiments

that are not possible using existing techniques. Moreover, our strategies are easily adaptable to circuit mapping in any genetic system.

Disclosures: **L.J. Macpherson:** None. **E.E. Zaharieva:** None. **P.J. Kearney:** None. **T. Lin:** None. **Z. Turan:** None. **C. Lee:** None. **M. Gallio:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.02

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: MEXT/JSPS KAKENHI

Title: A correlative approach to study the *Drosophila* brain with light and electron microscopy

Authors: ***S.-J. YANG**, M. WOLF;
Okinawa Inst. of Sci. and Technol., Okinawa, Japan

Abstract: Genetically encoded tags for correlated light and electron microscopy (CLEM) had been developed to observe protein localization in different spatial resolution. *Drosophila* melanogaster is a model organism well known for its sophisticate genetic toolbox. Multiple neuronal mapping projects and structural functional analysis of individual genes or neurons have provided new insight to biomedical research. Adaptation of the CLEM tags into *Drosophila* will provide the capability to study various questions in *Drosophila* under light and electron microscopy. Here we demonstrate how the tags can be used in revealing the morphology of specific neurons in larval brains, and the arborization pattern of olfactory receptor neurons (ORNs) in antennal lobes of adult brain.

Disclosures: **S. Yang:** None. **M. Wolf:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.03

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH DC008983

NIH EY019049

Packard Fellowships for Science and Engineering

Title: Generation and characterization of STARS (stochastic gene activation with regulated sparseness) transgenic mouse line

Authors: *L. IBRAHIM[1], S.-Z. WANG[2], Y. J. KIM[1], H. W. TAO[1], L. I. ZHANG[1];
[1]USC, Los Angeles, CA; [2]UCSF, San Francisco, CA

Abstract: We generated a Cre dependent reporter mouse line that expresses GFP in a very sparse population of cells (~10% of all Cre positive neurons are labeled). The STARS (STochastic gene Activation with Regulated Sparseness) construct (Wang SZ et al., PLoS One 4(1):e4200, 2009) was inserted into the Rosa26 site using Targaat technology to generate the STARS transgenic mouse line. The construct is made such that two different pairs of lox sites are interleaved and the distance between one set of identical lox sites is very large. Due to the differential distances for the two mutually exclusive cassettes, the efficiency of Cre is geared mostly towards the Cre sites with a shorter distance, resulting in expression of GFP in only ~10% of all Cre positive cells. The STARS mice were crossed with different Cre lines to generate sparse labeling of parvalbumin (PV), vasoactive intestinal peptide (VIP), and Rbp4 positive neurons in the cortex and hippocampus. The number of labeled neurons is estimated to be 8-15% of those labeled by crossing with a traditional reporter line Ai14 (Cre dependent tdTomato expression). Taking advantage of the sparseness, we set out to examine the spiral ganglion innervation pattern, specifically of type II fibers, in the cochlea. Using the PV-ires-Cre crossed with STARS to label the spiral ganglion neurons (as well as hair cells) sparsely, we were able to trace individual type II fibers at different ages. We observed type II fiber innervation patterns different from previously thought. The STARS mouse can be used to label any cell type sparsely in a Cre dependent manner.

Disclosures: **L. Ibrahim:** None. **S. Wang:** None. **Y.J. Kim:** None. **H.W. Tao:** None. **L.I. Zhang:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.04

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: Wyss Synthetic Biology FISSEQ Grant

Title: Tracking gene expression in 3d: a look into the developing brain

Authors: *N. DONOGHUE[1,4,2], J. SCHEIMAN[1,2], J. LEE[5], Y. WANG[3,2], G. CHURCH[1,2]; [1]Dept. of Genet., [2]Wyss Inst. for Biologically Inspired Engin., [3]Program of Biol. and Biomed. Sci. at Harvard Med. Sch., Harvard Univ., Boston, MA; [4]Brown Univ., Providence, RI; [5]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: In developmental biology, methods for studying neural tube development have been limited by the inability to sequence RNA molecules as they are distributed within a cell. However, a novel technique called fluorescent *in situ* sequencing (FISSEQ) allows us to determine the spatial distribution of RNA molecules in models of neural tube formation. Using human induced pluripotent stem cells, we have successfully grown neural rosettes as an *in vitro* model for neural tube development. We applied the FISSEQ RNA library preparation methods of fixation, reverse transcription, circularization and rolling circle amplification to generate stable DNA libraries. We then performed sequencing by ligation chemistry with 35 rounds of 2-base imaging on a scanning head confocal microscope. We were able to sequence transcriptome-wide RNA molecules present in each type of cell in this developmental model. It is particularly interesting that many of our enriched hits are long non-coding RNAs, of which the functions have mostly not been identified. RNA was determined to be abundant in aggregate cells, which clearly distinguished those cells from the aggregates in which they originally neighbored. For the first time, we have demonstrated that FISSEQ can be successfully used to sequence a heterogeneous population of neural progenitor cells. Through the discovery of novel biomarkers and by presenting spatial information about the distribution of RNA, we hope to provide a new data set for the study of the developing brain.

Disclosures: **N. Donoghue:** None. **J. Scheiman:** None. **J. Lee:** None. **Y. Wang:** None. **G. Church:** Other; Please see: http://arep.med.harvard.edu/gmc/tech.html.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.05

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: NSFC 31171015

NSFC 31470820

Title: Inversion of CTCF binding sites by CRISPR alters genome topology and gene expression in the brain

Authors: *Q. WU;
Shanghai Jiao Tong Univ., Shanghai, China

Abstract: The mammalian protocadherin (Pcdh) alpha, beta, and gamma gene clusters provide a striking example of CTCF/cohesin-mediated enhancer/promoter interactions in cell-specific gene expression in the brain. The CTCF/cohesin complex plays a central role in insulator function and topological organization of mammalian genomes. Recent studies have identified a correlation between the orientation of CTCF-binding sites (CBS) and chromatin contacts. However, the functional significance of this observation has not been demonstrated. Here we developed an in-situ CRISPR inversion technology, and in conjunction with chromosome conformation capture methods, to show that the location and relative orientations of CBSs within well characterized enhancer elements in the mammalian protocadherin and beta-globin gene clusters determine the specificity of long-range DNA-looping interactions between the enhancers and target promoters. We find that inversion of the relative orientations of CBS elements re-configures the topology of DNA looping and alters the pattern of gene expression. Thus, contrary to the prevailing view that enhancer function is orientation-independent, in the context of the native chromosome enhancer orientation determines both the architecture of chromatin domains and enhancer/promoter specificity. In addition, directional CTCF binding to CBSs determines chromosome topology and enhancer insulation. This mechanism of CTCF-determined looping directions have important implications regarding chromosomal architecture and insulator functions of genome-wide CBSs in genome folding and gene regulation.

Disclosures: Q. Wu: None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.06

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: SCRM Porcine Center Grant

Title: Potent spinal parenchymal AAV9-mediated gene delivery by subpial injection in adult rats and pigs

Authors: *M. MARSALA[1], A. MIYANOHARA[1], K. KAMIZATO[1], S. JUHAS[2], M. R. NAVARRO[1], S. MARSALA[1], J. JUHASOVA[2], N. LUKACOVA[3];
[1]Dept. of Anesthesiol., UCSD, La Jolla, CA; [2]Inst. of Animal Physiol. and Genet., Czech Academy of Sciences, Czech Republic; [3]Inst. of Neurobio., Slovak Academy of Sciences, Slovakia

Abstract: The *in vivo* use of AAV-based vectors to achieve gene-specific silencing or upregulation in the CNS and spinal cord is gaining its utility in the treatment of several spinal neurodegenerative disorders including ALS, SMA, muscle spasticity and chronic pain. In general, satisfactory spinal parenchymal expression is achieved when the AAV vector is delivered intravenously or intrathecally (i.e., the delivery route with most clinical relevance) in young animals; however, in comparison, rather limited parenchymal expression is seen once AAV is delivered using the same routes in adult animals. These characteristics represent a major limitation for more effective utilization of AAV9-based therapies with a spinally targeted route of delivery once employed in adult patients. Here we demonstrate that the spinal pia mater represents the primary barrier limiting effective AAV9 penetration into the spinal parenchyma after intrathecal AAV9 delivery in adult rats and pigs. By using a novel subpial (SP) AAV delivery technique and AAV9-dextran formulation, we show: i) potent spinal parenchymal transgene expression in white and gray matter including neurons and glial cells after single bolus SP AAV9 delivery, ii) near complete descending motor axon labeling throughout the length of the spinal cord after cervical or thoracic SP AAV9 injection, iii) potent retrograde transgene expression in brain motor centers (motor cortex and brain stem), and iv) safety of this approach by defining normal neurological function for up to 3 months after AAV9 delivery. These data demonstrate that subpial AAV delivery technique in adult animals represents a highly effective delivery approach to achieve well-controlled spinal trans-parenchymal and brain motor center transgene expression and may have a wide range of experimental and clinical utilization including: i) multi-segmental white and gray matter gene over-expression or silencing, ii) upregulation of neurotrophic genes in descending motor tract to promote sprouting (after spinal trauma-induced injury, for example), and iii) specific spinal segment-restricted gene modulation to alter neuronal hyper-excitability (localized spinal injury-induced pain or muscle spasticity). The highly potent transgene expression seen in adult pig spinal cord and brain motor centers also suggests that this technique can readily be used in the clinical setting in patients receiving spinally-delivered, AAV9-mediated gene-based therapies.

Disclosures: **M. Marsala:** None. **A. Miyanohara:** None. **K. Kamizato:** None. **S. Juhas:** None. **M.R. Navarro:** None. **S. Marsala:** None. **J. Juhasova:** None. **N. Lukacova:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.07

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: Board of Governors Regenerative Medicine Institute of Cedars-Sinai

Samuel Oschin Comprehensive Cancer Institute Research Forum Award

Thrasher-Broidy Trinity College Research Fellowship

Smidt Family Foundation

Paul and Vera Guerin Family Foundation

Title: The pb-tet-goi inducible system for direct differentiation, regulated growth factor secretion, and *in vivo* identification of quiescent tumor cell populations

Authors: ***A. A. AKHTAR**, M. DUTRA-CLARKE, J. MOLINA, G. KIM, R. LEVY, W. SCHREIBER-STAINTHORP, B. SHELLEY, G. GOWING, C. SVENDSEN, M. DANIELPOUR, J. J. BREUNIG;
RMI, Cedars Sinai Med. Ctr. Regenerative Med. Inst., West Hollywood, CA

Abstract: Precise control of transgene expression is fundamentally important for the investigation of biological systems and for gene therapy in the clinic. To address this, we have created a genetic system for the stable, inducible and reversible genetic control of cell lineages derived from proliferating neural stem and progenitor cells. Specifically, we have constructed an optimized piggyBac-transposable system that integrates into the genome of proliferating cells through pBase-mediated transposition, circumventing the problems associated with plasmid dilution. The system incorporates the latest generations of tetracycline transactivators, reverse tetracycline transactivators, and variants in order to provide regulated “on” and “off” transgene expression using doxycycline (dox). This novel system termed pB-Tet-GOI (piggyBac-Tetracycline inducible system for the expression of a gene of interest) allows for precise temporal control of transgene expression in neural stem and progenitor cells both *in vitro* and *in vivo*, with robust inducibility and minimal leakiness. Furthermore, incorporation of fluorescent

protein and luciferase allows for live imaging or bioluminescent detection, respectively, of cells expressing a gene of interest *in vivo*. We have used this system to direct differentiation of human neural progenitor cells to subtype specific neurons *in vitro*, reprogram mouse olfactory bulb interneurons to projection neuron-like subtypes *in vivo*, regulate growth factor secretion *in vitro* and *in vivo*, and identify quiescent tumor cell populations after oncogene misexpression in mouse neural stem cells *in vivo*. As various transgenes can be readily introduced into the system, this approach provides a robust and versatile strategy for the temporal regulation of transgene expression *in vitro* and *in vivo*.

Disclosures: **A.A. Akhtar:** None. **M. Dutra-Clarke:** None. **J. Molina:** None. **G. Kim:** None. **R. Levy:** None. **W. Schreiber-Stainthorp:** None. **B. Shelley:** None. **G. Gowing:** None. **C. Svendsen:** None. **M. Danielpour:** None. **J.J. Breunig:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.08

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: CIHR

Ontario Research Fund

McEWEN Centre for Regenerative Medicine

Title: Culture of isolated photoreceptors in hyaluronic acid based hydrogels enables their survival and maturation *in vitro*

Authors: ***N. MITROUSIS**[1,2], R. Y. TAM[2], D. VAN DER KOOY[2], M. S. SHOICHET[2]; [1]IBBME, Shoichet Lab., Toronto, ON, Canada; [2]Univ. of Toronto, Toronto, ON, Canada

Abstract: Research into photoreceptor development and degeneration can currently only be conducted *in vivo*, due to the lack of methods for *in vitro* culture of photoreceptors. Conventional 2 dimensional (2D) culture of photoreceptors leads to massive cell death and morphological changes, that impede such studies. This project uses 3 dimensional (3D) culture of dissociated photoreceptors on hyaluronic acid (HA) - based hydrogels, to investigate the effects of the photoreceptor extracellular matrix on their survival and maturation *in vitro*. Our goal is to develop a method that will enable maintaining photoreceptors in tissue culture. We isolated rod photoreceptors by cell sorting from P11 NrlGFP mice, which express GFP under a rod

photoreceptor specific promoter. The NrlGFP+ photoreceptors were cultured in isolation in standard 2 dimensional culture or in HA-furan hydrogels, crosslinked with PEG-(maleimide)2. Survival was assessed by GFP immunofluorescence for live cells and ethidium homodimer staining for dead cells, while immunostaining was performed for the maturation markers peripherin and ABCA-4. We found that when cultured in our HA-based hydrogels, the NrlGFP+ photoreceptors exhibited significantly improved survival and expression of both maturation markers. We further assessed the mechanism of action of our hydrogels, and found that modifying stiffness over a 100-fold range, did not alter the gel effect on the photoreceptors. Experiments using hydrogels without HA, or adding soluble HA in 2D culture conditions demonstrated that our gels act through an interaction between the HA and the photoreceptors. We conclude that culture in HA-based gels enables rod photoreceptors to be maintained in culture for up to 14 days, while promoting their maturation. This effect is mediated by interactions between the HA and the photoreceptors. The signaling pathways that are activated by HA need to be investigated and may provide cues for translational research on photoreceptor degeneration.

Disclosures: **N. Mitrousis:** None. **R.Y. Tam:** None. **D. van der Kooy:** None. **M.S. Shoichet:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.09

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: NIMH-IRP 1ZIAMH002386

NIMH-IRP 1ZIAMH002592

Title: Cell lines expressing known and putative CNS-expressed Gs-coupled GPCRs for screening of compounds for translational focusing and drug discovery

Authors: ***L. E. EIDEN**[1], M. FERRER[4], C. WESTOVER[2], R. A. ALVAREZ[3], W. XU[3], S. Z. JIANG[3], A. C. EMERY[3], M. V. EIDEN[2];
[1]Sec Molec Neurosci, [2]Section on Directed Gene Transfer, [3]Section on Mol. Neurosci., NIH, NIMH-IRP, Bethesda, MD; [4]Div. Pre-clinical Innovation, Nat. Ctr. Accel Transl Sci., Rockville, MD

Abstract: G-protein coupled receptors (GPCRs) that engage Gs and adenylate cyclase activate multiple cAMP sensors to exert neuronal effects. Protein kinase A (PKA), and the guanine nucleotide exchange factors Epac2/Rapgef4 and neuritogenic cAMP sensor (NCS)/Rapgef2, in particular, mediate CREB, p38, and ERK1/2 phosphorylation, and cell survival, growth arrest, and neuritogenesis, respectively (Emery et al., J. Biol. Chem. 289:10126, 2014). Thus, drugs developed as agonists, antagonists, or biased ligands for CNS Gs-coupled GPCRs are most usefully screened for translational focusing of known and orphan putative Gs-coupled GPCRs using assays that monitor not only cAMP elevation, but also downstream activation of CREB, p38, and ERK1/2. A HEK293 cloned cell line (HEK293_CBS) expressing a luciferase split-enzyme activated by cAMP was constructed, and used to create further subclones expressing known and putative Gs-coupled GPCRs for high-throughput screening. ORFs for GPCRs and downstream luminescence-based cAMP elevation and protein kinase activation detectors were introduced into HEK293 cells via rapid, high-efficiency retroviral transduction, allowing creation of reproducible biochemical and functional cell-based read-outs, based upon physiological cellular stoichiometries of the expressed proteins. HEK293_CBS lines expressing the family B receptors PAC1hop, VPAC1, VPAC2 and GLP1R, and the family A receptors ADRB1 and ADRB2, have been created and shown to produce dose-response curves, with appropriate ligands, with sensitivity, reliability and reproducibility required for high-throughput screening. The cAMP sensor NCS/Rapgef2 is functionally expressed, and linked to ERK activation, specifically neurons and neuroendocrine cell lines (Emery et al., Sci. Signaling 6(281), ra51, 2013). The neuroendocrine cell line NS-1 was used to create sub-lines expressing ~30 of the ~70 known and putative Gs-coupled GPCRs, in which GPCR-mediated signaling. These lines have allowed the categorization of Gs-coupled GPCRs into those that do and do not activate NCS/Rapgef2, which has been linked to the action of various Gs-coupled GPCR ligands, including PACAP and dopamine, in the central nervous system. High-throughput screening of HEK293_CBS_GPCR cell lines for inhibition of ligand-dependent cAMP elevation, followed by medium throughput and high-content screening of high-throughput hits using NS-1_CBS_GPCR lines will allow assessment of the specificity and functional activity of known Gs-GPCR-directed drugs, and potential pharmacological deorphanization of CNS-expressed GPCRs of suspected importance in neuronal cellular signaling.

Disclosures: **L.E. Eiden:** None. **M. Ferrer:** None. **C. Westover:** None. **R.A. Alvarez:** None. **W. Xu:** None. **S.Z. Jiang:** None. **A.C. Emery:** None. **M.V. Eiden:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.10

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant 5R01NS075531-04

NIH Grant 5U01 MH078844-05

NSFC Grant 31471037

NSFC Grant 91432106

Title: Combinatorial genetic targeting of GABAergic neuron subpopulations in mouse neocortex

Authors: *M. HE[1,2], S. KELLY[1], J. TUCCIARONE[1], J. LEVINE[1], P. WU[1], M. NIGRO[3], I. KRUGLIKOV[3], Y. HASHIKAWA[3], S. LEE[3], Y. KIM[1], Y. HOU[2], Y. CHEN[2], A. ADLER[3], D. CAI[4], B. RUDY[3], P. OSTEN[1], W. GAN[3], J. W. LICHTMAN[5], J. R. SANES[5], Z. HUANG[1,2]; [1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Inst. of Brain Science, State Key Lab. of Med. Neurobiology, Collaborative Innovation Ctr. for Brain Science, Fudan Univ., Shanghai, China; [3]NYU Sch. of Med., New York, NY; [4]Univ. of Michigan Med. Sch., Ann Arbor, MI; [5]Mol. and Cell. Biol., Harvard Univ., Cambridge, MA

Abstract: Systematic genetic access to GABAergic neurons will facilitate studying the organization and function of cortical inhibitory circuits. However, most single gene-driven mouse recombinase lines target relatively broad GABA populations. Although combinatorial approaches are expected to improve precision, it is unclear to what extent they can capture specific cell types defined by location, morphology, and connectivity. Here we demonstrate that combinatorial strategies based on just two markers, cell lineage and birth order, and their combinations target highly restricted populations characterized by laminar location, morphology, physiologic properties, and activity pattern during behavior. Properly designed intersection and subtraction reporters and brainbow reporter enhance the precision and versatility of combinatorial drivers. Conditional viral vectors activated according to lineage progression and mature markers further capture bona fide cell types. Together these second generation tools will accelerate progress in exploring the developmental assembly and functional operation of cortical GABAergic circuits.

Disclosures: M. He: None. **S. Kelly:** None. **J. Tucciarone:** None. **J. Levine:** None. **P. Wu:** None. **M. Nigro:** None. **I. Kruglikov:** None. **Y. Hashikawa:** None. **S. Lee:** None. **Y. Kim:** None. **Y. Hou:** None. **Y. Chen:** None. **A. Adler:** None. **D. Cai:** None. **B. Rudy:** None. **P. Osten:** None. **W. Gan:** None. **J.W. Lichtman:** None. **J.R. Sanes:** None. **Z. Huang:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.11

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Pre-doctoral Training Grant 5T32 GM008541

BrightFocus Foundation

Alzheimer's Association

Massachusetts Neuroscience Consortium

Title: Characterization of TREM2-TYROBP signaling through novel real-time TREM2-TYROBP coupling reporter system with split-luciferase complementation

Authors: *M. M. VARNUM[1], G. YONEMOTO[1], H. ASAI[1], T. IKEZU[1,2];
[1]Dept. of Pharmacol. and Exptl. Therapeut., Boston Univ., Boston, MA; [2]Dept. of Neurol., Boston Univ. Sch. of Med., Boston, MA

Abstract: Triggering receptor expressed on myeloid cells 2 (TREM2) is expressed on myeloid cells, including microglia and macrophages. It couples to the adaptor protein TYRO protein tyrosine kinase binding protein (TYROBP/DAP12) for reorganization of the actin cytoskeleton to endocytose phagocytosed apoptotic bodies. Mutations in TREM2 are associated with the rare Nasu-Hakola disease, frontotemporal lobar degeneration (FTLD), Alzheimer's disease (AD), Parkinson's disease, and amytrophic lateral sclerosis. These mutations are associated with reductions in TREM2 processing and induction of phagocytosis *in vitro* as well as increases in the release of proinflammatory cytokines. This may be the cause of reduced clearance of amyloid and apoptotic bodies in AD, leading to increased inflammation and secondary necrosis due to build-up of apoptotic debris. To develop a high throughput screening modality for real-time monitoring of TREM2 signaling *in vitro*, we developed a construct by utilizing split-luciferase complementation technology and fusing the C-terminal region of the Renilla luciferase gene to the cytoplasmic region of TREM2, and the N-terminal region of the luciferase gene to the C-terminal region of TYROBP (TREM2-CLuc-TYROBP-NLuc) with an internal ribosomal entry site (IRES) in the same vector. We show that transient transfection of HEK293 cells with our TREM2-CLuc-TYROBP-NLuc construct successfully reconstitutes luciferase activity up to 10-fold when cells are stimulated with a TREM2 antibody, indicating TREM2 activation and coupling to TYROBP. We also measured the effects of stimulation with amyloid-β (Aβ) peptide and anti-TYROBP antibody. We then incorporated the AD- and FTLD-associated mutations, R47H, T66M, and S116C and measured their luciferase activity in response to antibody stimulation, as well as Aβ and anti-TYROBP antibody. T66M TREM2 mutation enhanced

TYROBP coupling independent of TREM2 antibody stimulation, indicating that this mutation elicits constitutive coupling to TYROBP. Flow cyometry for both surface and intracellular TREM2 expression show a reduction in surface, but not intracellular TREM2 when the T66M mutation is present. These results demonstrate that our TREM2-CLuc-TYROBP-NLuc construct is a novel tool for measuring the TREM2-TYROBP interaction in real-time and will be utilized for biological studies and drug screening of complex molecules for the treatment of TREM2-associated neurodegenerative disorders.

Disclosures: **M.M. Varnum:** None. **G. Yonemoto:** None. **H. Asai:** None. **T. Ikezu:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.12

Topic: G.01. Molecular, Biochemical, and Genetic Techniques

Support: Celavie Biosciences Inc.

Title: A phase I clinical trial of intraputaminal transplantation of human fetal-derived stem cells (hfSC) in patients with advanced Parkinson´s Disease: six-month follow-up

Authors: ***I. MADRAZO**[1], O. KOPYOV[2], M. AVILA-RODRIGUEZ[3], H. CARRASCO[4], F. OSTROSKY[3], F. JIMENEZ[1], R. RIVERA[1], R. FRANCO-BOURLAND[5], T. VALENZUELA[6], A. KOPYOV[2], C. ZAMORANO[6], E. MAGALLÓN[6], F. PALMA[7], G. GUIZAR[8];
[1]Hosp. Ángeles Del Pedregal, Mexico DF, Mexico; [2]Celavie Biosci. Inc., Los Angeles, CA; [3]Univ. Nacional Autonoma de Mexico, Mexico City, Mexico; [4]Hosp. Central Militar, Mexico City, Mexico; [5]Biochemestry, Inst. Nacional de Rehabilitación, Mexico City, Mexico; [6]Neurosurg., [7]Anesthesiol., Inst. Mexicano del Seguro Social, Mexico City, Mexico; [8]Neurobio., Camina Lab., Mexico City, Mexico

Abstract: We report the six-month follow-up of seven patients (2f, 5m, 43-75y, mean 55y) with Parkinson´s Disease (PD) after transplantation of the hfSC. Stem cells were derived from a fetal brainand manufactured according to GMP requirements. They express Oct-4, SOX-2, SSEA4, Nanog and do not produce tumors in immunodeficient animals. No clinical, radiological or serological signs of immune reaction or infection were observed. All patients received hfSC bilaterally into the putamen. Clinical follow-up included evaluations with UPDRS; Schwab & England; and Hoehn&Yahr scales, and a neuropsychological test battery. UPDRS and neuropsycological evaluations were performed during on and off medication conditions.

Additionally, patients were examined with Positron Emission Tomography (PET) using 3 radiopharmaceuticals to evaluate presynaptic and postsynaptic dopaminergic function at baseline and six month after transplantation. Radiopharmaceuticals evaluated were [11C]DTBZ, [11C]Raclopride (RAC) and [18F]FDOPA. All patients underwent DTBZ-PET scans and one additional study with either FDOPA or RAC, at least one week apart. Parametric images of non-displaceable binding potential (BPND) and distribution volume ratio (DVR) were generated using a reference tissue model.At six months after surgery, neurological evaluations have shown a gradual but consistent decrease in UPDRS part II and III scores with no evidence of any motor complications, and a trend of improvement in the daily living activities scales. Similarly, an amelioration of the frontal motor signs, depressive symptomatology and a slight improvement in memory tasks which required an active organization of the response was observed in the neuropsychological evaluations, while verbal fluency, immediate memory and retrieval difficulties remained unchanged. Statistical parametric mapping (SPM) demonstrated a gradual but statistically significant ($p<0.0001$) decreased RAC uptake in the putamen of the 4 patients evaluated with this radioligand, suggesting an ongoing restoration of postsynaptic dopaminergic function. DTBZ scans showed also a trend of improvement, but even though some patients show an increased uptake in the putamen, changes are not statistically significantgiven its lower sensitivity to small changes, similarly to FDOPA evaluations.One interesting finding inneurological and PET evaluations is that patients with a more advanced disease tend to improve more than less affected patients. In summary, the preliminary results of this phase I clinical trial show a trend of improvement with no evidence of side effects or progression of the disease, which warrant a phase II study.

Disclosures: **I. Madrazo:** None. **O. Kopyov:** None. **M. Avila-Rodriguez:** None. **H. Carrasco:** None. **F. Ostrosky:** None. **F. Jimenez:** None. **R. Rivera:** None. **R. Franco-Bourland:** None. **T. Valenzuela:** None. **A. Kopyov:** None. **C. Zamorano:** None. **E. Magallón:** None. **F. Palma:** None. **G. Guizar:** None.

Nanosymposium

471. Molecular, Biochemical, and Genetic Techniques

Location: N227

Time: Tuesday, October 20, 2015, 8:00 AM - 11:15 AM

Presentation Number: 471.13

Topic: D.09. Tactile/Somatosensory Systems

Support: NIH Grant F32NS087860

NIH Grant F31DC013240

NIH Grant R01-NS050835

Title: Connectivity of mouse somatosensory and prefrontal cortex examined with transsynaptic tracing

Authors: *L. A. DENARDO[1], D. S. BERNS[1,2], K. DELOACH[1], L. LUO[1,3];
[1]Biol., Stanford Univ., Stanford, CA; [2]Neurosciences Grad. Program, Stanford, CA; [3]Howard Hughes Med. Inst., Stanford, CA

Abstract: Information processing in neocortical circuits requires integrating inputs over a wide range of spatial scales, from local microcircuits to long-range cortical and subcortical connections. We used rabies-based transsynaptic tracing to analyze the laminar distribution of local and long-range inputs to pyramidal neurons in the mouse barrel cortex and medial prefrontal cortex (mPFC). In barrel cortex, while confirming synaptic connections previously identified via electrophysiological methods, we observed significant inputs from layer 3 (L3) to L6 and prevalent translaminar inhibitory inputs. We also observed long-range inputs to barrel cortex L2/3 or L5/6 preferentially from L2/3 or L5/6, respectively, of other cortical areas in the sensorimotor network. These layer-specific input patterns are largely independent of NMDA receptor function in the recipient neurons. mPFC L5 received proportionally more long-range inputs and more local inhibitory inputs than barrel cortex L5. These results provide new insight into the organization and development of neocortical networks and identify important differences in the circuit organization in sensory and association cortices.

Disclosures: **L.A. DeNardo:** None. **D.S. Berns:** None. **K. DeLoach:** None. **L. Luo:** None.

Nanosymposium

555. Sigma Receptors: Emerging Roles in Health and Disease

Location: S405

Time: Tuesday, October 20, 2015, 1:00 PM - 3:15 PM

Presentation Number: 555.01

Topic: B.04. Ion Channels

Support: NIH Grant AG037337

NIH Grant AG047059

NIH Grant NS083175

ADDF grant 20100501

Alzheimer's Research UK

Title: Selective antagonists of the sigma-2/PGRMC1 receptor displace Abeta oligomer receptor binding in Alzheimer's disease

Authors: *N. J. IZZO, JR[1], T. M. SPIRES-JONES[2], R. YURKO[3], C. HENSTRIDGE[2], C. SILKY[3], C. REHAK[3], K. MOZZONI[3], G. LOOK[3], G. RISHTON[3], H. SAFFERSTEIN[3], S. M. CATALANO[3];
[1]Cognition Therapeut., Pittsburgh, PA; [2]Univ. of Edinburgh, Edinburgh, United Kingdom; [3]Cognition Therapeut. Inc., Pittsburgh, PA

Abstract: Soluble oligomers of Amyloid beta cause synaptotoxicity-related cognitive dysfunction in Alzheimer's disease (AD). Specific receptors mediate saturable oligomer binding to neuronal synapses, and reducing the binding of Abeta oligomers to surface receptors represents a tractable approach to disease modification in AD. We have discovered novel antagonists of a receptor not previously associated with AD (sigma-2/PGRMC1). We sought to define the role of this receptor in mediating Abeta oligomer binding and resultant synaptotoxicity. Knockdown of sigma-2/PGRMC1 (progesterone receptor membrane component 1) protein expression *in vitro* using siRNA results in a highly correlated reduction in binding of exogenous Abeta oligomers to neurons of more than 90%. Expression of sigma-2/PGRMC1 protein is upregulated *in vitro* by treatment with Abeta oligomers, and is dysregulated in Alzheimer's disease patients' brain vs. age-matched, normal individuals. Specific, high affinity small molecule receptor antagonists can displace synthetic Abeta oligomer binding to synaptic puncta *in vitro* and reverse the effects of Abeta oligomers on membrane trafficking and synapse loss *in vitro* and cognitive deficits in AD mouse models. Displacement Abeta oligomers from human AD brains was examined by incubating ex-vivo, fresh frozen tissue sections of human AD donor brains with 0.1 to 10 uM of a selective sigma-2/PGRMC1 antagonist for 1 hr at RT. Immuno-labeling for Abeta was decreased in Thio-S labeled dense-core plaques and in a 2 micron oligomer-enriched region surrounding those plaques in a concentration-dependent manner with two different antagonists of sigma-2/PGRMC1, CT1344 and CT1812. Western blot analysis of the material eluted the human brain tissue by CT1812 revealed a consistent pattern of discrete oligomeric species of Abeta ranging from 22 to 85 Kd. CT1812 increased the amount of the Abeta oligomers displaced from the tissue in a concentration dependent manner. These findings suggest sigma-2/PGRMC1 receptors mediate saturable oligomer binding to synaptic puncta on neurons and that brain penetrant, small molecules can displace endogenous and synthetic oligomers and improve cognitive deficits in AD models. We propose that sigma-2/PGRMC1 is a key mediator of the pathological effects of Abeta oligomers in AD and is a tractable target for small molecule disease-modifying therapeutics.

Disclosures: **N.J. Izzo:** A. Employment/Salary (full or part-time); Cognition Therapeutics. **T.M. Spires-Jones:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Cognition Therapeutics. **R. Yurko:** A. Employment/Salary (full or part-time);

Cognition Therapeutics Inc. **C. Henstridge:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Cognition Therapeutics. **C. Silky:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **C. Rehak:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **K. Mozzoni:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **G. Look:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **G. Rishton:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **H. Safferstein:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **S.M. Catalano:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc..

Nanosymposium

555. Sigma Receptors: Emerging Roles in Health and Disease

Location: S405

Time: Tuesday, October 20, 2015, 1:00 PM - 3:15 PM

Presentation Number: 555.02

Topic: B.04. Ion Channels

Support: Cognition Therapeutics, Inc

NIA AG037337,

NIA AG047059

NINDS NS083175

Alzheimer's Drug Discovery Foundation 20100501

Title: Sigma-2/PGRMC1 antagonist CT1812 displaces Abeta oligomer binding and improves cognitive performance in aged Alzheimer’s transgenic mice

Authors: *C. SILKY, N. J. IZZO, C. REHAK, R. YURKO, K. MOZZONI, G. RISHTON, G. LOOK, H. SAFFERSTEIN, S. M. CATALANO;
Cognition Therapeut. Inc, Pittsburgh, PA

Abstract: We have identified a sigma-2/PGRMC1 receptor antagonist that displaces Abeta oligomers from neuronal receptors and reverses synapse loss *in vitro* and restores cognition in a mouse AD model. Behavioral studies were conducted in transgenic. Transgenic mice (Thy1-hAPPLond/Swe+ male mice 3.5-4.5 months of age) or wild-type (WT) littermates were administered vehicle (5% DMSO, 5% solutol in phosphate buffered saline) or CT1812 once daily by oral gavage at 10 mg/kg/day for 9-10 weeks in two separate studies (N = 12/13

animals/group). Several behavioral tests of cognitive function were performed in each study at the same intervals following study start: Y-Maze Fear Conditioning, and Morris Water Maze (measuring spatial memory). Drug concentrations in the plasma and brain and histopathological analysis were determined at study completion. Treatment of WT animals with CT1812 did not significantly alter motor behavior or other observable behaviors, and did not change their cognitive performance vs. WT vehicle-treated animals in either study. Treatment with CT1812 improved transgenic animal spatial working memory in the Y-Maze, cue- and context-dependent learning and memory in the Fear Conditioning assay and spatial learning and memory in the Morris Water Maze. WT animals treated with CT1812 had average trough plasma concentrations of 26.6 ng/mL (54.7 nM) and corresponding brain concentrations of 15.4 ng/g (35.6 nM), while transgenic APP+ animals treated with CT1812 had average trough plasma concentrations of 27.7 ng/mL (64.2 nM) and corresponding brain concentrations of 19.9 ng/g (46.0 nM). This translates to estimated receptor occupancy at sigma-2/PGRMC1of 81% and 84% respectively. This is consistent with previous studies (Izzo et al., PLOSONE 2014) demonstrating that brain concentrations of related sigma-2/PGRMC1 antagonists corresponding to greater than 80% estimated receptor occupancy improved cognitive function in transgenic animals, whereas concentrations corresponding to 50% receptor occupancy did not. Histopathological analysis of tissue indicated no signs of toxicity in any group. Taken together, this study indicates that treatment with CT1812 effectively improved several of the cognitive deficits detected in this experimental model of AD at a dose that was without obvious behavioral or histopathologic signs of toxicity. CT1812 is thus a promising disease-modifying Alzheimer' therapeutic.

Disclosures: **C. Silky:** A. Employment/Salary (full or part-time); Cognition therapeutics. **N.J. Izzo:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **C. Rehak:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **R. Yurko:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **K. Mozzoni:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **G. Rishton:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **G. Look:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **H. Safferstein:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **S.M. Catalano:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc.

Nanosymposium

555. Sigma Receptors: Emerging Roles in Health and Disease

Location: S405

Time: Tuesday, October 20, 2015, 1:00 PM - 3:15 PM

Presentation Number: 555.03

Topic: B.04. Ion Channels

Title: Sigma-2 receptor 18 kDa and PGRMC1 are distinct gene products

Authors: ***A. E. RUOHO**[1], T. A. MAVLYUTOV[2], U. B. CHU[1], M. CHU[2], L. ZHAO[2], H. YANG[2], C. R. MCCURDY[3], L.-W. GUO[2];
[1]Neurosci., Univ. of Wisconsin, Madison, WI; [2]Surgery, Univ. of Wisconsin, Madison, Madison, WI; [3]BioMolecular Sci., Univ. of Mississippi, Oxford, MS

Abstract: The Sigma-2 Receptor (S2R) is highly expressed in the Central Nervous System (CNS) (eg; in retina and motor areas of the brain) and in tumors. The progesterone receptor membrane component 1 (PGRMC1), a 25 kDa protein, has been recently reported to be the S2R. Historically, the identity of S2R has been pharmacologically defined by the following characteristics: (1) the affinity of progesterone for the S2R-18 kDa is very low; 2) the S2R binds with high affinity to 1,3-di-o-tolylguanidine (DTG) (Kd = 50-100 nM and haloperidol (Kd = 10-20 nM) but not to the Sigma-1 Receptor ligand, (+)-pentazocine ; (3) The apparent size of S2R, when specifically photolabeled with [3H]Azido-DTG or [125I]-iodoazidofenpropimorph ([125I]IAF) is in the range of 18kDa. The following data differentiate the S2R-18 kDa from PGRMC-1: 1) Progesterone affinity for PGRMC1 has been reported to be 35 nM, while the Ki of progesterone for S2R-18Kda is 10 μmolar (approximately 300 times higher); 2) The binding constant for DTG to PGRMC1 (Ki = 5 - 25 μmolar) is 100 - 250 times lower affinity than to the S2R18 kDa (Ki = 50-100 nM); 3) In NSC34 cells devoid of PGRMC1 (Knock out cells using CRISPR/Cas9 technology) the maximum binding (Bmax) of haloperidol protectable high affinity [3H]-DTG binding (Ki = 50-100 nM) was similar to that of wild-type control cells indicating no effect of PGRMC1 removal. Further, NSC34 cells overexpressing PGRMC1 did not show an increase of [3H]-DTG binding; 4) In both control and PGRMC1-KO cells, [125I]-IAF selectively photolabeled the DTG protectable S2R- 18kDa protein. 5) A series of previously reported highly selective S2R compounds showed selective protection of [125I]-IAF photolabeling of the S2R-18kDa in PC12 cell membranes that contain both PGRMC1 and S2R-18kDa. These results support the conclusion that PGRMC1 and S2R-18kDa are separate gene products. Cloning and characterization of the S2R-18kDa will provide further clarification.

Disclosures: **A.E. Ruoho:** None. **T.A. Mavlyutov:** None. **U.B. Chu:** None. **M. Chu:** None. **L. Zhao:** None. **H. Yang:** None. **C.R. McCurdy:** None. **L. Guo:** None.

Nanosymposium

555. Sigma Receptors: Emerging Roles in Health and Disease

Location: S405

Time: Tuesday, October 20, 2015, 1:00 PM - 3:15 PM

Presentation Number: 555.04

Topic: B.04. Ion Channels

Support: NIH NIGMS Grant 5T32GM077995

NIH NIGMS Grant R25GM083270

Title: Factors that affect sensitivity to sigma-2 receptor-mediated cell death in human SK-N-SH neuroblastoma

Authors: *Z. LIU, H. E. NICHOLSON, E. SAVOCA, W. D. BOWEN;
Mol. Pharmacol. and Physiol., Brown Univ., Providence, RI

Abstract: Sigma-2 receptors are highly expressed in various tumor cell lines and are more highly upregulated in proliferative than in quiescent cells. Sigma-2 receptor agonists induce apoptotic cell death. Here, we examine the effect of cell type, cell confluence at the time of harvest, and cell plating density on the cytotoxic potency of various sigma-2 agonists (siramesine, CB-64D, and CM572). We have observed that neuronal cell types appear to be generally more sensitive than non-neuronal cell types. To examine differences in sensitivity to siramesine in various cell types with the same origin (SK-N-SH) but with different phenotypes, we purified the heterogeneous SK-N-SH population into neuronal-like and epithelial-like populations and determined cytotoxic dose-response with the MTT assay. Siramesine EC50 values in SK-N-SH parental line (mixed phenotype), SK-N-SH purified neuronal-like, SH-SY5Y thrice cloned neuronal type, SK-N-SH purified epithelial cells, and SH-EP epithelial subclone ranged 6.46 - 14.8 μM, with the neuronal types being only modestly more sensitive. Thus, there was not a large effect of cell phenotype. Sensitivity to sigma-2 agonists also appears to vary with cell confluency, an effect likely due to proliferative state. To examine SK-N-SH cell sensitivity to sigma-2 agonists, we varied two parameters: cell confluence at the time of harvest (cells harvested upon reaching 60% confluency or cells harvested after remaining at 100% confluency for 3 days) and cell plating density (low: 7,000, medium: 15,000, or high: 30,000 cells/well). Cells were treated with sigma-2 agonist 24 hours after plating. We found that both 100% cell confluence at the time of harvest and higher cell plating density decrease sensitivity to CB-64D. Interestingly, EC50 values for CM572 (an irreversible sigma-2 agonist) for cells harvested at 60% confluence were similar regardless of cell plating densities (μM): 4.92, 7.6, and 6.06 for cells plated at low, medium, and high densities, respectively. In contrast, CM572 EC50 values for cells harvested at 100% confluence for 3 days were significantly dependent on plating density (μM): 17.62, 35.33, and >50 for cells plated at low, medium, and high densities, respectively. Therefore, sensitivity to CM572 only decreases after the cells are confluent for 3 days at 100%. Taken together, these results show that sensitivity of SK-N-SH cell cultures to sigma-2 agonists is not dependent on cell type. Cell density over longer time periods plays a stronger role, suggesting possible downregulation of sigma-2 receptors related to SK-N-SH cells transitioning from a proliferative to quiescent state.

Disclosures: **Z. Liu:** None. **H.E. Nicholson:** None. **E. Savoca:** None. **W.D. Bowen:** None.

Nanosymposium

555. Sigma Receptors: Emerging Roles in Health and Disease

Location: S405

Time: Tuesday, October 20, 2015, 1:00 PM - 3:15 PM

Presentation Number: 555.05

Topic: B.04. Ion Channels

Support: NIH Grant GM086192

Title: Development of novel therapeutics targeting Sig2R/PGRMC1 for Alzheimer's disease

Authors: J. J. SAHN[1], *L. L. SCOTT[2], G. ZUNIGA[2], P. SATARASINGHE[2], T. WONG[2], P. M. ARDESTANI[4], J. PIERCE-SHIMOMURA[3], M. SHAMLOO[5], S. F. MARTIN[1]; [1]Chem., [2]Waggoner Ctr. for Alcohol and Addiction Res., [3]Ctr. for Learning and Memory, The Univ. of Texas at Austin, Austin, TX; [4]Stanford Behavioral and Functional Neurosci. Lab., [5]Neurosurg., Stanford Univ., Palo Alto, CA

Abstract: Alzheimer's disease (AD) is a devastating health disorder that eventually robs afflicted individuals of all memory and the ability to function independently. Despite extensive efforts directed toward developing drugs to treat this debilitating disease, the only approved medications merely provide transient symptomatic relief for a subset of patients; they do not treat the underlying causes of AD or alter its progression. *There is thus an urgent and unmet need for the discovery and development of more effective drugs to treat those suffering from AD.* It is thus significant that we recently discovered that small molecule antagonists of sigma 2 receptor/progesterone receptor membrane component 1 (Sig2R/PGRMC1) reduce cholinergic neuron death in a *C. elegans* model of neurodegeneration; gene knock-out and RNAi experiments confirmed that neuroprotection is mediated through a Sig2R/PGRMC1 pathway. We subsequently identified a lead Sig2R/PGRMC1 antagonist that achieves excellent murine brain exposure and rescues cognitive deficits in a transgenic AD mouse model. Importantly, no signs of toxicity were observed when our lead was administered to transgenic mice daily for 60 days. Moreover, the maximum tolerated dose was determined to be ten times that of the dose used in preliminary experiments to enhance cognition. Collectively, these data suggest that Sig2R/PGRMC1 can be targeted to mitigate the effects of neurodegenerative pathways and that small molecule antagonists of Sig2R/PGRMC1 may be developed as potential neuroprotective and nootropic agents for use as therapeutics for age-related neurodegenerative diseases.

Disclosures: **J.J. Sahn:** None. **L.L. Scott:** None. **G. Zuniga:** None. **P. Satarasinghe:** None. **T. Wong:** None. **P.M. Ardestani:** None. **J. Pierce-Shimomura:** None. **M. Shamloo:** None. **S.F. Martin:** None.

Nanosymposium

555. Sigma Receptors: Emerging Roles in Health and Disease

Location: S405

Time: Tuesday, October 20, 2015, 1:00 PM - 3:15 PM

Presentation Number: 555.06

Topic: B.04. Ion Channels

Support: CA 102869

P50 AG05681

Title: Quantitative autoradiography analysis of Sigma-1 and Sigma-2 receptor densities in striatal and extra-striatal regions of the aged human brain

Authors: ***J. XU**[1], J. SUN[1], N. CAIRNS[2], J. PELMUTTER[2], N. NIZZO[3], S. CATALANO[3], R. MACH[4];
[1]Radiology, [2]Neurol., Washington Univ. Sch. of Med., Saint Louis, MO; [3]Cognition Therapeut. Inc., Pittsburgh, PA; [4]Radiology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: *N*-[4-(3,4-dihydro-6,7-dimethoxyisoquinolin-2(1H)-*yl*)butyl]-2-methoxy-5-methyl-benzamide (**RHM-1**), a conformationally-flexible benzamide analogue, have been shown to have high affinity and selectivity for sigma-2 receptor versus sigma-1 receptor and the dopamine D_2 and D_3 receptors (*Bioorg. Med. Chem. Lett.* **2004**: 14; 195-202, *Eur. J. Pharmacol*. **2005**; 525: 8-17). Its high sigma-2 receptor affinity (K_i <10 nM) and selectivity (sigma-1: sigma-2 ratio > 300) indicates that it may be a useful radioligand to assess the sigma-2 receptors in the brain. Therefore, **RHM-1** was radiolabeled with tritium (specific activity = 80 Ci/mmol) and the binding of [^{3}H]**RHM-1** to Sigma-2 receptors of aged human brain tissue was evaluated *in vitro*. Saturation binding studies showed that [^{3}H]**RHM-1** has a high sigma-2 receptor binding affinity, with a dissociation constant (K_d) of ~7.1 nM to human postmortem brain sections. Sigma-1 receptor selective radioligand [^{3}H]pentazocine was evaluated and used for determining the sigma-1 receptor binding densities in different brain regions. We found that [^{3}H]pentazocine has a K_d value of ~4 nM for binding to fontal neocortex. The sigma-1 and sigma-2 receptor densities in striatal and extra-striatal regions of 11 congnitively normal aged human brains (age range: 77 to 107 years) were measured. The sigma-1 and sigma-2 receptors are found to be extensively distributed in different brain regions, sigma-2 density is about two-fold higher than sigma-1

receptor density in most brain regions: frontal cortex, precommissural caudate and putamen, postcommissural caudate and putamen, nucleus accumbens, globus pallidus, thalamus and substantial nigra, with the exception of red nucleus where sigma-1 and sigma-2 densities are equal. The binding densities in red nucleus for both sigma-1 and sigma-2 are lower than the other regions mentioned above. The high binding density of sigma-2 receptor in the aged brains suggests that sigma-2 receptor may play an important role in the brain disorders such as Alzheimer and Parkinson diseases.

Disclosures: **J. Xu:** None. **J. Sun:** None. **N. Cairns:** None. **J. Pelmutter:** None. **N. Nizzo:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc. **S. Catalano:** A. Employment/Salary (full or part-time); Cognition Therapeutics Inc.. **R. Mach:** None.

Nanosymposium

555. Sigma Receptors: Emerging Roles in Health and Disease

Location: S405

Time: Tuesday, October 20, 2015, 1:00 PM - 3:15 PM

Presentation Number: 555.07

Topic: B.04. Ion Channels

Support: NIH NIGMS IMSD R25GM083270

Brown University Upjohn Professorship in Pharmacology

NIH NIDA R01DA023205

Title: A potential neuroprotective function for the sigma-2 receptor

Authors: ***H. E. NICHOLSON**[1], C. MESANGEAU[2], C. R. MCCURDY[2], W. D. BOWEN[1]; [1]Mol. Pharmacology, Physiology, and Biotech., Brown Univ., Providence, RI; [2]Sch. of Pharm., Univ. of Mississippi, University, MS

Abstract: Sigma-2 receptors are pharmacologically defined membrane bound receptors that are highly upregulated in rapidly proliferating cancer cells as compared to non-cancerous tissues. Recently, a relationship to PGRMC1 has been proposed. When activated, sigma-2 receptors induce apoptotic cell death, and have thus been of interest as targets for novel anticancer agents or as mediators of neurodegenerative disease. However, this role of promoting cell death is incongruous with the overexpression of sigma-2 receptors in cancer cells, indicating that our understanding of the function of this receptor is incomplete. We previously reported that CM769, an isothiocyanate derivative of the well-characterized sigma-2 receptor antagonist SN79, had the unusual effect of stimulating MTT reduction in SK-N-SH neuroblastoma cells (Nicholson et al.,

Soc. Neurosci. Abstr. #299.17, 2014). We have subsequently determined that the active compound was actually a degradation product of CM769. Here we report characterization of CM764 (sigma-2 Ki=3.5 nM with greater than 10-fold selectivity over sigma-1), which has revealed a novel stimulative and potentially neuroprotective function for the sigma-2 receptor. As compared to untreated cells, treatment of SK-N-SH neuroblastoma cells with 10 uM CM764 resulted in increased mitochondrial reduction of MTT without corresponding proliferation. This effect could be attenuated by 30 uM SN79 and low-dose (0.3 uM) CM572, indicating a sigma-2-mediated effect. Additionally, treated cells demonstrated a trend towards increased production of NAD+, NADH, and ATP. These data together indicate that the sigma-2 receptor may play a role in supporting cellular metabolism. Furthermore, when cells were exposed to 50 uM DCFDA, treatment with 10 uM CM764 caused a marked reduction in reactive oxygen species that exceeded the antioxidant properties of 200 ug/mL alpha-tocopherol. Taken together, this data suggests a role for the sigma-2 receptor in promoting cell survival and a potential avenue for neuroprotection. This supports our previously presented hypothesis of a dual role of the sigma-2 receptor in both promotion and prevention of apoptosis, dependent on the mode of activation (Garcia and Bowen, Soc. Neurosci. Abstr. #470.17, 2010). CM764 and related compounds with sigma-2-mediated stimulative activity will be useful tools in investigating this novel function of the sigma-2 receptor and its potential role in neuroprotection.

Disclosures: H.E. Nicholson: None. **C. Mesangeau:** None. **C.R. McCurdy:** None. **W.D. Bowen:** None.

Nanosymposium

555. Sigma Receptors: Emerging Roles in Health and Disease

Location: S405

Time: Tuesday, October 20, 2015, 1:00 PM - 3:15 PM

Presentation Number: 555.08

Topic: B.04. Ion Channels

Title: The controversial identity of the sigma-2 receptor with PGRMC1: is the PGRMC1/sigma-2 protein, that binds Abeta oligomer, made of two independent molecular entities?

Authors: C. ABATE[1], M. NISO[1], M. L. PATI[1], *N. A. COLABUFO[2,1], F. BERARDI[1]; [1]Dept. di Farmacia-Scienze del Farmaco, Univ. degli Studi di Bari, Bari, Italy; [2]Dept. di Farmacia-Scienze del Farmaco-Università degli Studi di Bari, Biofordrug S.r.L., Bari, Italy

Abstract: Sigma-2 receptors are intriguing targets under study for their involvement in tumors and neurodegenerative diseases. However, the ‘sigma enigma’ is not over yet, with controversies about sigma-2 receptor identity. In one of the last attempts for the characterization, the

identification of the sigma-2 protein with the progesterone receptor membrane component 1 (PGRMC1) was proposed and generally accepted. Recently, the so-called PGRMC1/sigma-2 protein was identified as a neuronal receptor for Abeta oligomers binding, with Abeta oligomers behaving as 'regular' ligands at such proteins. Very importantly, a few sigma-2 receptor antagonists were able to displace synthetic Abeta oligomers from synaptic puncta, as well as human Abeta oligomers from brain sections of Alzheimer's disease (AD) patients, in a dose-dependent manner. *In vivo*, these compounds showed to reverse cognitive deficits restoring memory and sustaining long-term improvement in AD mice models. Starting from the consideration that PGRMC1 and sigma-2 are the same molecular entity, the PGRMC1/sigma-2 protein involvement in these activities was demonstrated by radioactive sigma-2 ligand binding together with PGRMC1 silencing. Nevertheless, we feel that the clear identification of the proteins involved in the described effects is crucial for future development of AD disease-modifying therapies. With this perspective, we verified how the expression of sigma-2 receptor is independent of PGRMC1 expression by western blotting and Scatchard analyses. Such assays were perfomed on human breast adenocarcinoma MCF7 cells where sigma-2 receptors were constitutively present, and where PGRMC1 was alternatively silenced or overexpressed. In addition, the sigma-2 mediated activity, which was studied through sigma-2 agonists, was independent of the presence and amount of PGRMC1. In order to further investigate the connection between sigma-2 and PGRMC1, the profiling of these proteins in a number of cell lines is in progress. Confocal microscopy and flow-cytometry studies employing sigma-2 fluorescent tracers are undergoing in cell lines where PGRMC1 is silenced, overexpressed and/or constitutively present. Results from this work will contribute to clarify the controversial relationship between sigma-2 and PGRMC1, so that unbiased research focused on these targets for the development of AD-modifying agents may be conducted.

Disclosures: C. Abate: None. **M. Niso:** None. **M.L. Pati:** None. **N.A. Colabufo:** None. **F. Berardi:** None.

Nanosymposium

555. Sigma Receptors: Emerging Roles in Health and Disease

Location: S405

Time: Tuesday, October 20, 2015, 1:00 PM - 3:15 PM

Presentation Number: 555.09

Topic: B.04. Ion Channels

Title: PGRMC1 expression correlates with the sigma-2 fluorescent probe (SW120) staining in rat hippocampus cells

Authors: *R. H. MACH, C. ZENG, N. GARG, B. LIEBERMAN;
Radiology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Progesterone receptor membrane component 1 (PGRMC1) is a cytochrome-related protein. The PGRMC1 protein complex was previously identified as the putative sigma-2 receptor binding site. The sigma-2 receptor/PGRMC1 has been primarily characterized as a biomarker for measuring cell proliferation in tumors. However, PGRMC1 is also present in the central nervous system (CNS) and is responsible for axon path finding in zebrafish and mediates progesterone-elicited neuroprotective effects. Recently, it was reported that PGRMC1 is a potential receptor for amyloid-β (Aβ) oligomers in rat primary neurons, and sigma-2 receptor antagonists block the binding of Aβ oligomers in neurons and reduce Aβ-induced neuronal toxicity. These findings indicate that the PGRMC1 plays an important role in the CNS. However, the molecular and cellular mechanisms of sigma-2 receptor/PGRMC1 in normal brain and neurological disorders such as Alzheimer's disease (AD) are largely unknown. In order to better understand the biological function of this protein complex in the CNS, we examined PGRMC1 protein levels by immunohistochemistry and Western blot analysis in rat primary cultures of neurons, astrocytes, oligodendrocytes and microglia cells of E18 rat hippocampus. We also examined the sigma-2 receptor binding using a sigma-2 fluorescent probe (SW120) in the same primary cell types. Our data show that the expression of PGRMC1 and SW120 staining are prominent in neurons, moderate in oligodendrocytes and microglia cells, and low in astrocytes. In dual labeling studies, there was a linear correlation between PGRMC1 protein expression levels and SW120 uptake. These results indicate that PGRMC1 expression levels correlate with sigma-2 receptor densities in four different rat brain cell types, supporting our previous finding that PGRMC1 is associated with the sigma-2 receptor binding site. The results also suggest that the sigma-2 receptor radiotracers can potentially be used to noninvasively image neuron/synapse densities in human CNS with positron emission tomography (PET).

Disclosures: **R.H. Mach:** F. Consulting Fees (e.g., advisory boards); Cognition Therapeutics. **C. Zeng:** None. **N. Garg:** None. **B. Lieberman:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.01

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Agence Nationale pour la Recherche (ANR-08-MNP-039, ANR-12-BLAN-SVSE2-HURIT

DIM-NeRF Ile de France

Fondation pour la Recherche Médicale (FRM, équipe labellisée, F.S.

NIH/NINDS (J.Bo.)

Association pour la Recherche sur le Cancer

Title: Proteolysis of huntingtin releases non-polyQ fragments that cause death through dynamin 1 dysregulation

Authors: *F. SAUDOU[1], M.-T. ELDAHER[1], E. HANGEN[1], J. BRUYERE[1], I. AL-RAMAHI[2], G. POIZAT[1], C. MAYET[3], N. BOURG[3], S. LEVEQUE-FORT[3], J. BOTAS[2], S. HUMBERT[1]; [1]Grenoble Inst. of Neuroscience, GIN, La Tronche, France; [2]Dept. of Mol. and Human Genet., Baylor Col. of Med., Houston, TX; [3]ISMO, CNRS, UMR8214, Univ. Paris Sud, Orsay, France

Abstract: Cleavage of mutant huntingtin (HTT) is an essential process in Huntington's disease (HD), an inherited neurodegenerative disorder. Cleavage generates N-ter fragments that contain the polyQ stretch and whose nuclear toxicity is well established. However, the functional defects induced by cleavage of full-length HTT remain elusive. Moreover, the contribution of non-polyQ C-terminal fragments is unknown. Using time- and site-specific control of full-length HTT proteolysis, we show that specific cleavages are required to disrupt intramolecular interactions within HTT and to cause toxicity in cells and flies. Surprisingly, in addition to the canonical pathogenic N-ter fragments, the C-ter fragments generated, that do not contain the polyQ stretch, induced toxicity via dilation of the endoplasmic reticulum (ER) and increased ER stress. C-ter HTT bound to dynamin 1 and subsequently impaired its activity at ER membranes. Our findings support a role for HTT on dynamin 1 function and ER homeostasis. Proteolysis-induced alteration of this function may be relevant to disease.

Disclosures: **F. Saudou:** None. **M. ElDaher:** None. **E. Hangen:** None. **J. Bruyere:** None. **I. Al-Ramahi:** None. **G. Poizat:** None. **C. Mayet:** None. **N. Bourg:** None. **S. Leveque-Fort:** None. **J. Botas:** None. **S. Humbert:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.02

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH RO1 NS088192

Title: Mutant Huntingtin interacts with AAA-ATPase VCP to trigger mitochondrial dysfunction *in vitro* and *in vivo*

Authors: *X. GUO, X. QI;
physiology and biophysics, Case Western Reserve Univ., Cleveland, OH

Abstract: Huntington's disease (HD) is caused by an expanded CAG repeat in the huntingtin gene, which encodes an expanded polyglutamine stretch in the huntingtin (HTT) protein. Prevalence of HD is 4-10 per 100 000 in the western world, with many more people at risk of the disease. Although the HD mutation has been identified, the molecular and cellular basis of HD is far less known. Basic research and clinical studies indicate that mutant Huntingtin (mtHtt) causes defects of mitochondrial function which subsequently leads to neuronal degeneration, however, the underlying mechanism is not yet clear. In our study, we found that mtHtt interacted with AAA-ATPase Valosin-Containing Protein(VCP)on the mitochondria of HD models in culture and in mice, and promotes VCP translocation to mitochondria. To examine the functional outcome of mtHtt-induced mitochondria accumulated VCP in HD pathology, we used a rational approach to develop a peptide inhibitor, HV-3, that selectively interferes with the protein-protein interaction between VCP and Htt. We demonstrated that treatment with HV-3 blocked the interaction between Htt and VCP and inhibited VCP translocation to mitochondria in both HD cell cultures and HD animal models. Significantly, we found that treatment with peptide HV3 reduced mitochondrial dysfunction and cell death in both HD mouse striatal cells and HD patients-iPS derived neurons. The treatment also greatly reduced neuropathology in HD transgenic mice. Taken together, our findings reveal a causal role of mtHtt-induced mitochondria-accumulated VCP in the pathology of HD. We propose that a selective peptide inhibitor of VCP/Htt binding, such as HV3, is a useful therapeutic agent for treatment of HD.

Disclosures: X. Guo: None. **X. Qi:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.03

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: CIHR MOP-8443

GPG-102165

Title: Caspase cleavage of huntingtin releases a hidden autophagy inducing domain dependent on myristoylation that is associated with increased mutant huntingtin clearance

Authors: *D. D. O. MARTIN[1], D. E. EHRNHOEFER[1], M. SCHMIDT[2], S. S. SANDERS[1], B. NGUYEN[1], N. LAZIC[1], R. J. HEIT[3], M. C. YAP[3], L. G. BERTHIAUME[3], M. R. HAYDEN[1]; [1]Med. Genet., [2]Neurosci., Univ. of British Columbia, Vancouver, BC, Canada; [3]Cell Biol., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Huntington disease (HD) is a debilitating neurodegenerative disease characterized by the loss of motor control and cognitive ability. It is caused by a polyglutamine expansion at the N-terminus of huntingtin (HTT) that promotes aggregation. Consequently, many studies have focused on promoting the removal of mutant HTT (mHTT) through several mechanisms including autophagy. We recently identified an autophagy inducing domain within HTT that is released by caspase cleavage and is dependent on myristoylation. HTT is posttranslationally myristoylated (PTMyr) following exposure of the N-terminal Gly553 after caspase-cleavage at Asp552. Myristoylated HTT released by caspase cleavage at Asp552 and Asp586 (myr-HTT553-585-EGFP) was shown by live cell microscopy to induce the formation of autophagosomes that use the ER as a lipid donor. Overexpression of myr-HTT553-585-EGFP was also associated with elevated levels of LC3-II, indicating an increase in autophagic flux. Notably, HTT553-586 partially aligns with the autophagy regulatory domain of ATG14L, known as Barkor/Atg14(L) autophagosome-targeting sequence (BATS) domain. We propose that myr-HTT553-586 acts as a membrane curvature sensing domain that induces the formation of autophagosomes similar to the BATS domain; by sensing membrane curvature at the ER and inducing membrane curvature as cleavage of HTT progresses, suggesting a novel and unexpected role for wild-type HTT in autophagosome formation and processing. The build-up of toxic aggregates displayed in HD is in part due to dysfunctional autophagy, wherein cargo loading of autophagosomes and their fusion with lysosomes are disrupted. PTMyr of HTT was significantly decreased in mHTT transiently expressed in HeLa cells, suggesting a loss in the ability of this peptide to associate with membranes and, consequently, a decrease in autophagic flux. Therefore, the loss of PTMyr in mHTT provides a novel molecular mechanism by which autophagic flux is impaired in HD. However, blocking proteolysis at D586 significantly increases PTMyr at G553. Previously, we have shown that blocking caspase cleavage at D586 completely ameliorates the disease phenotype in HD mice. Our new data now suggests that this protection is mediated by correcting the autophagy pathway thereby promoting mHTT clearance.

Disclosures: D.D.O. Martin: None. **D.E. Ehrnhoefer:** None. **M. Schmidt:** None. **S.S. Sanders:** None. **B. Nguyen:** None. **N. Lazic:** None. **R.J. Heit:** None. **M.C. Yap:** None. **L.G. Berthiaume:** None. **M.R. Hayden:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.04

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Title: The Hippo/YAP pathway: A novel pathogenic mechanism in Huntington's disease

Authors: *G. SADRI-VAKILI[1], K. A. MUELLER[1], K. E. GLAJCH[1], M. N. HUIZENGA[1], M. LAQUAGLIA[2], K. VAKILI[2];
[1]Dept Neurol, Massachusetts Gen Hosp, Charlestown, MA; [2]Boston Children's Hosp., Boston, MA

Abstract: The Hippo/YAP signaling pathway has been implicated in mammalian organ size regulation and tumor suppression. Specifically, this pathway plays a critical role in regulating the activity of the transcriptional co-activator Yes-associated protein (YAP), which modulates a proliferative transcriptional program by binding to the transcription factor TEAD. While the Hippo/YAP pathway is known to be activated during tumorigenesis, recent studies have revealed that it may also play a role in neurodegeneration. For example, mammalian sterile 20 (STE20)-like kinase 1 (MST1), a downstream pro-apoptotic protein kinase in the Hippo pathway, mediates oxidative stress-induced neuronal death. In addition, MST1 activity leads to caspase activation and impairment of autophagy in a mouse model of Amyotrophic Lateral Sclerosis. Importantly, homozygous deletions of MST1 in this mouse model delayed symptom onset and improved the survival of spinal cord motor neurons. Finally, activation of the Hippo pathway has been linked to alterations in autophagy. Together, these findings implicate the Hippo/YAP pathway in the underlying mechanisms of neurodegeneration. Therefore, we investigated the possible role of this pathway in Huntington's disease (HD) pathogenesis. Our results demonstrate that there is a significant increase in phosphorylated MST1 (pMST1), active form, in post-mortem human cortex from patients. Additionally, pMST1 was also increased in the striatum and cortex of mutant Hdh111/111 mice compared to control as well as in mutant STHdh111/111 cells compared to control STHdh7/7 cells. There was also a significant and concomitant increase in YAP phosphorylation in Hdh111/111 striatum. Together, these results demonstrate that the Hippo/YAP pathway is altered in HD and may provide a novel therapeutic target for the treatment of HD.

Disclosures: G. Sadri-Vakili: None. **K.A. Mueller:** None. **K.E. Glajch:** None. **M.N. Huizenga:** None. **M. LaQuaglia:** None. **K. Vakili:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.05

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH RO1 ES016931

NIH F31 NS077632

NIH T32 ES007028

Title: Mn-handling deficit in a prodromal HD mouse model underlies metabolic alterations

Authors: *A. B. BOWMAN[1], T. J. V. BICHELL[2], M. WEGRZYNOWICZ[1], E. M. BRADLEY[1], K. G. TIPPS[1], N. FISHER[2], K. D. DUDEK[2], A. M. TIDBALL[2], M. A. UHOUSE[1], M. R. BRYAN[2], G. F. KWAKYE[2];
[1]Neurol., [2]Vanderbilt Brain Inst., Vanderbilt Univ., Nashville, TN

Abstract: CAG triplet repeat expansion in the Huntingtin (HTT) gene causes striatal neurodegeneration in Huntington's disease (HD). Expression of mutant HTT decreases net uptake of manganese (Mn) into neuronal cells and suppresses biological responses to Mn exposure both *in vitro* and *in vivo*. These data support the hypothesis that neuronal Mn homeostasis is disrupted in HD, and that this disruption may contribute to HD pathophysiology. Members of the arginase protein family are obligate Mn-dependent enzymes with roles in the urea and citrulline-nitric oxide cycles. Systemic alterations in these metabolic pathways have been reported in HD and HD models. Here, we directly test whether alterations in arginase-related metabolic pathways occur in the striatum of prodromal (3-month) YAC128Q mice, and whether increasing *in vivo* Mn levels influences arginase-related metabolism. We report a significant reduction in basal arginase activity in the striatum of HD mice versus wild-type. Striatal arginase activity was substantially elevated by a one-week systemic Mn exposure paradigm in both genotypes. We assessed protein and mRNA levels of both arginase isoforms (Arg1 and Arg2) to evaluate their relationship to the observed activity changes. At 3-months of age (before detectable gliosis in this HD model) striatal Arg1 is undetectable in either genotype. Instead, striatal Arg2 mRNA and protein are observed. Striatal Arg2 protein levels are similar in wild-type and YAC128Q under basal conditions, despite reduced arginase activity in the HD model. In contrast, Arg2 mRNA levels are significantly elevated in YAC128Q striatum. Mn-exposure substantially increased Arg2 protein levels in both genotypes, without a corresponding increase in mRNA, suggesting that protein levels are regulated by the cofactor Mn. Thus, the

decreased arginase activity in YAC128Q striatum, despite elevated Arg2 expression, is consistent with a decreased biological availability of Mn in HD. Mass spectrometry analysis revealed significant changes in several related metabolites in the YAC128Q model. Mn-exposure rescued these HD metabolic phenotypes. These data strongly support the hypothesis that a HD Mn-handling defect causes alterations in Mn-dependent neurophysiology that may contribute to disease.

Disclosures: **A.B. Bowman:** None. **T.J.V. Bichell:** None. **M. Wegrzynowicz:** None. **E.M. Bradley:** None. **K.G. Tipps:** None. **N. Fisher:** None. **K.D. Dudek:** None. **A.M. Tidball:** None. **M.A. Uhouse:** None. **M.R. Bryan:** None. **G.F. Kwakye:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.06

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Ministerio de Economía y Competitividad (SAF2012-39142)

Cure Huntington’s Disease Initiative (CDHI)

CIBERNED (CB06/05/0054 and CB06/05/0042)

Title: p75NTR/TrkB imbalance in Huntington´s disease:Implications for future therapeutic approaches

Authors: S. GINES[1], V. BRITO[1], A. GIRALT[1], L. ENRIQUEZ-BARRETO[2], M. PUIGDELLIVOL[1], N. SUELVES[1], E. MARTIN[3], M. MORALES[2], *E. PEREZ-NAVARRO[1], J. ALBERCH[1];
[1]Dept. Cell Biology, Immunol. and Neurosciences, Univ. of Barcelona, Barcelona, Spain; [2]Ctr. de Investigación Biomédica de la Rioja, La Rioja, Spain; [3]Inst. for Res. in Neurolog. Disabilities (IDINE), Albacete, Spain

Abstract: Basal ganglia dysfunction is a clear hallmark of Huntington´s disease (HD) involved in the classical motor disturbances that have been commonly associated to striatal neurodegeneration. However, it is clear that HD encompasses more than motor deficits, with evidence of cognitive dysfunction years before chorea symptoms appear. Therefore, the perfect scenario will be one in which by targeting a unique pathway memory disturbances could be ameliorated or prevented at early disease stages while slowing motor coordination impairments

at middle disease stages. In searching for this “perfect target” we have focused on neurotrophic receptors given the dual role as modulators of both neuronal survival and synaptic plasticity and cognition. Moreover, and supporting the potential role of these receptors as a therapeutic approach in HD it is known that the levels of brain-derived neurotrophic factor (BDNF) in the striatum and hippocampus of HD mouse models and HD human brain are reduced. In this study we have demonstrated an imbalance between p75NTR and TrkB expression at early disease stages in the striatum of two distinct HD mouse models that was also manifested in the putamen of HD patients and was associated with a reduction of BDNF-mediated neuroprotection. Notably, in the hippocampus such imbalance was not found until 6 months of age since the increase in p75NTR protein levels was earlier (4 months) than the TrkB reduction. The role of p75NTR in the adult brain has been mainly associated with apoptosis, whereas its involvement in synaptic plasticity and memory is poorly understood. It is known that null p75NTR mice exhibit enhanced LTP and impaired LTD, while both null and heterozygous p75NTR mice display improved spatial memory. In this scenario we wondered whether normalization of p75NTR levels in HD mutant mice would recover HD memory deficits. In agreement with our hypothesis new double-mutant mice expressing mutant huntingtin but “normal” p75NTR levels showed preserved spatial, recognition, and associative memories along with an amelioration of dendritic spine abnormalities, likely through normalization of the activity of the GTPase RhoA. Altogether, our findings demonstrate a detrimental role of TrkB/ p75NTR imbalance in striatal vulnerability and dysfunction as well as a role for hippocampal p75NTR upregulation in synaptic and memory alterations in HD. These results, underline the need to address the benefits of neuroprotective therapies based on BDNF administration to treat HD pathology an open a new and exciting therapeutic alternative based on TrkB and p75NTR signalling as a target to treat both cognitive and motor disturbances in HD

Disclosures: **S. Gines:** None. **V. Brito:** None. **A. Giralt:** None. **L. Enriquez-Barreto:** None. **M. Puigdellivol:** None. **N. Suelves:** None. **E. Martin:** None. **M. Morales:** None. **E. Perez-Navarro:** None. **J. Alberch:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.07

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: IDIBAPS Postdoctoral Fellowship-BIOTRACK (EC FP7/2007-2013)

MINECO (SAF2011-29507)

RETICS (RD06/0010/0006)

Generalitat de Catalunya (2014SGR- 968)

CIBERNED

CHDI

Title: Fingolimod (FTY720) enhances hippocampal synaptic plasticity and memory in Huntington's disease by preventing astrocyte-mediated inflammation and p75NTR up-regulation

Authors: A. MIGUEZ[1,2], G. GARCÍA-DÍAZ BARRIGA[1,2], V. BRITO[1,2], M. STRACCIA[1,2], A. GIRALT[1,2], S. GINÉS[1,2], J. M. CANALS[1,2], *J. ALBERCH[1,2];
[1]Fac Medicina, Univ. Barcelona, Barcelona, Spain; [2]IDIBAPS, Barcelona, Spain

Abstract: Huntington's disease (HD) is a hereditary neurodegenerative disorder caused by the expansion of a CAG tract in the exon-1 of the *huntingtin* gene. Although clinical diagnosis relies on the manifestation of motor abnormalities, cognitive and behavioral impairments are evident at least 15 years before motor symptoms. The primary regions of neurodegeneration in HD have long been considered the striatum and cerebral cortex, but other structures involved in cognition, particularly the hippocampus, are affected in early stages of the disease. Synaptic and memory dysfunction in HD mouse models have been related to low levels of brain-derived neurotrophic factor (BDNF) and imbalance between TrkB and $p75^{NTR}$ receptors. In addition, astrocyte over-activation has also been suggested to contribute to HD cognitive deficits. Fingolimod (FTY720), an agonist of sphingosine-1 phosphate receptors commonly used as an immunomodulator in Multiple Sclerosis patients, has recently been shown to increase BDNF levels and to reduce astrogliosis, proving its potential to regulate trophic support and inflammatory response. In this view, we have investigated whether FTY720 improves synaptic plasticity and memory in the R6/1 mouse model of HD, through regulation of hippocampal BDNF signaling and astroglial reactivity. Chronic administration of FTY720 from pre-symptomatic stages ameliorated long-term memory deficits and dendritic spine loss in CA1 hippocampal neurons from R6/1 mice. Furthermore, FTY720 delivery prevented astrogliosis and over-activation of nuclear factor kappa beta (NF-κB) signaling in the R6/1 hippocampus, reducing tumor necrosis factor alpha (TNFα) and induced nitric oxide synthase (iNOS) levels. TNFα decrease correlated with the normalization of $p75^{NTR}$ expression in the hippocampus of FTY720-treated R6/1 mice, thus preventing $p75^{NTR}$/TrkB imbalance. In addition, FTY720 increased cAMP levels and promoted phosphorylation of CREB and RhoA in the hippocampus of R6/1 mice, further supporting its role in the enhancement of synaptic plasticity. Our findings provide new insight into the mechanism of action of FTY720, and suggest that administration of this drug at the early stages of HD could help restoring normal BDNF signaling and preventing synaptic and memory impairments.

Disclosures: **A. Miguez:** None. **G. García-Díaz Barriga:** None. **V. Brito:** None. **M. Straccia:** None. **A. Giralt:** None. **S. Ginés:** None. **J.M. Canals:** None. **J. Alberch:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.08

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: CIHR

Title: BDNF and homeostatic plasticity in cortical neurons from the YAC128 mouse model of Huntington's disease

Authors: ***A. I. SMITH-DIJAK**, L. A. RAYMOND;
Psychiatry, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Huntington disease (HD) is a neurodegenerative disorder caused by a polyglutamine expansion in the huntingtin protein, producing mutant huntingtin (mHtt). This causes neurodegeneration beginning in the striatum, and produces a range of motor, cognitive and behavioural symptoms. Many pre- and postsynaptic proteins interact with mHtt, and the function of at least some of these proteins is affected by the disease-causing mutation. This includes the neurotrophin brain-derived neurotrophic factor (BDNF), the release of which in impaired in HD. One of the consequences of these changes in protein function is alterations in synaptic signaling and plasticity. Particularly affected are the cortico-striatal synapses, especially those between cortical neurons and striatal spiny projection neurons (SPNs). We set out to examine changes in synaptic scaling, a form of homeostatic plasticity in which the strength of a neuron's synapses are uniformly increased or decreased in order to keep the neuron's overall level of activity within an optimal range, in excitatory synapses onto cortical pyramidal neurons. We used patch clamp recording to measure the amplitude and frequency of miniature excitatory postsynaptic currents (mEPSCs) following 48 hours of treatment with either tetrodotoxin (TTX) or water (vehicle), in cortical pyramidal neurons from either wild-type (WT) or YAC128 mice cultured *in vitro* to DIV 21, to determine the effect of treatment with TTX on synaptic strength. The frequency of mEPSCs increased in WT cells treated with TTX relative to those treated with vehicle. The amplitude of mEPSCs in TTX-treated WT cells also tended to increase relative to that of mEPSCs in vehicle-treated WT cells. TTX treatment caused no change in either frequency or amplitude of mEPSCs in YAC128 cells. We then tested whether impaired BDNF release could be responsible for the observed deficit in YAC128 cells by adding BDNF or TrkBFc to the cell

culture medium 48 hours before treatment with either TTX or vehicle. We also used immunocytochemical techniques to further assess the changes taking place in WT and YAC128 cells in response to treatment with TTX or vehicle. This will allow us to better understand the dysfunction occurring on the presynaptic side of the cortico-striatal synapse in HD and what makes this synapse particularly vulnerable to the HD mutation.

Disclosures: A.I. Smith-Dijak: None. **L.A. Raymond:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.09

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: CEA annual funds 2009-2014

CNRS annual funds 2009-2014

European Community's Seventh Framework Program FP7/2007-2013 under grant agreement no. HEALTH-F5-2008-222925

Fondation pour la Recherche Médicale (France)

DIM Neuropôle de Recherche Francilien

IMAGEN European integrated project (EUR617037286)

Title: Characterization of the striatal kinase Dclk3 and its neuroprotective effects against mutant huntingtin

Authors: *E. P. BROUILLET[1], L. FRANCELLE[1], L. GALVAN[1], M.-C. GAILLARD[1], M.-A. CARRILLO-DE SAUVAGE[1], G. LIOT[2], L. DE LONGPREZ[1], M. DE CHALDÉE[3], M. GUILLERMIER[1], D. HOUITTE[1], C. JOSÉPHINE[1], F. PETIT[1], C. JAN[1], N. DUFOUR[1], A. PRIGENT[4], K. H. EL HACHIMI[4], S. HUMBERT[2,5], P. HANTRAYE[1], F. SAUDOU[2,5], K. MERIENNE[6], A. L. PERRIER[7], N. DÉGLON[1,8,9], A. BEMELMANS[1];
[1]Neurodegenerative Dis. Lab., UMR 9199, CEA, MIRCen, UMR 9199, CEA, CNRS, Univ. Paris-Sud,, Fontenay-aux-Roses, France; [2]Inst. Curie, CNRS UMR 3306, INSERM U1005, Orsay F-91405, France; [3]Inst. for Integrative Biol. of the Cell (I2BC), UMR 9198 CEA-CNRS-Univ. Paris Sud, Gif-sur-yvette, France; [4]Lab. de Neurogénétique EPHE, ICM UPMC, Inserm

UMR_S1127/CNRS UMR 7225, Hôpital Pitié-Salpêtrière, Paris, France; [5]Grenoble Inst. of Neuroscience, Inserm U836 – Univ. Joseph Fourier, Grenoble, France; [6]Lab. de Neurosciences Cognitives et Adaptatives (LNCA) UMR 7364, Univ. de Strasbourg- CNRS, F-67000 Strasbourg, France; [7]I-Stem, INSERM U861, F-91030 Evry, France; [8]Lausanne Univ. Med. Sch. (CHUV), Dept. of Clin. Neurosciences (DNC), Lab. of Cell. and Mol. Neurotherapies (LNCM), Lausanne, Switzerland; [9]Lausanne Univ. Med. Sch. (CHUV), Neurosci. Res. Ctr. (CRN), Lab. of Cell. and Mol. Neurotherapies (LNCM), Lausanne, Switzerland

Abstract: Double-cortin-like kinases (Dclks) play major roles in development and maintenance of neuronal functions. The neurobiological role of the third member of this family, the striatal-enriched Dclk3 is unknown. We characterized the cytoplasmic and nuclear localization of Dclk3 in the striatum in non-human primates and in man. A yeast-two hybrid screen identified seven Dclk3 interactors, all possessing zinc finger domains. One candidate is known to regulate many transcription activating factors (TAFs), p53 and lysine acetyl transferases. In line with this, expression of Dclk3 kinase domain in human striatal neural stem cells produces transcriptional changes that are mainly linked to chromatin remodeling. Chromatin and transcriptional perturbations have been described in Huntington's disease (HD). Interestingly, we found that Dclk3 expression is reduced in HD mouse models. We examined the effects of Dclk3 overexpression *in vivo* in the striatum of HD mouse models using viral vectors and found that it produced a significant neuroprotective effect *in vivo*. In contrast, lowering the expression of Dclk3 using shRNA strategy increased mutant huntingtin toxicity. Expression of a Dclk3 protein truncated in its N-terminus but containing the C-terminal kinase domain was sufficient to produce neuroprotection. The study of mutants inactivating the kinase domain of Dclk3 demonstrated that its neuroprotective effect is mediated through the catalytic activity of the kinase. The present findings suggest that Dclk3 participates in a striatal-specific regulation of epigenetic mechanisms maintaining the integrity of the striatum. In HD, decreased Dclk3 expression may play a role in the vulnerability of the striatum against mutant huntingtin.

Disclosures: **E.P. Brouillet:** None. **L. Francelle:** None. **L. Galvan:** None. **M. Gaillard:** None. **M. Carrillo-de Sauvage:** None. **G. Liot:** None. **L. de Longprez:** None. **M. de Chaldée:** None. **M. Guillermier:** None. **D. Houitte:** None. **C. Joséphine:** None. **F. Petit:** None. **C. Jan:** None. **N. Dufour:** None. **A. Prigent:** None. **K.H. El Hachimi:** None. **S. Humbert:** None. **P. Hantraye:** None. **F. Saudou:** None. **K. Merienne:** None. **A.L. Perrier:** None. **N. Déglon:** None. **A. Bemelmans:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.10

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH Grant NS084298-02

Title: Overexpression of Alzheimer's disease risk gene TREM2 to improve the immune response to neurodegeneration

Authors: *A. DAGGETT, C. Y. D. LEE, K. MURILLO, X. W. YANG;
UC Los Angeles, Los Angeles, CA

Abstract: Triggering Receptor Expressed on Myeloid cells 2 (TREM2) is an immune cell receptor expressed in brain microglia that is thought to be involved in regulating the phagocytic response to apoptotic cells and microglial survival. Mutations of both copies of TREM2 in humans lead to an early-onset neurodegenerative disorder characterized by widespread microglia activation. Recently, heterozygous mutations in TREM2, including the R47H mutation, have been associated with Alzheimer's disease (AD), amyotrophic lateral sclerosis, Parkinson's disease, and frontotemporal dementia. In cultured microglia, TREM2 downregulation leads to an excessive inflammatory cytokine response, thought to be detrimental in the context of a degenerating brain. TREM2 activation dampens the inflammatory response while simultaneously increasing phagocytic capacity. These effects are thought to be beneficial in the context of neurodegeneration and suggest that overexpression of TREM2 could drive microglia in a protective direction. To test this idea, human TREM2 bacterial artificial chromosome (BAC) transgenic mice were created to genetically overexpress human TREM2 under its endogenous promoter. The effects on microglia *in vitro* and *in vivo* are being tested, and TREM2 BAC mice have been crossed with mouse models of Huntington's disease (HD) and AD. Microglia from cultured TREM2 BAC mice microglia show a modified inflammatory response to LPS. Behavioral and pathological studies of TREM2 BAC mice crossed with HD and AD mice are ongoing. These studies will enable us to test the hypothesis that genetic overexpression of human TREM2 with its endogenous regulatory elements will suppress neuroinflammatory and neurodegeneration phenotypes. In addition, we will also be able to evaluate whether overexpression of R47H version of TREM2 will have distinct or opposite effects on disease phenotypes.

Disclosures: A. Daggett: None. **C.Y.D. Lee:** None. **K. Murillo:** None. **X.W. Yang:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.11

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Agence Nationale pour la Recherche ANR-12-BLANC-SVSE4

Fondation pour la Recherche Médicale FRM

INSERM

Title: Huntingtin regulates cortical development: consequences for Huntington's disease

Authors: ***S. HUMBERT**, M. BARNAT, E. APARICIO, C. BENSTAALI;
Gin-Inserm U836-University Joseph Fourier, La Tronche, France

Abstract: The bulk of interest in the huntingtin protein has centered on the fact that, when mutated, huntingtin causes Huntington's disease (HD), a devastating neurodegenerative disorder. The mutation causing HD is an abnormal polyglutamine stretch in huntingtin. Given the adult onset and dysfunction and death of adult neurons characterizing HD, most studies have focused on the toxic effects elicited by mutant huntingtin in post-mitotic neurons. However, the protein is ubiquitous and expressed in the developing embryo where it plays an essential role as revealed by the early embryonic lethality at day 7.5 of the complete knock-out of the huntingtin gene in mouse. Anyway, the roles of the wild-type protein during development have been overlooked. We will discuss how huntingtin regulates several steps of mouse embryonic corticogenesis including the division and cell fate of cortical progenitors of the ventricular zone, and the polarization and migration processes of newly generated neurons. We will also show the consequences of the presence of an abnormal polyglutamine expansion in huntingtin during cortical neurogenesis and consider the viewing of HD as a developmental disorder.

Disclosures: S. Humbert: None. **M. Barnat:** None. **E. Aparicio:** None. **C. Benstaali:** None.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.12

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: CIHR grant: MOP-84438

Teva Pharmaceuticals

Title: Toward developing a personalized allele-specific gene silencing therapy for Huntington's disease

Authors: *N. S. CARON, A. L. SOUTHWELL, C. KAY, M. YE, M. R. HAYDEN;
Med. Genet., Ctr. for Mol. Med. and Therapeut., Vancouver, BC, Canada

Abstract: Huntington disease (HD) is a fatal neurodegenerative disorder for which there is no treatment. HD is caused by a C-A-G trinucleotide repeat expansion in the HTT gene (>35 repeats) that encodes an elongated polyglutamine tract within the huntingtin protein. The expansion of the polyglutamine tract in mutant huntingtin results in both the gain and loss of cellular functions which ultimately leads to the complex pathogenesis observed in HD. Therefore, reducing levels of mutant huntingtin in patients represents an attractive therapy for HD. Huntingtin lowering can be achieved through non-selective silencing of total huntingtin expression or by specifically silencing the mutant allele. To date, gene silencing strategies have undergone significant preclinical evaluation as therapies for HD. Non-selective silencing using antisense oligonucleotides (ASOs) or RNA interference methods have been shown to improve behavioural and neuropathological phenotypes in multiple animal models of HD. These studies suggest that reduction of wild type huntingtin is safe and well tolerated. However, wild type huntingtin is involved in numerous cellular functions and is essential for neuronal health, and it remains unclear whether its sustained reduction will be well tolerated over the long treatment durations likely required in humans. Therefore, selectively silencing mutant HTT in patients represents a more promising therapeutic approach for HD. One strategy to selectively inhibit the production of mutant huntingtin is to silence the mutant gene using ASOs targeted to single nucleotide polymorphisms (SNPs) at the HTT locus that are strongly associated with the CAG expansion (HD-SNPs). Our lab has previously evaluated ASOs targeted to one such HD-SNP and identified potent, selective, and well tolerated candidates currently undergoing pre-clinical validation. However, targeting any individual HD-SNP with an ASO would only provide a treatment option for a portion of the HD population. Therefore, we are developing a panel of ASOs targeting HD-SNPs specific to the three most common HD HTT haplotypes to maximize the number of HD patients that could be treated through selective silencing of mutant HTT. Using this approach, each individual ASO drug in the panel would treat a distinct subset of the HD population and in combination would provide a personalized treatment option for the majority of HD patients.

Disclosures: **N.S. Caron:** None. **A.L. Southwell:** None. **C. Kay:** None. **M. Ye:** None. **M.R. Hayden:** A. Employment/Salary (full or part-time); Teva Pharmaceutical Industries.

Nanosymposium

556. Huntington's Disease Mechanisms II

Location: N426A

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 556.13

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: CHDI Foundation, Inc A-3433

National Health and Medical Research Council (NHMRC) 606650

Royal Australian and New Zealand College of Psychiatrists (RANZCP) New Investigator Grant 2013 (FAW)

University of Melbourne for computing infrastructure in Canberra

Self-funding for infrastructure and travel to coordinate research (JCLL)

NIH U54 EB020403

Title: Striatal shape differs before and after symptom onset in Huntington's disease and relates to clinical severity: the IMAGE-HD study

Authors: *Z. ABARYAN[1], F. WILKES[3], C. R. K. CHING[1,4], B. A. GUTMAN[1], S. MADSEN[1], M. WALTERFANG[5], J. STOUT[6], A. CHURCHYARD[7], P. CHUA[8], D. VELAKOULIS[5], G. EGAN[6], J. LOOI[3,5], P. M. THOMPSON[1,2], N. GEORGIOU-KARISTIANIS[6];
[1]Imaging Genet. Center, Dept. of Neurol., USC, Marina Del Rey, CA; [2]Departments of Neurology, Psychiatry, Radiology, Engineering, Pediatrics, and Opthamology, USC, Los Angeles, CA; [3]Academic Unit of Pyschiatry and Addiction Med., Australian Natl. Univ. Med. School, Canberra Hosp., Canberra, Australia; [4]Interdepartmental Neurosci. Grad. Program, UCLA Sch. of Med., Los Angeles, CA; [5]Neuropsychiatricy Unit, Royal Melbourne Hosp., Univ. of Melbourne & Northwestern Mental Health, Melbourne Neuropsychiatry Ctr., Melbourne, Australia; [6]Sch. of Pyschological Sci., Monash Univ., Me, Australia; [7]Dept. of Neurol., Monash Univ., Melbourne, Australia; [8]Dept. of Psychiatry, Sch. of Clin. Sci., Monash University, Monash Med. Ctr., Melbourne, Australia

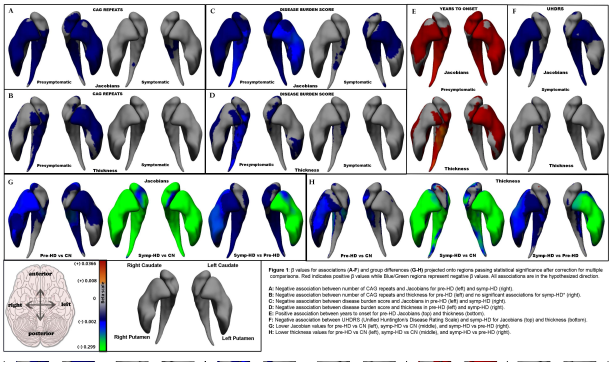
Abstract: Huntington’s disease (HD) is an inherited neurodegenerative disorder affecting motor, cognitive, and emotional functions. We used our novel shape analysis technique to test for regional differences in subcortical brain structure between groups of healthy controls (CN), and people with presymptomatic, or symptomatic HD (pre-HD, symp-HD) and associations with clinical measures. Participants were recruited as part of the IMAGE-HD study 36 CN (12M:24F, mean age: 42.41+/-13 yrs), 36 pre-HD (14M:22F, age: 42+/- 10 yrs), 37 symp-HD (21M:16F, age: 52+/-9 yrs)). T1-weighted MRI images were manually segmented. A surface-based parametric mapping protocol derived two pointwise shape measures: thickness (radial distance) and the Jacobian determinant (surface dilation ratio), across thousands of points on the surface of the left and right caudate and putamen. A multiple linear regression was fit at each thickness and

Jacobian point to test for group differences and associations with clinical features. All analyses were adjusted for age, sex, and intracranial volume. A standard FDR correction was applied (q=0.05). Significant negative associations were detected between shape metrics and the number of CAG repeats, disease burden score, HD disease rating score (UHDRS), and years to onset in pre-HD, symp-HD, or both. Significant group differences were detected between CN, pre-HD and symp-HD. See Table 1 and Figure 1 for details. High-dimensional shape analysis revealed significant striatal morphometry differences between groups and associations with age of disease onset and severity. This method yields a potentially strong biomarker for disease-related subcortical changes.

1A: Associations	Jacobians	Jacobians	Thickness	Thickness		Jacobians	Jacobians	Thickness	Thickness
Left Caudate	Presymptomatic-HD	Symptomatic-HD	Presymptomatic-HD	Symptomatic-HD	Right Caudate	Presymptomatic-HD	Symptomatic-HD	Presymptomatic-HD	Symptomatic-HD
CAGrepeats Disease Burden Score UHDRS Years to Onset	0.034 (67%) 0.047 (95%) --- 0.043 (86%)	0.006 (24%) 0.032 (65%) 0.006 (64%) ---	0.008 (16%) 0.022 (44%) --- 0.023 (46%)	--- --- ---	CAGrepeats Disease Burden Score UHDRS Years to Onset	0.032 (63%) 0.049 (97%) --- 0.041 (82%)	0.006 (12%) 0.011 (24%) 0.022 (45%) ---	0.032 (64%) 0.041 (82%) --- 0.038 (76%)	---0.016 (32%)0.004 (9%)---
Left Putamen	Presymptomatic-HD	Symptomatic-HD	Presymptomatic-HD	Symptomatic-HD	Right Putamen	Presymptomatic-HD	Symptomatic-HD	Presymptomatic-HD	Symptomatic-HD
CAGrepeats Disease Burden Score UHDRS Years	0.046 (93%) 0.047 (96%) --- 0.046 (92%)	0.000 (0%)0.031 (61%) 0.022 (43%) ---	0.038 (75%) 0.043 (87%) --- 0.039 (78%)	--- --- ---	CAGrepeats Disease Burden Score UHDRS Years	0.043 (86%) 0.045 (90%) --- 0.030 (60%)	--- --- --- 0.045 (91%) ---	0.017 (35%) 0.020 (40%) --- 0.015 (30%)	--- --- ---

to Onset					to Onset				
1B: Group Differences									
Left Caudate	Jacobians	Thickness			Right Caudate	Jacobians	Thickness		
Pre-HD vs CN Symp-HD vs CN Symp-HD vs Pre-HD	0.045 (90%) 0.050 (100%) 0.043 (86%)	0.028 (56%) 0.046 (91%) 0.015 (31%)			Pre-HD vs CN Symp-HD vs CN Symp-HD vs Pre-HD	0.035 (69%) 0.050 (100%) 0.042 (85%)	0.028 (55%) 0.044 (89%) 0.038 (76%)		
Left Putamen	Jacobians	Thickness			Right Putamen	Jacobians	Thickness		
Pre-HD vs CN Symp-HD vs CN Symp-HD vs Pre-HD	0.032 (64%) 0.050 (100%) 0.050 (100%)	0.002 (3%) 0.049 (99%) 0.046 (98%)			Pre-HD vs CN Symp-HD vs CN Symp-HD vs Pre-HD	0.049 (99%) 0.050 (100%) 0.048 (99%)	0.038 (77%) 0.043 (96%) 0.045 (91%)		

Table1: Critical q values and percentage of significant surface points for Jacobian and thickness group differences and associations.



Disclosures: **Z. Abaryan:** None. **F. Wilkes:** None. **C.R.K. Ching:** None. **B.A. Gutman:** None. **S. Madsen:** None. **M. Walterfang:** None. **J. Stout:** None. **A. Churchyard:** None. **P. Chua:** None. **D. Velakoulis:** None. **G. Egan:** None. **J. Looi:** None. **P.M. Thompson:** None. **N. Georgiou-Karistianis:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.01

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Target ALS

William Randolph Hearst Fund Award

Title: Ion channel gene expression and excitability of human and mouse ALS motor neurons at a single cell level

Authors: ***S. LEE**[1], K. ROET[1], O. WISKOW[2], S. GHOSH[2], K. J. LIVAK[3], B. P. BEAN[4], K. EGGAN[2], C. J. WOOLF[1];
[1]F.M. Kirby Neurobio. Ctr., Boston Children's Hosp., Boston, MA; [2]Stem cell and Regenerative Biol., Harvard Univ., Boston, MA; [3]Fluidigm Corp., South San Francisco, CA; [4]Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disease of spinal and cortical motor neurons. Clinical investigations and some ALS animal model studies show that the disease is associated with motor neuronal hyperexcitability. We have recently found that a hyperexcitability phenotype is present in

induced pluripotent stem cell (iPSC)-derived motor neurons from ALS patients harboring distinct SOD1 mutations, C9orf72 repeat expansions, and FUS mutations (Wainger et al., Cell Reports, 2014). However, it is not clear how mutations in the disease-causing genes produce this hyperexcitability and if a single mechanism is involved. Since membrane excitability is determined by the relative expression and activities of ion channel subtypes, we hypothesized that a change in transcription of ion channels may be responsible for the ALS hyperexcitability. Here we report an approach to link excitability and gene expression differences at a single cell level, by collecting RNA from individual MNs after whole cell patch clamp recordings. Such single cell gene expression profiling in functionally characterized neurons has been conducted both in ALS patient iPSC-derived MNs and in cultured embryonic mouse spinal MNs (HB9::GFP hSOD1G93A). The expression data is reliable in terms of housekeeping gene and motor neuron marker expression, and suggests that KCNQ3 (Kv7.3) and KCNE2 (MiRP1) channels are down-regulated in hSOD1G93A HB9 positive mouse spinal MNs compared to controls. We are expanding the recording/single cell expression profiling to a broader gene set that includes voltage- and ligand-gated ion channels, S- and F-type MN markers, and ALS markers to both human and mouse ALS MNs, and anticipate that this approach will reveal which ion channel subtypes contribute to motor neuron hyperexcitability in familial ALS.

Disclosures: **S. Lee:** None. **K. Roet:** None. **O. Wiskow:** None. **S. Ghosh:** None. **K.J. Livak:** None. **B.P. Bean:** None. **K. Eggan:** None. **C.J. Woolf:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.02

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Target ALS Grant: A potassium channel and hyperexcitability screen for novel ALS therapeutics

Title: Interrogating iPSC derived ALS motor neuron excitability changes with high throughput thallium flux and single cell GCAMP6 analysis

Authors: *K. C. D. ROET[1], J. KLIM[2], Y. ZHANG[2], J. SHAO[1], A. GRANTHAM[1], D. BAKER[2], L. BARRETT[1], K. EGGAN[2], C. J. WOOLF[1];
[1]FM Kirby Neurobio. Center, Boston Children's Hosp. and Dept. of Neurobiology, Harvard Med. Sch., Boston, MA; [2]The Howard Hughes Med. Institute, USA; Harvard Stem Cell Institute, Dept. of Stem Cell and Regenerative Biology, Harvard Univ., Cambridge, MA

Abstract: The Woolf and Eggan labs have recently jointly discovered that motor neurons (MNs) derived from ALS patient induced pluripotent stem cells (IPSC) carrying SOD1, C9orf72 and FUS mutations are hyperexcitable relative to those from control subjects, with higher spontaneous action potential discharge, and that this is due to reduced delayed rectifier potassium-channel activity, likely caused by calcium overload and ER stress. This raises the questions: which specific potassium-channel subtypes out of the large family contribute to ALS MN hyperexcitability and can this drive therapeutic intervention? We have developed a new high-throughput thallium-flux assay (FluxOR) which very precisely quantifies potassium ion flow across the membrane of derived MNs. Using this technique we have revealed that after an initial increase, the potassium flux decreases in IPSC derived MNs that carry SOD1_A4V and C9orf72 repeat expansion mutations compared to isogenic corrected controls. By combining the thallium-flux assay with potassium-channel RNAi knockdown, we can use this technique to identify exactly which potassium-channel subtypes are active in derived ALS and control MNs, and from this which channel is decreased in the disease state. With the use of pharmacological modulators the thallium assay also provides a powerful tool to study potassium channel subtypes functionally. Previous work in our lab has shown that MNs carrying the SOD1_A4V mutation have a higher frequency of fast firing MNs than those of isogenic controls. Since voltage gated potassium channels often function as a natural brake on excitability, knockdown of potassium channels can have different effects on MNs with different spike rates. We have therefore also developed methods to quantify the spike rate of MNs using the genetically encoded calcium indicator GCaMP6 and the calcium sensitive dye FLIPR and have confirmed the hyperexcitability phenotype based on calcium spike analysis. We are now combining RNAi based knockdown with single cell activity imaging using an automated live cell screening instrument (ArrayScan™ VTI HCS) to identify which potassium-channel's activity is reduced and drives MN hyperexcitability. This work has been made possible through the support of Target ALS.

Disclosures: **K.C.D. Roet:** None. **J. Klim:** None. **Y. Zhang:** None. **J. Shao:** None. **A. Grantham:** None. **D. Baker:** None. **L. Barrett:** None. **K. Eggan:** None. **C.J. Woolf:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.03

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: GACR 14-10504P

GACR 15-06958S

GACR P304/12/G069

Title: Human neural precursors derived from induced pluripotent stem cells slow down ALS progression and preserve perineuronal nets

Authors: *S. FOROSTYAK[1,2], J. KWOK[3], P. JENDELOVA[1,2], A. HOMOLA[2], M. SENEKLOVA[1,2], J. FAWCETT[3], E. SYKOVA[1,2];
[1]Inst. of Exptl. Med. ASCR, Prague, Czech Republic; [2]2nd Fac. of Medicine, Charles Univ., Prague, Czech Republic; [3]Dept. of Clin. Neurosciences, John van Geest Ctr. for Brain Repair, Cambridge, United Kingdom

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that specifically affects upper and lower motor neurons (MNs), leading to a progressive decline in motor functions and inevitable death. Stem cells have brought new perspectives and hope for the treatment ALS. We studied the effects of human neural precursors derived from induced pluripotent stem cells (NP-iPS) in the SOD1-transgenic rat model of ALS. Asymptomatic and symptomatic rats (7 and 25 weeks old, respectively) were intraspinally grafted with NP-iPS. The animals' motor functions were tested throughout the course of the disease. Spinal cords and cerebrospinal fluid (CSF) were collected to study graft-host interaction, NP-iPS fate, protein and gene expression studies. We also studied the expression of chondroitin sulphate proteoglycans (CSPGs) in spinal cord and CSF at the presymptomatic, symptomatic and terminal (untreated and NP-iPS-treated) stages of the disease and in wild-type (WT) littermates. The mRNA expression of CSPGs, several growth factors and apoptosis-related genes were analyzed using RT-qPCR. The CSF collected from patients with a confirmed diagnosis of ALS and non-ALS controls were tested for CSPGs content. The transplantation of NP-iPS cells into symptomatic and presymptomatic animals resulted in significantly prolonged survival (by 13 and 20 days, respectively) and slowed disease progression compared with vehicle-treated littermates. Presymptomatic grafting of NP-iPS also postponed disease onset. Both groups of cell-treated rats presented significantly better motor activity. Grafting of NP-iPS up-regulated the expression of growth factors' (NGF, IGF-1 and BDNF) and stabilized the expression of apoptosis-related genes' (BAX, BCL-2 and Casp-3) compared to sham-treated rats. We found that CSPGs could be detected in the CSF of healthy and SOD1-transgenic rats, however at the symptomatic stage animals had a significantly higher amount of CSPGs compared to the presymptomatic or age-related WT animals. Vehicle-treated animals at the terminal disease stage lost substantial expression of spinal CSPGs, whereas NP-iPS-treated rats had significantly higher CSPGs expression. CSF from ALS patients also revealed differences in the expression of several CSPGs compared with non-ALS patients. We conclude that the administration of human NP-iPS alleviates the progression of ALS and extends lifespan. Grafting of NP-iPS safeguards PNNs and remodels the recipients' pattern of protein and gene expression. Evaluation of CSPGs in the patients' CSF could potentially serve as biological markers of ALS.

Disclosures: **S. Forostyak:** None. **J. Kwok:** None. **P. Jendelova:** None. **A. Homola:** None. **M. Seneklova:** None. **J. Fawcett:** None. **E. Sykova:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.04

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH Grant K99AG047335

Title: *In vitro* disease modeling of ALS using neuronally enriched populations derived from human induced pluripotent cells

Authors: ***A. M. MAROOF**, K. EGGAN;
Stem Cell and Regenerative Biol., Harvard Univ., Cambridge, MA

Abstract: ALS and FTLD are neurodegenerative diseases that share similar pathologies and cellular dysfunction. ALS and FTLD are thought to lie on a clinical spectrum based on the presence of mutations in similar genes that can predispose specific neuronal populations to degenerative processes. In particular, a hexanucleotide repeat expansion in the C9ORF72 gene is the most common cause of ALS and FTLD, although the mechanisms linking the disruption of this gene to defined neurodegenerative processes have not been well established. Efforts to characterize phenotypes of the stem cell-derived neurons have been hampered by several factors, including heterogeneity between differentiations and differences in fate potential between lines. In this study, we identified tools to obtain post-mitotic neuronally committed cells derived from ALS patient and control pluripotent stem cells. Protocols to differentiate pluripotent stem cells into cortical projection neurons, cortical interneurons, and spinal motor neurons were implemented, and neuronal enrichment was demonstrated using several surface marker combinations. Transcriptional profiling of isolated neuronal populations revealed enrichment of terminally differentiated neurons that enriched for genes known to be associated either with cortical motor neurons, interneurons, or spinal motor neurons. In particular, using a novel protocol to generate deep layer cortical neurons, we observed increased expression of CTIP2, vGLUT1, FezF2, and TBR1 using FACS and immunofluorescence. Enriched cultures were depleted of EdU+, proliferative progenitors and exhibited typical neuronal characteristics, including spontaneous firing and synaptic puncta. Further efforts are currently being pursued to identify differences in molecular pathways affected during ALS disease onset and progression.

Disclosures: **A.M. Maroof:** None. **K. Eggan:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.05

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: the Department of Veterans Affairs

Title: Investigating the effects of caprylic triglyceride on mitochondrial function in cell models of amyotrophic lateral sclerosis

Authors: ***S. TIANO**[1], J. WANG[2,3], L. DUBNER[2], D. J. LANGE[4,5], G. M. PASINETTI[2,3]; [1]Neurol., Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Neurol., Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Geriatric Res. and Clin. Ctr., James J. Peters Veterans Affairs Med. Ctr., Bronx, NY; [4]Neurol., Weill Med. Col. of Cornell Univ., New York, NY; [5]Neurol., Hosp. for Special Surgery, New York, NY

Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder. It manifests itself with paralysis, skeletal muscle wasting, and ultimately death. The symptoms of ALS are caused by the progressive degeneration and death of upper motor neurons in the cerebral cortex and lower motor neurons in the brainstem and spinal cord. Currently there is no effective medical treatment for ALS. Mitochondrial abnormalities have been observed in the spinal motor neurons of ALS patients and impaired energy balance has been seen in the spinal cord. Previously, our group showed that treatment with caprylic triglyceride, a medium chain triglyceride that can be metabolized into ketone bodies, delays disease progression in the SOD1-G93A mouse model of ALS, coincidental with less motor neuron loss. In mechanistic studies of mitochondrial function, we found that treatment with caprylic triglyceride significantly improves the oxygen consumption rate (OCR) in the treatment group compared to vehicle treated control group, suggesting that caprylic triglyceride may be beneficial as a treatment for ALS by restoring the energy metabolism of mitochondria. Our *in vitro* study also showed that caprylic triglyceride can promote mitochondrial respiration in the NSC-34 cell line, a hybrid cell line produced by the fusion of embryonic spinal cord cells with mouse neuroblastoma. Based on this evidence, we hypothesize that caprylic triglyceride may influence the function of the mitochondrial permeability transition pore (mPTP), which plays an important role in axonal degeneration. The mPTP opens under calcium overload, which leads to mitochondrial swelling, dissipation of the proton motive force, uncoupling of oxidative phosphorylation, and cell death. mPTP function is

evaluated in isolated mitochondria from NSC-34 cells stably transfected with SOD1 G93A in the presence or absence of caprylic triglyceride. The OCR of the isolated mitochondria is analyzed using the Seahorse XF24 Extracellular Flux analyzer. In addition, the rate of ATP production is measured. In parallel, similar studies will be carried out in primary motor neurons isolated from SOD1-G93A mouse. Our study will provide information on the mechanism underlying the effects of caprylic triglyceride on mitochondrial function in models of ALS. In addition, the studies will provide guidance for translational clinical studies currently being designed by our group for the treatment of ALS.

Disclosures: S. Tiano: None. **J. Wang:** None. **L. Dubner:** None. **D.J. Lange:** None. **G.M. Pasinetti:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.06

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: ALSA Milton Safenowitz fellowship

NIH Grant NS073873

Title: Mutant PFN1-dependent cytoskeletal disruption affects mRNA post-transcriptional regulation in ALS

Authors: *C. FALLINI, M. JEON, J. E. LANDERS;
Neurol., UMASS Med. Sch., Worcester, MA

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease specifically affecting cortical and spinal motor neurons. ALS is the most common neuromuscular disease worldwide, with an average age of onset of 55 years and a mean survival of about 3-5 years from the beginning of symptoms. Death due to progressive motor neuron loss and muscle paralysis occurs within 3-5 years from the first symptoms. Although several pathways have been proposed to play a major role in the development of ALS, no consensus has yet emerged on a pathogenic mechanism common to different forms of ALS. Recently we identified mutations in two cytoskeletal genes, the actin binding protein profilin 1 (PFN1) and the microtubule subunit α-tubulin 4A (TUBA4A), as associated with familial ALS, which suggests that alterations in the cytoskeleton architecture and dynamics may play an important role in the pathogenesis of ALS.

In particular, we hypothesize that disruption to the actin and microtubule cytoskeleton affects multiple pathways, including protein degradation and mRNA post-transcriptional processing due to the inhibition of cellular trafficking. To explore this hypothesis, we investigated the effects of PFN1 mutations on the localization and aggregation propensity of the RNA-binding protein TDP-43 and other mRNA regulatory proteins. Aggregation and nuclear depletion of TDP-43 and other mRNA binding proteins such as FUS is a hallmark of ALS pathology. Our results show that mutant PFN1 leads to increased aggregation of TDP-43, possibly due to the inhibition of the ubiquitin proteasome system. Using quantitative immunofluorescence, we show that mutant PFN1 causes specific defects in the nuclear and axonal localization of TDP-43 and other mRNA processing factors, and that these defects are dependent on the ability of PFN1 to bind actin. Together, our results support the hypothesis that alterations to mRNA post-transcriptional processing represents a common pathogenic mechanism in different forms of ALS.

Disclosures: **C. Fallini:** None. **M. Jeon:** None. **J.E. Landers:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.07

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: MNDI Australia

Title: Amyotrophic Lateral Sclerosis-associated profilin I mutations impact dendritic morphology of central nervous system neurons

Authors: ***T. FATH**, M. BRETTLE, A. SUCHOWERSKA, S. W. CHUA, L. M. ITTNER; Sch. of Med. Sci., Univ. of New South Wales, Sydney, Australia

Abstract: Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease and Charcot disease, is a devastating neurodegenerative disease for which treatments are very limited. People diagnosed have an average life span of 3 years post-diagnosis. Both upper and lower motor neurons are affected, leading to muscle weakness and atrophy throughout the body. Although familial forms of the disease only account for approximately 10% of all cases, various histopathological hallmarks, such as TDP-43 inclusions, are conserved across familial and sporadic cases. Mutations in the profilin 1 (PFN1) gene were identified in familial ALS by exome sequencing and the mutations and *in vitro* analysis of the mutations showed an inhibitory effect on axonal growth of motor neurons. PFN1 is a 12-15kDa ubiquitous actin-binding protein

and a key regulator of actin filament dynamics, linking the regulation of the actin cytoskeleton with ALS pathology. Here, we studied the impact of the most prominent ALS-associated PFN1 mutation (C71G) on neuronal morphogenesis in mouse primary neurons. Analysis of developing hippocampal neurons, expressing wt and mutant PFN1, revealed that mutant PFN1 leads to a specific increase in the length of dendrites and dendritic arborisation without impacting axonal growth. Furthermore, C71G PFN1 expression results in increased dendritic spine density in mature cultures of hippocampal neurons. To our knowledge, this is the first study to show dendrite-specific morphological changes in neurons expressing ALS-associated mutant profilin 1.

Disclosures: **T. Fath:** None. **M. Brettle:** None. **A. Suchowerska:** None. **S.W. Chua:** None. **L.M. Ittner:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.08

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH R00NS077435

Title: Haploinsufficiency of c9orf72 implicates endosomal trafficking in ALS and FTD

Authors: *J. ICHIDA;
USC, Los Angeles, CA

Abstract: A massive expansion of a GGGGCC repeat in an intron of *C9orf72* recently emerged as the most common cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), making it a key therapeutic target. However, the neurodegenerative mechanisms underlying *C9orf72* ALS/FTD are unclear. Here, we use induced motor neurons (iMNs) generated using transcription factor-mediated reprogramming to show that the loss of C9orf72 protein expression, which results from transcriptional stalling within the repeat expansion, is the major cause of neurodegeneration. Longitudinal tracking showed that *C9orf72* patient iMNs undergo accelerated degeneration (3 patients, 3 controls, p=.002) and possess the hallmark pathology of *C9orf72* ALS. In contrast, induced dopaminergic neurons from *C9orf72* patient iPSCs do not undergo rapid degeneration, suggesting this phenotype is motor neuron specific. Removing the repeat expansion from patient iPSCs using CRISPR/Cas9 editing fully rescued iMN survival. Thus, *C9orf72* iMNs faithfully model ALS disease processes. Similar to

postmortem studies, patient-derived iMNs had low C9orf72 protein levels. We found that exogenously restoring C9orf72 expression rescued patient iMN survival. Conversely, knocking out C9orf72 protein expression in control iMNs using CRISPR/Cas9 editing induced rapid degeneration at rates similar to patient iMNs. Thus, the loss C9orf72 protein induces neurodegeneration. C9orf72 shares homology with guanine exchange factors that control endosomal trafficking. Consistent with this function, we found that C9orf72 is localized in endosomes in iMNs. We used a biochemical assay with purified C9orf72 and RAB GTPase proteins to show that C9orf72 acts as a guanine exchange factor for a RAB GTPase that controls the trafficking of early endosomes. The lack of C9orf72 function caused improper endosomal trafficking of glutamate receptors and hyperexcitability in patient and C9orf72-deficient iMNs. This caused excitotoxicity, which induced the rapid neurodegeneration. An FDA-approved drug that suppresses neuronal firing rescued patient iMN survival. Our results from the iMN model indicate that the loss of C9orf72 protein function plays a major role in *C9orf72* ALS and provide a clear link between the causal mutation, endosomal trafficking, and excitotoxic neuron death.

Disclosures: J. Ichida: None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.09

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Wellcome Trust Research Training Fellowship to RB: Grant Number 107196/Z/15/Z

Leonard Wolfson Experimental Neuroscience Centre Fellowship to RB

MNDA

Title: Molecular mechanisms and therapeutic strategies in amyotrophic lateral sclerosis caused by mutations in the C9orf72 gene

Authors: *R. BALENDRA[1,2], A. DEVOY[1], P. FRATTA[1], S. GROENKE[4], S. MIZIELINSKA[1], T. MOENS[1,3], T. NICCOLI[2], C. RIDLER[1], R. SIMONE[1], G. PARKINSON[5], S. NEIDLE[5], N. WOODLING[2], R. PATANI[6], L. PARTRIDGE[2,4], A. ISAACS[1];
[1]Dept. of Neurodegenerative Dis., London, United Kingdom; [2]Dept. of Genetics, Evolution and Envrn., [3]Inst. of Healthy Ageing, Univ. Col. London, London, United Kingdom; [4]Max Planck

Inst. for Biol. of Ageing, Cologne, Germany; [5]UCL Sch. of Pharm., London, United Kingdom; [6]Dept. of Mol. Neuroscience, UCL Inst. of Neurol., London, United Kingdom

Abstract: Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterised by motor neuron degeneration. A hexanucleotide expansion in the C9orf72 gene is a common cause of ALS. We have recently published evidence in a *Drosophila* model that neurotoxicity is mediated by dipeptide repeat (DPR) proteins generated by repeat-associated non-ATG translation. Emerging evidence suggests that DPR proteins cause nucleolar dysfunction and resolving this in relevant models will significantly increase our understanding of and ability to treat C9orf72-mediated ALS. Aims: To evaluate in C9orf72-ALS models if DPR proteins cause nucleolar dysfunction and interact with RNA and whether novel small molecules binding C9orf72-repeat RNA reduce DPR formation, nucleolar dysfunction and neurotoxicity. Methods: In an integrated approach across model systems nucleolar function is assessed in 1) novel *in vivo Drosophila* models, with subsequent validation in 2) C9orf72 human induced pluripotent stem cell (iPSC)-derived motor neurons. Small molecules binding C9orf72-repeat RNA are fed to *Drosophila* and will subsequently be applied to C9orf72 iPSC-derived motor neurons evaluating rescue of disease phenotype. Results and Conclusions: These experiments may provide novel mechanistic insights into a common form of ALS and deliver pre-clinical data on an exciting therapeutic approach.

Disclosures: **R. Balendra:** None. **A. Devoy:** None. **P. Fratta:** None. **S. Groenke:** None. **S. Mizielinska:** None. **T. Moens:** None. **T. Niccoli:** None. **C. Ridler:** None. **R. Simone:** None. **G. Parkinson:** None. **S. Neidle:** None. **N. Woodling:** None. **R. Patani:** None. **L. Partridge:** None. **A. Isaacs:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.10

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: GU medical center internal funds

Title: Tyrosine kinase inhibition ameliorates nucleocytoplasmic TDP-43 shuttling and reverses cell death and muscle denervation

Authors: *C. E. MOUSSA[1], L. HEYBURN[2], M. HEBRON[2], I. LONSKAYA[2], Y. FENG[2]; [1]Neurol., Georgetown Univ., Washington, DC; [2]Neurol., Georgetown Univ., Washington DC, DC

Abstract: The importance of RNA metabolism was highlighted by the discovery of TAR DNA binding protein-43 (TDP-43) as a primary component of insoluble aggregates in patients with sporadic and familial motor neuron disease (MND). TDP-43 pathology not only provides a link between sporadic and familial MND as the basis of motor neuron death, but it is also an underlying mechanism in the spectrum of MND and Fronto-Temporal Lobar Dementia (FTLD-TDP) disorder. In healthy neurons, TDP-43 is predominantly nuclear, but in MND and FTLD, TDP-43 is translocated to the cytosol where it is ubiquitinated and/or phosphorylated and cleaved. However, the underlying pathomechanism(s) leading to TDP-43 modification is not well understood and TDP-43 accumulation can lead to neuronal loss either through enhanced cytoplasmic function and/or diminished nuclear function. We intra-peritoneally injected (5-6 months old) mice that express neuronal wild type human TDP-43 (Tg-TDP-43) with 10mg/kg nilotinib or 5 mg/kg bosutinib or DMSO daily for 3 consecutive weeks. Nilotinib and bosutinib are Abelson (Abl) tyrosine kinase inhibitors (TKIs) that are FDA-approved for chronic myeloid leukemia (CML). We found that these TKIs significantly reduce nuclear TDP-43 levels and attenuate cell death in the hippocampus and motor cortex, suggesting increased nucleocytoplasmic shuttling of TDP-43. Myelin thickness and axons within the dorso-cortical spinal tract (DCST) were reduced in DMSO treated Tg-TDP-43 mice, and TKIs reversed myelin thinning and protected against axonal loss. Interestingly, pathology was also detected in skeletal muscle as both angulated fibers (denervation) and centric nuclei (regeneration/degeneration), suggesting that neuronal TDP-43 expression affects spinal cord axons and muscle fibers, reminiscent of MND pathology. These mice also exhibited significant weakness at 1-2 years of age but TKI treatment for 4 weeks did not reverse weakness. TDP-43 mice showed memory deficit compared to control but TKIs improved memory. Taken together these data indicate that neuronal expression of human TDP-43 leads to spinal cord and muscle pathology as well as motor and cognitive defects. Nilotinib and bosutinib may induce critical post-translational TDP-43 modifications that affect nucleocytoplasmic shuttling and protect against neuronal death, providing drug candidates as diseases modifying therapies in MND-FTD-TDP disorders.

Disclosures: C.E. Moussa: Other; I have an IP to Use TKIs in neurodegenerative diseases. **L. Heyburn:** None. **M. Hebron:** None. **I. Lonskaya:** None. **Y. Feng:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.11

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH grant NS079339

MDA grant 254860

Title: Inhibition of BACE1 in the SOD1G93A mouse model of ALS enhances neuromuscular junction remodeling

Authors: *C. TALLON[1], M. H. FARAH[2];
[2]Neurol., [1]Johns Hopkins Univ. SOM, Baltimore, MD

Abstract: In the early stages of motor neuron disease, evidence of distal axonal degeneration begins to occur long before the onset of clinical symptoms. As the disease advances, degeneration progresses proximally and eventually reaches the cell body, leading to motor neuron cell death. Despite this ongoing degenerative process, surviving motor neurons attempt to reinnervate the denervated regions of the muscle by sending out axonal processes. Unfortunately, this repair process cannot keep up with the degeneration and patients begin to lose function in their extremities, greatly decreasing their quality of life. Here we propose using the Ly2886721 beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitor to enhance this endogenous regeneration in the G93A mutant super oxide dismutase 1 (SOD1) mouse model of amyotrophic lateral sclerosis (ALS). Previously, our lab had observed that inhibiting BACE1 leads to augmented nerve regeneration in a sciatic nerve crush model. To assess regeneration specifically in motor nerves, we utilized the lateral thoracic nerve (LTN) and the cutaneous maximus muscle (CMM) system as the LTN is a purely motor nerve while the CMM is thin enough to allow whole tissue staining and imaging. We compared the physiological function of the LTN-CMM system between treated and untreated mice by performing electrophysiological recordings at three sites along the CMM. We also compared the number of innervated neuromuscular junctions at these same three sites between treated and untreated mice to assess morphological changes. Our preliminary results show an increase in the number of innervated neuromuscular junctions in mice treated with the BACE1 inhibitor as well as improved physiological function. While these experiments are still ongoing, we believe that BACE1 inhibitors may be a potential therapy for patients suffering from motor neuron diseases. By enhancing regeneration of the surviving motor axons, function in the extremities may be preserved for longer and will greatly improve patient quality of life for slow progressing diseases.

Disclosures: C. Tallon: None. **M.H. Farah:** None.

Nanosymposium

557. Motor Neuron Disease

Location: N230

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 557.12

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NINDS R21NS064349

NICHD R21HD57402

NICHD R01HD064850

Title: Novel small molecules that increase SMN protein and extend survival of SMA mice

Authors: *A. RIETZ[1], E. Y. OSMAN[2], H. LI[1], C. L. LORSON[3], J. J. CHERRY[1], S. K. CUSTER[1], G. D. CUNY[4], M. A. GLICKSMAN[4], K. J. HODGETTS[4], E. J. ANDROPHY[1]; [1]Dept. of Dermatol., Indiana Univ., Indianapolis, IN; [2]Dept. of Vet. Pathobiology, [3]Dept. of Vet. Pathobiology, Dept. of Mol. Microbiology and Immunol., Univ. of Missouri, Columbia, MO; [4]Lab. for Drug Discovery in Neurodegeneration, Brigham and Women's Hosp. and Harvard Med. Sch., Cambridge, MA

Abstract: Spinal muscular atrophy (SMA) is the leading genetic cause of infant death. Most campaigns that aim to identify treatments for SMA have the goal of increasing survival motor neuron (SMN) protein levels. Although the level of SMN needed to maintain motor neurons is not known, doubling or tripling the amount of full-length SMN2 mRNA or protein should be clinically significant. Previously, we developed a high-through put assay that employs a SMN2-luciferase construct allowing identification of compounds that act transcriptionally, enhance splicing or stabilize SMN protein. Using this assay we identified two novel scaffold series, LDN-76 and LDN-75, which increase SMN protein by two distinctive mechanisms. LDN-76 series increased SMN mRNA, while LDN-75 series does not alter transcription or splicing of SMN2 mRNA. Using a structure-based activity approach, we have now identified analogs with high potency for both series. For the LDN-76 series we identified a novel analog that exists as a racemic mixture. Racemic separation resulted in the identification of an active and inactive stereoisomer. The active isomer increased SMN transcriptionally without altering SMN mRNA stability. For the 75-series, we identified 20 active analogs with improved solubility (EC50 <400 nM). One of these leads activates SMN2-luciferase by ~400% with an EC50 of 0.3 μM after 48 hr, while the control Renilla luciferase was unaffected. There was no cell viability loss at 100x the EC50 after 48 hrs. SMN protein increased in GM003813T (hTert-immortalized SMA fibroblasts) by 2-fold. This analog does not alter SMN mRNA expression but increases half-life of the SMN2-luciferase protein (t1/2 >24 hrs), without affecting the half-life of control Renilla

luciferase protein. These effects are not mediated via proteasome inhibition. Consistent with this interpretation, it did not affect cellular protein levels of short-lived proteins such as p53 or p21. When administered every other day by IP injection, survival of severe SMNΔ7 mice increased by >200% compared to vehicle. In the Smn2B/- mice, all vehicle-treated mice died by PND 49, whereas ~50% of drug-treated mice were alive, had gained weight, and were fully mobile at PND 112. With a modest SAR campaign, we identified novel and active analogs of both series. These achieve increased levels of SMN protein by either transcriptional activation (76-series) or by reducing its metabolic turnover (75-series). The 75-series lead is biologically active in mouse models of SMA, extending survival and motor function. This represents a novel therapeutic mechanism for treatment of SMA that should be accretive to other modalities currently under investigation.

Disclosures: **A. Rietz:** None. **E.Y. Osman:** None. **H. Li:** None. **C.L. Lorson:** None. **J.J. Cherry:** None. **S.K. Custer:** None. **G.D. Cuny:** None. **M.A. Glicksman:** None. **K.J. Hodgetts:** None. **E.J. Androphy:** None.

Nanosymposium

558. Major Mental Disorders: Novel Approaches for Patient Evaluation

Location: S102

Time: Tuesday, October 20, 2015, 1:00 PM - 3:30 PM

Presentation Number: 558.01

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Netherlands Organisation for Scientific Research

Neuroscience and Cognition Utrecht

Title: 7T proton magnetic resonance spectroscopy of GABA, glutamate, and glutamine in schizophrenia reveals altered metabolite concentrations in patients and unaffected relatives

Authors: *K. N. THAKKAR[1,3], L. RÖSLER[1], J. P. WIJNEN[2], V. O. BOER[2], D. W. J. KLOMP[2], W. CAHN[1], R. S. KAHN[1], S. F. W. NEGGERS[1];
[1]Psychiatry, [2]Radiology, Univ. Med. Ctr. Utrecht, Utrecht, Netherlands; [3]Dept. of Psychology, Michigan State Univ., East Lansing, MI

Abstract: Background: The NMDA-receptor hypofunction model of schizophrenia predicts dysfunction in both glutamatergic and GABAergic transmission in individuals with schizophrenia. In the current study we aimed to address this hypothesis by measuring γ-aminobutyric acid (GABA), glutamate (Glu), and glutamine (Gln), and Gln+Glu (Glx)

concentrations *in vivo* in patients with schizophrenia using proton magnetic resonance spectroscopy (1H-MRS) at an ultra-high field strength of 7.0 Tesla, which allows separation of these metabolites that would otherwise overlap at lower field strengths. In addition, we investigated the degree to which putatively altered levels of GABA, Glu, Gln, and Glx reflect genetic vulnerability towards schizophrenia by including healthy first-degree relatives. Methods: 21 chronic, medicated schizophrenia patients, 23 healthy first-degree relatives of schizophrenia patients, and 24 healthy non-relatives underwent 1H-MRS at 7T. Glu, Gln, and GABA were measured cortically and subcortically in bilateral striatum and occipital cortex. Metabolites were quantified using an automated fitting procedure and concentrations were corrected for partial volume effects. Results: Reduced cortical GABA in was observed in individuals with schizophrenia, compared with both healthy relatives and healthy non-relatives, suggesting that altered GABAergic transmission in schizophrenia is associated with either illness state or medication effects. On the other hand, reduced cortical Glu and Glx were observed in both healthy relatives and schizophrenia patients, suggesting both that altered glutamatergic transmission is associated with illness liability and that reduced Glu and Glx in schizophrenia patients cannot be solely attributed to medication effects. A statistical trend for a larger ratio of GABA to Glx was observed in healthy relatives compared to both healthy controls and patients. These group differences remained even after controlling for differences in tissue composition across individuals. No group differences in metabolite concentrations or ratios were found in the striatum, and no differences in Gln were observed in any of the measurement regions. Conclusions: Combined, these findings are consistent with NMDA-receptor hypofunction in schizophrenia and provide novel insights into availability and transmission of glutamate and GABA in healthy relatives.

Disclosures: **K.N. Thakkar:** None. **L. Rösler:** None. **J.P. Wijnen:** None. **V.O. Boer:** None. **D.W.J. Klomp:** None. **W. Cahn:** None. **R.S. Kahn:** None. **S.F.W. Neggers:** None.

Nanosymposium

558. Major Mental Disorders: Novel Approaches for Patient Evaluation

Location: S102

Time: Tuesday, October 20, 2015, 1:00 PM - 3:30 PM

Presentation Number: 558.02

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: A neurocognitive model of ambivalence in schizophrenia

Authors: *F. TREMEAU[1], D. ANTONIUS[2], J. CACIOPPO[3], D. JAVITT[4];
[1]Nathan Kline Inst., Orangeburg, NY; [2]Univ. of Buffalo, Buffalo, NY; [3]Univ. of Chicago, Chicago, IL; [4]Univ. of Columbia, New York, NY

Abstract: Background: Most affective neuroscience models posit that affective information is processed by two separate but interacting systems: one evaluative system for Positivity and one evaluative system for Negativity, and their co-activation produces ambivalence (the simultaneous experience of pleasure and displeasure). Ambivalence impairs motivation and action readiness. To limit the occurrence of ambivalence from complex stimuli (which frequently contain positive and negative features), the more activated system inhibits the other system. Ambivalence is the major affective deficit in schizophrenia, suggesting impairment in cross-inhibition between the two affective systems. The present study examined ambivalence in schizophrenia, and the results were interpreted in terms of cross-inhibition. More specifically, two functional aspects were examined: the maximum efficiency factor (at maximum activation of one system, the other one should be completely inhibited, i.e. ratings of maximum intensity are not ambivalent) and the gain function (as the activation of one system increases, the other one gets more inhibited, i.e. as intensity ratings increase, ambivalent ratings are less frequent). Methods: One hundred twenty individuals with schizophrenia and 62 non-patient control participants completed an evocative affective task with 40 IAPS pictures of different valences and intensities. Following each presentation, participants rated their induced levels of pleasantness and unpleasantness on two separate ratings of five different intensity levels each. All patients were also assessed on level of psychopathology. Results: Group differences of large effect sizes were found for the frequency of ambivalent ratings. When schizophrenia participants rated stimuli as extremely pleasant or extremely unpleasant, they gave ambivalent ratings more frequently than controls. As stimuli were rated as more negative, the frequency of ambivalent ratings decreased to a lesser extent in schizophrenia patients. No group differences were found with positive ratings. Conclusion: Individuals with schizophrenia showed more affective ambivalence, which suggests a deficit in the cross-inhibition between the positivity and negativity affective systems. Inhibition at maximal efficiency was impaired for both systems in schizophrenia. A specific deficit in gain control was observed for the Negativity but not the Positivity system, reinforcing the need to differentiate these two systems. Future research should examine the association between cross-inhibition and excitatory and inhibitory neurotransmission impairment in schizophrenia.

Disclosures: F. Tremeau: None. **D. Antonius:** None. **J. Cacioppo:** None. **D. Javitt:** None.

Nanosymposium

558. Major Mental Disorders: Novel Approaches for Patient Evaluation

Location: S102

Time: Tuesday, October 20, 2015, 1:00 PM - 3:30 PM

Presentation Number: 558.03

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Howard Hughes Medical Institute

Office of Naval Research N000141310672

NIH NS040522

Swartz Foundation

Title: Bringing order to the neurophysiological chaos underlying sensory processing dysfunction in schizophrenia

Authors: C. LAINSCSEK[1], A. SAMPSON[1], T. COGS INVESTIGATORS[2], G. LIGHT[3], *T. J. SEJNOWSKI[1];
[1]Salk Inst. CNL-S, La Jolla, CA; [3]Psychiatry, [2]UCSD, La Jolla, CA

Abstract: There is compelling evidence that sensory processing impairments contribute to the cognitive and psychosocial dysfunction affecting the majority of schizophrenia (SZ) patients. An informative probe for sensory processing dysfunction in neuropsychiatric disorders is event-related potentials (ERPs) time-locked to presentations of deviant stimuli interspersed in a train of standard tones, which elicits a response complex dominated by two peaks, labeled mismatch negativity (MMN) and P3a positivity. Conventional approaches to electrocephalogram (EEG) analysis do not access the full wealth of information contained in the ERPs. We have used a new method to analyze EEG data based on nonlinear data analysis that extracts the dynamical structure of the data, which allows for classification of raw data in nearly real time and is highly generalizable across patients. Delay Differential Analysis (DDA) is a time domain classification framework based on embeddings in chaos theory (Lainscsek and Sejnowski, 2015). An embedding reveals the nonlinear invariant properties of an unknown dynamical system (here the brain) from a single time series (here EEG data). The embedding in DDA serves as a low-dimensional nonlinear functional basis onto which the data are mapped. Since the basis is built on the dynamical structure of the data, preprocessing of the data (such as filtering) is not necessary. DDA yields a small number of features (around 4), far fewer than traditional spectral techniques, which greatly reduces the risk of overfitting. We applied DDA to EEG data segments from 1630 subjects (normal control subjects n=753, SZ n=877) who underwent MMN testing as part of a Consortium on the Genetics of Schizophrenia (COGS-2) study. Receiver operating characteristic (ROC) curves were used to evaluate the extent to which DDA and traditional ERP components differentiated the 2 groups. The results of the present study show that DDA improved the differentiation of SZ from NCS (area under the ROC curve was 0.80) relative to conventional ERP analysis (area under the ROC curve was 0.75). Perfect discrimination occurs

with the area under the ROC curve is 1. In conclusion, DDA is a powerful technique that capitalizes on information contained in entire EEG signal, revealing hidden information about nonlinear couplings that are not apparent in conventional ERP analyses. Moreover, DDA does not require data cleaning, extensive data processing or computational demands for rapid analysis of EEG results. Lainscsek, C. Sejnowski, T. J. Delay Differential Analysis of Time Series, Neural Computation, 27, 594-614, 2015

Disclosures: C. Lainscsek: None. **A. Sampson:** None. **T. COGS Investigators:** None. **G. Light:** None. **T.J. Sejnowski:** None.

Nanosymposium

558. Major Mental Disorders: Novel Approaches for Patient Evaluation

Location: S102

Time: Tuesday, October 20, 2015, 1:00 PM - 3:30 PM

Presentation Number: 558.04

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIH Grant R24 MH106057

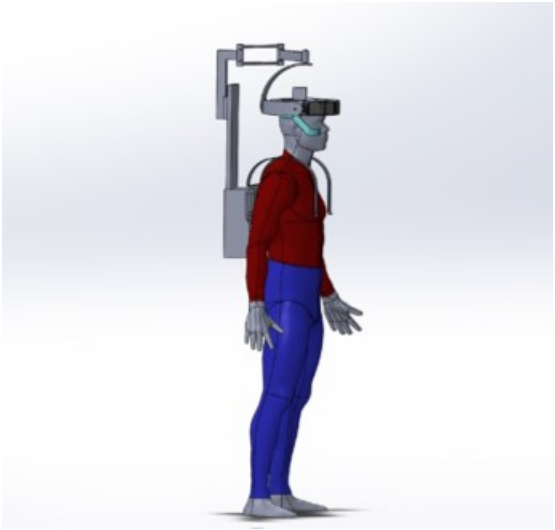
NIH Grant R01 EB00194

Title: Ampet: a brain initiative planning project to design a wearable, microdose pet imager

Authors: *J. A. BREFCZYNSKI-LEWIS[1], S. MAJEWSKI[2], R. MANJESHWAR[3], A. STOLIN[1], P. KINAHAN[4], J. QI[5], S. DOLINSKY[3], R. HARRISON[4], M. RISHEL[3], B. ELSTON[4], K. GONG[5], K. VAIGNEUR[6];
[1]West Virginia Univ., Morgantown, WV; [2]UVA, Charlottesville, VA; [3]GE Global Res., Niskayuna, NY; [4]UW, Seattle, WA; [5]UC Davis, Davis, CA; [6]Agile Technologies, Knoxville, TN

Abstract: Brain imaging has been limited by the motion intolerance of big, bolted-to-the-floor imagers like MRI, PET and MEG and by low resolution, surface-only imaging of EEG and Near Infrared Imaging. In this project, we are designing a wearable imager that will enable high resolution imaging of both deep and surface brain, all while the subject is upright and moving. Our initial simulation results have shown a more than 400% increase in sensitivity by the helmet scanner over the conventional whole-body PET scanner. With further improvements in time-of-flight (TOF) and depth of interaction information, we expect the injected radioligand dose can be very low. Pilot data results show that it will be better than 1/10th of the standard dose. Advances will be shown, including designs of physical detectors and mechanical support prototypes, including one that is worn like a backpack and allows a high degree of motion freedom. Our

team has investigated potential uses in the neuroscience and clinical worlds. Application ideas will be discussed, including those enabled by different uses of radioligands such as low-dose O15 with its relative short half-life that will allow for functional PET imaging, and other studies utilizing different neurotransmitter and microglia targets. Novel areas of study may include balance, physical therapies, natural social interactions, virtual reality as well as disorders like stroke, Alzheimer's, Parkinson's, multiple sclerosis and traumatic brain injury (e.g. testing effects of exercise on brain recovery). By helping future users of the imager understand the different design optimizations necessary to account for sensitivity, resolution, brain coverage and weight of detector (freedom of movement), we can discover the best uses for our imager and focus on creating the best prototype designs, while developing future partnerships.



Disclosures: **J.A. Brefczynski-Lewis:** None. **S. Majewski:** None. **R. Manjeshwar:** A. Employment/Salary (full or part-time); GE Global Research. **A. Stolin:** None. **P. Kinahan:** None. **J. Qi:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Toshiba. **S. Dolinsky:** A. Employment/Salary (full or part-time); GE Global Research. **R. Harrison:** None. **M. Rishel:** A. Employment/Salary (full or part-time); GE Global Research. **B. Elston:** None. **K. Gong:** None. **K. Vaigneur:** A. Employment/Salary (full or part-time); Agile Technologies.

Nanosymposium

558. Major Mental Disorders: Novel Approaches for Patient Evaluation

Location: S102

Time: Tuesday, October 20, 2015, 1:00 PM - 3:30 PM

Presentation Number: 558.05

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH

Title: Characterization of cellular autofluorescence as a mechanism-guided high throughput biomarker for schizophrenia

Authors: N. J. ELKINS[1], A. RAMOS[1], T. TSUJIMURA[1], C.-Y. LIN[1], H. JAARO-PELED[1], J. GALLEGO[2], D. ROBINSON[2], T. SAITOH[3], T. W. SEDLAK[1], A. K. MALHOTRA[2], K. ISHIZUKA[1], *A. SAWA[1];
[1]Dept. of Psychiatry, Johns Hopkins Univ., Baltimore, MD; [2]Zucker Hillside Hosp., Glen Oaks, NY; [3]Aomori Univ., Aomori, Japan

Abstract: Establishment of a biomarker for psychiatric diseases such as schizophrenia (SZ) is an important step in early diagnosis and intervention prior to full escalation of symptoms. Here we report a study in which we found augmented cellular autofluorescence (AF) measured by fluorescence activated cell sorting in lymphoblasts of SZ patients (n=46) as compared to age-, race-, and gender-matched controls (n=38). Levels of AF were inversely correlated to overall cognitive function (composite scores), suggesting important clinical implications. As levels of AF are correlated with reactive oxygen species levels, the oxidative stress-elicited GAPDH nuclear pathway might be involved in the cellular mechanisms underlying pathological AF in SZ. In addition, we found that the excitatory amino-acid carrier-1 (EAAC1) knockout and dominant-negative DISC1 mice exhibited elevated levels of AF together with augmented oxidative stress in prefrontal cortex. Importantly, their cognitive deficits were ameliorated following treatment with the GAPDH nuclear pathway inhibitor, “RR”. We are now studying cell-type and region-specific AF and GAPDH pathology in these animals to link the cellular mechanism and cognitive deficits at the neurocircuitry level.

Disclosures: **N.J. Elkins:** None. **A. Ramos:** None. **T. Tsujimura:** None. **C. Lin:** None. **H. Jaaro-Peled:** None. **J. Gallego:** None. **D. Robinson:** None. **T. Saitoh:** None. **T.W. Sedlak:** None. **A.K. Malhotra:** None. **K. Ishizuka:** None. **A. Sawa:** None.

Nanosymposium

558. Major Mental Disorders: Novel Approaches for Patient Evaluation

Location: S102

Time: Tuesday, October 20, 2015, 1:00 PM - 3:30 PM

Presentation Number: 558.06

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: K24 MH079510

2R01MH064821

RC1MH089704

Title: Amygdalo-frontal dysconnectivity

Authors: *Y. I. SHELINE[1], T. D. SATTERTHWAITE[1], P. A. COOK[2], S. E. BRUCE[4], C. CONWAY[5], E. MIKKELSEN[1], E. SATCHELL[1], S. N. VANDEKAR[3], T. DURBIN[5], R. T. SHINOHARA[3];
[1]Psychiatry, [2]Radiology, [3]Biostatistics and Epidemiology, Univ. of Pennsylvania, Philadelphia, PA; [4]Psychology, Univ. of Missouri - St. Louis, St. Louis, MO; [5]Psychiatry, Washington Univ., St. Louis, MO

Abstract: Depressive symptoms are common in multiple psychiatric disorders and are frequent sequelae of trauma. A dimensional conceptualization of depression suggests that symptoms should be associated with a continuum of deficits in specific neural circuits. However, most prior investigations of abnormalities in functional connectivity have typically focused on a single diagnostic category using hypothesis-driven seed-based analyses. Here, using a sample of 105 adult female participants from three diagnostic groups (healthy controls, n=17; major depression, n=38; post-traumatic stress disorder, n=50), we examine the dimensional relationship between resting-state functional dysconnectivity and severity of depressive symptoms across diagnostic categories using a data-driven analysis (multivariate distance-based matrix regression). This connectome-wide analysis identified foci of dysconnectivity associated with depression severity in the bilateral amygdala. Follow-up seed analyses using subject-specific amygdala segmentations revealed that depression severity was associated with amygdalo-frontal hypo-connectivity in a network of regions including bilateral DLPFC, anterior cingulate, and anterior insula. In contrast, anxiety was associated with elevated connectivity between the amygdala and the ventromedial prefrontal cortex. Taken together, these results emphasize the centrality of the amygdala in the pathophysiology of depressive symptoms, and suggest that dissociable patterns of amygdalo-frontal dysconnectivity are a critical neurobiological feature across clinical diagnostic categories.

Disclosures: Y.I. Sheline: None. **T.D. Satterthwaite:** None. **P.A. Cook:** None. **S.E. Bruce:** None. **C. Conway:** None. **E. Mikkelsen:** None. **E. Satchell:** None. **S.N. Vandekar:** None. **T. Durbin:** None. **R.T. Shinohara:** None.

Nanosymposium

558. Major Mental Disorders: Novel Approaches for Patient Evaluation

Location: S102

Time: Tuesday, October 20, 2015, 1:00 PM - 3:30 PM

Presentation Number: 558.07

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: CIHR

NIMH

HDRF

Title: Sex-specific transcriptional signatures in the brains of males and females with major depressive disorders (MDD)

Authors: *B. LABONTÉ[1], I. PURUSHOTHAMAN[2], O. ENGMANN[2], Z. LORSCH[2], J. SCARPA[2], O. ISSLER[2], G. HODES[2], D. WALKER[2], M. PFAU[2], E. CALIPARI[2], E. LOH[2], M. DOYLE[2], C. TAMMINGA[3], G. TURECKI[4], B. ZHANG[2], L. SHEN[2], E. J. NESTLER[2]; [1]Neurosci., [2]Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]UT Southwestern, Dallas, TX; [4]McGill Univ., Montreal, QC, Canada

Abstract: Introduction Females are 2-3 times more susceptible to MDD than males. Males and females also often exhibit different symptomatic profiles, respond differently to antidepressants, and show different biological adaptations to stress. These sex-specific differences in the expression of MDD are believed to be accompanied by different transcriptional signatures across brain regions. This study aims at defining the sex-specific transcriptional signatures and gene expression networks in the brain associated with MDD. Methods Transcriptional profiles from postmortem brains of humans with MDD (N=12 males, 12 females) and controls (N=12 males, 12 females) were analyzed in 6 brain regions (cingulate gyrus 25 (PFC; BA25), orbitofrontal cortex (OFC; BA11), dorsolateral PFC (dlPFC; BA8/9), anterior insula, hippocampus (HPC) and nucleus accumbens (NAc)) using RNAseq (50bp paired end). Transcriptional profiles from male and female mice after chronic variable stress (CVS) were also analyzed in the NAc and PFC. For both human and mice, differential analysis was performed with voom Limma and gene expression networks were constructed and analyzed through a weighted gene co-expression network analysis (WGCNA). Viral mediated gene transfer in mice was used to assess the functional relevance of our findings. Results Our analyses revealed differential expression of several hundreds of genes in each brain region investigated in both depressed males and females vs normal subjects. However, the overlap between males and females was strikingly small. A similar small overlap was also found in mice after CVS. WGCNA and differential network analysis uncovered several highly co-regulated gene subnetworks in MDD and in mice after CVS with a significant gain or loss of network connectivity. Our analysis also identified common and divergent gene subnetworks between males and females that were preserved in both species and that were enriched for differentially expressed genes in males or females,

respectively. Viral mediated gene transfer in the PFC and NAc of mice confirmed the functional role of our findings by promoting stress susceptibility in males and females. Conclusions Our findings suggest that males and females with MDD show largely distinct transcriptional signatures. Overall, our results suggest that altering the precise transcriptional balance existing within and across brain regions may disrupt normal brain activities and interfere with the regulation of mood-related behaviors differently in males and females.

Disclosures: **B. Labonté:** None. **I. Purushothaman:** None. **O. Engmann:** None. **Z. Lorsch:** None. **J. Scarpa:** None. **O. Issler:** None. **G. Hodes:** None. **D. Walker:** None. **M. Pfau:** None. **E. Calipari:** None. **E. Loh:** None. **M. Doyle:** None. **C. Tamminga:** None. **G. Turecki:** None. **B. Zhang:** None. **L. Shen:** None. **E.J. Nestler:** None.

Nanosymposium

558. Major Mental Disorders: Novel Approaches for Patient Evaluation

Location: S102

Time: Tuesday, October 20, 2015, 1:00 PM - 3:30 PM

Presentation Number: 558.08

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Impacts of cognitive training on cortical oscillations and implicit learning in patients with schizophrenia

Authors: *L. B. HINKLEY[1], B. BIAGIANTI[2], D. MIZUIRI[1], S. VINOGRADOV[2], S. NAGARAJAN[1];
[1]Radiology, UC San Francisco, San Francisco, CA; [2]Psychiatry, UCSF, San Francisco, CA

Abstract: An emerging hypothesis in the neuropathology of schizophrenia is that alterations in oscillatory activity contribute to cognitive and behavioral symptoms prevalent in the disorder. To test the hypotheses that 1) impoverished neural oscillations can impair skill learning in schizophrenia and that 2) computerized cognitive training paradigms can remediate these oscillations we use magnetoencephalographic imaging (MEGI) during implicit learning in a cohort of 24 patients with chronic schizophrenia. MEG data was collected using a 275-channel biomagnetometer (CTF) during a modified serial reaction time task (SRTT) using manual movements. Individuals were instructed to respond to a short vowel (/e/, /i/, /o/, /u/) presented in the auditory domain by pressing a button corresponding to one of four spatial locations. Stimuli were either presented randomly or in an eight-step movement sequence. MEG data was reconstructed in the time frequency domain using adaptive spatial filtering techniques, with oscillatory power changes examined in the beta (12-30Hz), gamma (30-55Hz) and high gamma (65-115Hz) bands. At baseline, patients were split based on performance during the SRTT into

either learner (SZ-L; significant difference in reaction time between the final sequence and final random blocks) or non-learner (SZ-NL; no implicit learning) groups. While no significant difference in behavioral performance is observed between the SZ-L and a cohort of healthy controls (HC), the SZ-L group showed significant increases ($p<0.005$) in gamma suppression over the left dorsolateral pre-frontal cortex (DLPFC), sensorimotor cortex (SMC), supplementary motor area (SMA) and posterior parietal cortex (PPC) compared to HC when performing the task. In the SZ-NL group, impoverished high-gamma synchronization over SMC ($p<0.005$) is observed compared to HC. Following training, the SZ-NL group shows gains in implicit learning, with >70% of non-learners now learning an implicit sequence. A within-group comparison in the SZ-NL group between sessions (post-training vs. pre-training) shows significant gains in gamma suppression over PPC and SMA_regions active in the SZ-NL group at baseline. This data indicates that different oscillatory signatures are associated with either abilities or impairments in implicit learning in schizophrenia. Specifically, gamma suppression over key regions of the sensorimotor network acts as a compensatory mechanism in SZ-NL and that adopting these oscillations through cognitive training permit patients to become implicit learners.

Disclosures: L.B. Hinkley: None. **B. Biagianti:** None. **D. Mizuiri:** None. **S. Vinogradov:** None. **S. Nagarajan:** None.

Nanosymposium

558. Major Mental Disorders: Novel Approaches for Patient Evaluation

Location: S102

Time: Tuesday, October 20, 2015, 1:00 PM - 3:30 PM

Presentation Number: 558.09

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: U.S. Army Material Command W911NF-14-2-0045

Title: Neural activity in the human subthalamic nucleus and globus pallidus internus during approach-avoidance decision making

Authors: *T. HERRINGTON[1], S. PATEL[2], E. ESKANDAR[2];
[1]Dept. of Neurol., Harvard / Massachusetts Gen. Hosp., Boston, MA; [2]Dept. of Neurosurg., Massachusetts Gen. Hosp., Boston, MA

Abstract: Neuropsychiatric symptoms including anxiety, apathy and depression are common in Parkinson's disease (PD) and reduce quality of life on par with the core motor symptoms. At the time of diagnosis, clinically significant apathy is present in 17%, depression in 14% and anxiety

in 25% of patients. These symptoms worsen over the course of the disease, affecting over two-thirds of patients with mild-moderate PD, and remain a major unmet therapeutic need. Motor symptoms in moderate or advanced PD can be alleviated by deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus internus (GPi). The STN and GPi are also important nodes in associative and limbic cortical-subcortical networks implicated in anxiety and depression. However, the continuous, high-frequency DBS used to treat movement disorders appears not to help, and may even worsen, neuropsychiatric symptoms. We aimed to elucidate the role of the STN and GPi in approach-avoidance behavior, a core neuropsychiatric dimension in parkinsonian depression and anxiety. Here were report single-neuron recordings from the human STN (n = 3 subjects, 11 neurons) and GPi (n = 3 subjects, 7 neurons) during a novel approach-avoidance decision-making task. Neurons in both regions are phasically modulated by information about potential rewarding and aversive outcomes, supporting the possibility that novel modes of DBS responsive to the neuropsychiatric functions of these nodes could one day help alleviate neuropsychiatric symptoms.

Disclosures: **T. Herrington:** None. **S. Patel:** None. **E. Eskandar:** None.

Nanosymposium

558. Major Mental Disorders: Novel Approaches for Patient Evaluation

Location: S102

Time: Tuesday, October 20, 2015, 1:00 PM - 3:30 PM

Presentation Number: 558.10

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: : DARPA grant no. W911NF1420045

Title: Physiological correlates of an emotional conflict resolution task obtained from intracranial recordings in humans

Authors: ***N. NOSSENSON**[1], D. I. VALLEJO LOPEZ[1], K. K. ELLARD[2], A. C. PAULK[3], E. N. ESKANDAR[3], T. DECKERSBACH[2], A. S. WIDGE[2], D. D. DOUGHERTY[2], S. S. CASH[1]; [1]Dept. of Neurol., Massachusetts Gen. Hospital, Harvard Med. Sc, Boston, MA; [2]Dept. of Psychiatry, [3]Dept. of Neurosurg., Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA

Abstract: The neural mechanisms underlying the detection and resolution of emotional conflicts and the ability to make decisions in the context of emotionally salient stimuli remain largely unknown. Understanding the physiology underlying these processes can shed light on a wide range of neuropsychiatric diseases including PTSD and depression and be essential in developing novel approaches to trying to alleviate these diseases. Prior work, primarily using fMRI, has

shown that the amygdala and anterior cingulate cortex play a central role in these processes. A detailed understanding of the neural activity underlying the role of these and other structures remains elusive. To investigate this in greater detail, three patients were implanted with intracranial electrodes and performed an affective version of the classic color-word Stroop task, the Emotion Conflict Resolution Task (ECR). The ECR task involves the presentation of pictures of faces which are either happy or fearful and which are overlaid with words ("HAPPY", "FEAR") which are either congruent or incongruent with the facial expression (see Etkin et al, Neuron 51, 2006, 871-882). All patients suffered from intractable epilepsy and were undergoing intracranial investigation to better localize their seizure foci as part of clinically indicated procedures. The research was approved by the local institutional review board and electrode placement was determined solely by clinical criteria. Event-related potentials (ERPs) during this task were present in widespread areas of the brain including the cingulate gyrus and amygdala, as observed in imaging studies. Hippocampus, and both lateral and medial frontal cortex also showed substantial potentials. The ERPs were often characterized by a sharp negative deflection at ~200 ms consistent with an N200 event. In some electrodes, the N200 deflection was followed by a positive sharp rising pattern, which later decayed exponentially to an intermediate voltage level and after about 600 ms fell back rapidly to the pre-stimulus baseline voltage level. Differences in ERP N200 amplitude were found in cingulate and mesial temporal structures when comparing happy and fearful face stimuli, face gender, and congruent and incongruent stimuli. These preliminary results support the notion that amygdala and cingulate work together in decision making in the context of emotionally salient information but also suggest that other areas may be involved in this important process. Further analysis of the temporal interactions between different areas may shed further light on the spatiotemporal sequence of events, which leads to conflict resolution in the human brain.

Disclosures: **N. Nossenson:** None. **D.I. Vallejo Lopez:** None. **K.K. Ellard:** None. **A.C. Paulk:** None. **E.N. Eskandar:** None. **T. Deckersbach:** None. **A.S. Widge:** None. **D.D. Dougherty:** None. **S.S. Cash:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.01

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: European Union Eureka/Eurostars Depression and Steroids" (DEPSTER project; grant number E!5291

Title: The synthetic neurosteroid, 3β-methoxypregnenolone (MAP4343) exerts an antidepressant-like efficacy in animal models and promotes neuron morphogenesis and plasticity in primary cultures

Authors: *N. FROGER[1], V. FOURNET[1], J. COTTIN[1], J. LEANDRI[1], N. LADURELLE[2], L. AMAZIT[3], L. PARESYS[1], E. FUCHS[4], I. VILLEY[1], E. E. BAULIEU[1,2];
[1]Mapreg SAS, Le Kremlin Bicêtre, France; [2]INSERM UMR 1195, Le Kremlin-Bicêtre, France; [3]Univ. Paris Sud, Le Kremlin-Bicêtre, France; [4]German Primate center, Gottingen, Germany

Abstract: Accumulating evidence suggest that depressive disorders (DDs) are associated with alterations of brain plasticity and neuron morphogenesis, as observed in depressed patients and in animal models. Microtubular system, one major component of cytoskeleton crucially involved in maintaining neuron morphology, may represent a new target for antidepressant strategies. Accordingly, 3βmethoxypregnenolone (MAP4343), a synthetic non-hormonal derivative from pregnenolone known to bind microtubule-associated protein type 2, may constitute an original therapeutic approach for treating DDs, as previously demonstrated in isolated-reared rats. To further validate the antidepressant-like efficacy of MAP4343, we used two animal models of DDs: (i) the Wistar Kyoto rats (WKY), a spontaneous model resistant to classic antidepressant treatments, and (ii) the tree shrews (TS) subjected to psychosocial stress, considered as a close-to-primate model showing similar alterations observed in depressed patients. WKY were treated subcutaneously by MAP4343 in an acute phase (4 days, 10 mg/Kg), while stressed TS received oral administration during a chronic phase (4 wks, 50 mg/kg). We found that MAP4343 was able to reverse the anxious-like behavior of WKY by increasing the time spent in the center of open-field arena. Similarly, MAP4343 reduced the depressive-like behavior of WKY by decreasing immobility time in forced-swimming test. In TS, oral administration of MAP4343 significantly reversed stress-elicited avoidance behavior and prevented stress-induced hypothermia, sleep disturbances, and hypersecretion of cortisol and noradrenaline. In parallel, we investigated the effects of MAP4343 on neuron morphology and plasticity using primary cultures from cerebral cortex of mice embryos (E16). Immunostaining experiments were used to visualize neuron morphology, while morphometric measurements, including neuron count, neurite length or branching point count, were obtained with a high content screening platform. These experiments revealed that 3-day incubation with MAP4343 promoted neuron morphogenesis in a dose-dependent manner (0.1, 1 and 5 μM), increased the spinophillin immunostainning, and reduced the proportion of bundled growth cones. Neurite length and branching points were found increased, without affecting the neuron count. These data validate the antidepressant-like efficacy of MAP4343 in animal models, and suggest its stimulant action *in vitro* on neuron morphogenesis and plasticity. Further investigations are underway to establish connections between these pharmacological actions of MAP4343.

Disclosures: **N. Froger:** A. Employment/Salary (full or part-time); Mapreg SAS. **V. Fournet:** A. Employment/Salary (full or part-time); Mapreg SAS. **J. Cottin:** A. Employment/Salary (full or part-time); Mareg SAS. **J. Leandri:** A. Employment/Salary (full or part-time); Mapreg

SAS. **N. Ladurelle:** None. **L. Amazit:** None. **L. Paresys:** A. Employment/Salary (full or part-time); Mapreg SAS. **E. Fuchs:** None. **I. Villey:** A. Employment/Salary (full or part-time); Mapreg SAS. **E.E. Baulieu:** A. Employment/Salary (full or part-time); Mapreg SAS. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patents on MAP4343: #WO2004067010 in Europe; #8,034,798 B2 and #12,232, 993 in USA.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.02

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: A social defeat model of post-traumatic stress disorder: Evidences for the participation of astrocytes and tachykininergic system

Authors: *E. C. SANTOS[1], M. ASSUNÇÃO BICCA[1], R. C. NUNES MARCHETTE[1], M. DUZZIONI[2], T. C. MONTEIRO DE LIMA[1];
[1]Federal Univ. of Santa Catarina, Florianopolis, Brazil; [2]Federal Univ. of Alagoas, Maceió, Brazil

Abstract: The social defeat (SD) model has been considered a naturalistic model of stress, characterized by unpredictable aggressive interactions that help to better understand brain responses to social conflict. It becomes a useful translational model to post-traumatic stress disorder (PTSD). We aimed to investigate the involvement of the tachykininergic system (TS) in a SD model. Male C57BL/6 mice (3 m.o.) used as defeat animals (DA) were inserted (inside a perforated metal cage) into the aggressor animals (AG) cage being male Swiss mice (4-8 m.o.). Conditioning sessions lasting 3h for 3 consecutive days were performed with random periods of physical interaction between the DA and AG, followed by the partition test 24 h later. Control animals (CTL) were submitted to the same protocol in the absence of the AG. In an independent experiment, a group of animals received L703,606 a selective antagonist of NK1 receptor (10 mg/kg; i.p.), 30 min before the partition test (Ethics Committee PP545). Parameters were evaluated in DA animals: barrier zone exploration time (BZET), risk assessment (RA), sawdust digging and rearing. Brains collected for immunofluorescence (IF), immunohistochemistry (IC), or the hippocampus (HP) and cortex (CT) freshly dissected for western blot (WB). In the partition test DA presented defensive behavior, namely decreased BZET and increased RAT behavior, compared to the CTL group. Notably, we found a significant increase in the levels of

SP by IC, in the CT and HP of the DA when compared to CTL. Additionally, DA presented neuronal death in the HP in comparison to CTL, as a result of the stress conditioning. As SP is a pro-inflammatory mediator we carried-out IF to neuroinflammatory markers, such as GFAP and Iba-1. Results revealed increased astrocyte, but not microglial activation/migration in the CT and HP of DA compared to CTL, indicating that astrocytes might be critical cells to the maintenance of the pathology. Likewise, co-localization between GFPA/NK1 receptor revealed higher co-localization in the HP of DA compared to CTL group. NK1 antagonism also induced lower levels of GFAP and co-localization with NK1 receptor, comparable to controls. Single treatment with L703,606 was also able to increase the BZET and reduce the RA behavior. Moreover, augmented levels of BDNF in the HP suggesting a possible neuroprotective effect of the antagonist. These data indicate the relevance of TS in the neuropathology of SD model. Overall, data suggest that SP is released as a consequence of the stress and induces cell death, possibly by activation of specific neuroinflammatory pathways. Thus, the NK1 receptor inhibition could be an attractive therapeutic approach to PTSD.

Disclosures: E.C. Santos: None. **M. Assunção Bicca:** None. **R.C. Nunes Marchette:** None. **M. Duzzioni:** None. **T.C. Monteiro de Lima:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.03

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Exercise has positive effects on the white matter and the myelinated fibers in the white matter of depression model of rats

Authors: *Y. TANG, F. F. WANG, C. X. TAN, L. M. CHEN, Y. GAO, C. X. HUANG, C. N. ZHOU, L. JIANG, Y. ZHANG, F. L. CHAO, L. ZHANG;
Chongqing Med. Univ., Chongqing, China

Abstract: It has been reported that the white matter changes might be involved in the pathogenesis of depression, and running exercise might have positive effects on depression. However, the effects of running exercise on the white matter of depression are unknown. The present study is the first study to investigate the effect of running exercise on the white matter and the myelinated fibers in the white matter of depression model of rats using the stereological methods. Male SD rats were randomly divided into the control group (10 rats) and depression model group (30 rats). The depression rats were made by giving rats the chronic unpredicted

stress (CUS) for four weeks. The behaviors were tested with the sucrose preference test, the forced swimming test and the open-field test. Twenty successfully made depression rats were randomly divided into the control depression group (10 rats) without running and the running depression group (10 rats). The running depression group rats ran for four weeks. After 4-week running exercise, the behaviors were tested again. 5 rats were randomly sampled from the control group, the control depression group and the running depression group. The white matter volume, the total length of the myelinated fibers, the total volume of the myelinated fibers and the total volume of the myelin sheaths in the white matter were estimated using the stereological methods. 4-week stress successfully established CUS rat model of depression. Running exercise could effectively improve anhedonia of depression rats. The total white matter volume, the total length of the myelinated fibers in the white matter, the total volumes of the myelinated fibers, the axons and the myelin sheaths in the white matter, the outer diameter of the the myelinated fibers, the thickness of the myelin sheaths in the white matter of the control depression group were significantly less than those of the control group. When compared to the control depression group, the total white matter volume, the total length of the myelinated fibers in the white matter, the total volumes of the myelinated fibers, the axons and the myelin sheaths in the white matter, the outer diameter of the the myelinated fibers, the thickness of the myelin sheaths in the white matter of the running depression group were significantly increased. Running exercise has positive effects on the white matter and the myelinated fibers in the white matter of depression model of rats, which might be one of the structure bases for the exercise-induced treatment of depression.

Disclosures: **Y. Tang:** None. **F.F. Wang:** None. **C.X. Tan:** None. **L.M. Chen:** None. **Y. Gao:** None. **C.X. Huang:** None. **C.N. Zhou:** None. **L. Jiang:** None. **Y. Zhang:** None. **F.L. Chao:** None. **L. Zhang:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.04

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: FCT PEst-C/SAU/ UI3282/2011

FCT, Portugal (UID/NEU/04539/2013), COMPETE-FEDER

Title: Speed blues: methamphetamine induces anhedonia and disrupts frontal cortical energetics in mice

Authors: *F. C. PEREIRA[1,2], R. FONSECA[1], R. A. CARVALHO[3,2,4], C. LEMOS[3], A. C. SEQUEIRA[1], C. D. SILVA[1], I. R. PITA[1], F. CARVALHO[3], R. D. PREDIGER[5], I. JARAK[3,2], R. A. CUNHA[3,2], C. A. FONTES RIBEIRO[1,2], A. KÖFALVI[3,2,6];
[1]IBILI/Faculty of Medicine, Univ. of Coimbra, Coimbra, Portugal; [2]CNC.IBILI, Univ. of Coimbra, Coimbra, Portugal; [3]CNC, Univ. of Coimbra, Coimbra, Portugal; [4]Dept. of Life Sciences, Fac. of Sci. and Technology, Univ. of Coimbra, Coimbra, Portugal; [5]Dept. de Farmacologia, Ctr. de Ciências Biológicas, Univ. Federal de Santa Catarina, UFSC, Florianópolis, Brazil; [6]Inst. for Interdisciplinary Research, Univ. of Coimbra, Coimbra, Portugal

Abstract: We recently showed that a single high dose of methamphetamine (METH) induced a persistent frontal cortical monoamine depletion that is accompanied by a depressive-like phenotype in mice. This recapitulates a METH addiction scenario in humans. However, the brain metabolic alterations underlying both neurochemical and mood alterations remain unknown. Herein, we aim to define the frontal cortical metabolic correlate of the early mood alterations triggered by METH. Therefore, adult C57BL/6 mice were injected with METH (30 mg/kg, i.p.) and their frontal cortical metabolic fingerprint was characterized after probing their anhedonic profile 3 days post-injection. METH triggered anhedonia, as indicated by the decreased grooming time in the splash test. At this time, METH did not alter anxiety-like behavior or motor functions. Depolarization-induced glucose uptake was reduced in frontocortical slices from METH-treated mice compared to controls. Consistently, astrocytic glucose transporter (GluT1) density was lower in the METH group. A proton high rotation magic angle spinning (HRMAS) approach revealed a significant decrease of the levels of N-acetyl aspartate (NAA), suggesting that METH decreased neuronal function in the frontal cortex. Additionally, METH also decreased the lactate/alanine ratio indicative of an increased oxidative stress. In conclusion, we report for the first time that a single METH injection impairs neuroenergetics, leading to neuronal dysfunction in frontal cortex, which underlies an anhedonic-like behavior.

Disclosures: F.C. Pereira: None. **R. Fonseca:** None. **R.A. Carvalho:** None. **C. Lemos:** None. **A.C. Sequeira:** None. **C.D. Silva:** None. **I.R. Pita:** None. **F. Carvalho:** None. **R.D. Prediger:** None. **I. Jarak:** None. **R.A. Cunha:** None. **C.A. Fontes Ribeiro:** None. **A. Köfalvi:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.05

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Newport Equities LLC

Title: Repeated Streptococcus pyogenes infections induce an autoimmune Th17 cell phenotype in the brain and impair blood-brain barrier integrity: a mouse model for PANS/PANDAS

Authors: *T. CUTFORTH[1], D. KNOWLAND[4], E. D. SMITH[4], T. DILEEPAN[5], M. HSU[4], M. PLATT[2], P. CLEARY[5], D. AGALLIU[3];
[1]Developmental & Cell Biol., [2]Neurobio. & Behavior, [3]Columbia Univ. Med. Ctr., New York, NY; [4]UC Irvine, Irvine, CA; [5]Univ. of Minnesota, Minneapolis, MN

Abstract: Streptococcus pyogenes infections are associated with two autoimmune diseases of the central nervous system (CNS): the movement disorder Sydenham's chorea and the neuropsychiatric syndrome PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus infections). This bacterium is known to induce autoreactive, mimetic antibodies against several CNS targets. Delivery of such antibodies in the mouse brain induces behavioral and motor deficits that are reminiscent of PANDAS symptoms, supporting a causal role for mimetic antibodies in this disease. How such autoreactive antibodies cross the blood-brain barrier (BBB) to attack CNS targets, however, is unknown. We have found that intranasal S. pyogenes infections lead to an antigen-specific Th17 cell response in the nasal-associated lymphoid tissue (NALT), a functional analog of human tonsils. Repeated infections drive those cells towards an IL-17+ IFN-γ+ phenotype that has been implicated in BBB breakdown during many autoimmune diseases. Moreover, repeated infections promote entry of S. pyogenes-specific T cells into the olfactory bulb and other CNS regions, whereas the bacteria remain within the nasal cavity. We also find microglial activation and barrier breakdown in close proximity to CNS-infiltrating T cells, as measured by leakage of both serum IgG and a low molecular weight tracer (biocytin-TMR) as well as disruption of endothelial cell tight junctions at a structural level. These findings not only provide novel insight into how recurrent Streptococcus infections might impair brain function and lead to motor and neuropsychiatric diseases, but also suggest a general mechanism by which infectious agents that induce Th17 immunity might exacerbate other CNS autoimmune diseases, such as multiple sclerosis, to provoke long-term neurovascular damage.

Disclosures: **T. Cutforth:** None. **D. Knowland:** None. **E.D. Smith:** None. **T. Dileepan:** None. **M. Hsu:** None. **M. Platt:** None. **P. Cleary:** None. **D. Agalliu:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.06

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD),

Jiangsu Province College Student's Practice and Innovation Training (201310315007Z)

Jiangsu Innovation and Entrepreneurship Project (2013455)

Title: Pre-pregnancy stress potentiates long-lasting postpartum depression and abnormal Disc1 signaling

Authors: *G. CHEN, B. XIA, H. ZHANG;
Nanjing Univ. of Chinese Med., Jiangsu, China

Abstract: Experience of stressful events and/or depression is one of the greatest risk factors for postpartum depression (PPD), a disorder affecting about 10% of new mothers. This, however, has not been modeled experimentally and thus hampered the understanding of the disorder. Here, we developed a novel model in which mice exposed to the chronic prepregnancy stress resulted in long-lasting PPD-like responses. We also investigated the underlying mechanisms, focusing on Disc1 and related signaling implicated in linking stress exposure to mental disorders. Female mice received mild stress for 3 weeks, followed with individually co-caged with a male. At 3 or 12 weeks postpartum,only mice experienced with both stress exposure and childbirth (SC) displayed depressive-like behaviors in sucrose preference test, forced swimming test, tail suspension test and novelty suppressed feeding test. The number of offspring of SC mice and their survival rate were significantly decreased, compared to those of prepregnantly non-stressed mothers. In the hippocampus, the PPD mice showed increased expression of NMDA receptor subunit NR1 and Disc1 expression, and decreased phosphorylation levels of AKT and mTOR/4EBP1/S6k. A single administration of the NMDA receptor antagonist, ketamine and a Traditional Chinese Medicine, Yueju, reversed the depressive-like responses in SC mice in a rapid and lasting manner, whereas chronic fluoxetine treatment did not show antidepressant effects. Additionally, ketamine and Yueju normalized the Disc1/AKT/mTOR signaling in PPD mice. Our study indicates prepregnant stress contributed to PPD, on which abnormal Disc1 signaling may mediate the effects, and Yueju may be potentially used for treatment of PPD.

Disclosures: G. Chen: None. **B. Xia:** None. **H. Zhang:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.07

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: OBI-POND

CFI 10435

NSERC 105112

Title: Connecting microbiota to behaviour and brain structure

Authors: *J. A. FOSTER[1,2], J. K. Y. LAI[1], K. C. RILETT[1], J. ELLEGOOD[3], J. LERCH[3]; [1]Psychiatry & Behav Neurosci, McMaster Univ., Hamilton, ON, Canada; [2]St. Joseph's Healthcare, Hamilton, ON, Canada; [3]The Hosp. for Sick Children, Toronto, ON, Canada

Abstract: Researchers in psychiatry and neuroscience are increasingly recognizing the importance of gut-brain communication in behaviour. To date work in animal and clinical studies has established the gut-brain axis modulates anxiety and cognitive behaviours, and influences activity of emotional brain centers. Mouse strain differences in anxiety-related behaviour are well-established and provide a good naturalist mouse model to examine the link between microbiota, behaviour, and brain structure. To assess strain differences in exploratory and anxiety-like behaviour, male and female Balb/C and CD1 mice were tested in the light/dark test at 6 weeks of age and in the elevated plus maze at 8 weeks of age. To examine whole brain structure, high resolution ex vivo MRI was performed. Fecal samples were collected at the time of behavioural testing and molecular profiling of the bacterial 16S rRNA gene is ongoing to examine bacterial diversity. Balb/C mice showed reduced exploratory behaviour in the light/dark box compared to CD1 mice including reduced rearing and reduced number of transitions between the light and dark chamber. In the elevated plus maze, CD1 mice spent more time in the open arms and showed increased number of risk assessment behaviours including poke around and head dips compared to Balb/C mice. Volumetric analysis of MRI data revealed numerous strain-related changes in brain volume. For example, Balb/C mice showed reduced relative brain volume of the hypothalamus and hippocampus compared to CD-1 mice. Initial analysis of the association between brain structure and behaviour revealed a significant interaction between time spent in the open arms and strain in several brain regions including the frontal lobe, the parieto-temporal lobe, the striatum and the amygdala. Interestingly, in these brain regions the relationship between open arm time and brain volume was different in the 2 strains. In Balb/C mice the more time spent in the open arms was associated with larger brain volumes, while in CD1 mice the more time spent in the open arms was associated with smaller brain volumes. Additional integrated analysis of behaviour and brain structure is ongoing, and these data will be

combined with microbiota diversity data. Overall, this approach will help us understand the anatomical and biological basis of differences in behaviour.

Disclosures: **J.A. Foster:** None. **J.K.Y. Lai:** None. **K.C. Rilett:** None. **J. Ellegood:** None. **J. Lerch:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.08

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: DoD Award: 10071009(W81XWH-11-2-0111)

Title: A novel approach to PTSD modeling in rats - alternating patterns of limbic activity in different types of stress reaction

Authors: ***G. RICHTER-LEVIN**[1], G. RITOV[2];
[1]Univ. Haifa, Haifa, Israel; [2]Sagol Dept. of Neurobio., Univ. of Haifa, Haifa, Israel

Abstract: Human reactions to trauma exposure are extremely diverse, with some individuals exhibiting only time-limited distress and others qualifying for posttraumatic stress disorder diagnosis (PTSD). Furthermore, whereas most PTSD patients mainly display fear-based symptoms, a minority of patients displays a co-morbid anhedonic phenotype. We employed an individual profiling approach to model these intriguing facets of the psychiatric condition in underwater-trauma exposed rats. Basing Based on long-term assessments of anxiety-like and anhedonic behavior, our analysis uncovered 3 separate subtypes of stress response; an anxious, fear-based phenotype (38%), a co-morbid, fear-anhedonic phenotype (15%), and an exposed-unaffected group (47%). Combining immunohistochemical assessments for cellular activation (c-Fos) and activation of inhibition (c-Fos+GAD67) revealed a differential involvement of emotion processing regions and distinct limbic co-activity patterns in for each of these different types of response, validating the behavior profiling-based categorization. Finally, in accordance to the predictions of the "high anxiety train to posttraumatic depression" model of Sandi and Richter-Levin (2009), p. re-trauma anxiety was found to be relates to the post-trauma progression of anhedonic behavior only in the co-morbid anhedonic phenotype. The results emphasize the importance of combining behavioral profiling and network level analyses to the translational power of models of when modeling a complex psychopathologies such as PTSD.

Disclosures: **G. Richter-Levin:** None. **G. Ritov:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.09

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Brain Research Foundation

NARSAD

R01-MH099248

Norton Gerali Foundation

Title: Identifying the effect of putative OCD risk gene BTBD3 on behavior in mice

Authors: ***S. L. THOMPSON**[1], E. V. HO[1], M. E. KLINGER[2], J. A. KNOWLES[3], S. C. DULAWA[1];
[1]Psychiatry & Behavioral Neurosciences, [2]Univ. of Chicago, Chicago, IL; [3]Psychiatry & The Behavioral Sci., USC, Los Angeles, CA

Abstract: BTBD3 was identified as genome-wide significant in the trio portion of the sample of the first GWAS for OCD. Specifically, the only genome-wide significant variant associated with OCD regulates expression of BTBD3 in frontal cortex. However, nothing is known about the role of BTBD3 in regulating behavior. In the present work, we assessed the role of BTBD3 in modulating exploratory and repetitive behaviors relevant to OCD. Male and female BTBD3 wild-type (WT), heterozygous (HT) and knockout (KO) mice were pair-housed by genotype and gender, and were assessed for barbering behavior. Mice were also assessed in the open field, the dig test, the splash test, and in the prepulse inhibition (PPI) paradigm. BTBD3 KO mice showed increased locomotion in the open field. In addition, HT and KO mice showed a robust reduction in the number of rearings and time spent rearing. In the dig test, KO mice had an increased latency to dig, decreased duration of digging bouts, and trended for less total time spent digging. In the splash test, HT and KO mice exhibited more frequent, but shorter grooming bouts. BTBD3 genotype did not affect PPI or startle. Both HT and KO mice barbered their cagemates significantly more than WT mice. We then assessed BTBD3 WT, HT, and KO mice for the effects of OCD-effective and OCD-ineffective treatments on behavioral phenotypes. Mice were pretreated with 10 mg/kg/day fluoxetine (OCD-effective), 20 mg/kg/day desipramine (OCD-

ineffective), or vehicle in the drinking water for fourteen weeks. After four weeks of drug treatment, mice were assessed in the open field, the dig test, the splash test, and PPI. Barbering was assessed weekly throughout the fourteen weeks of treatment. Interestingly, fluoxetine reduced barbering beginning at four weeks of treatment, whereas desipramine had no effect at any time point. Within genotype, fluoxetine significantly reduced barbering in WT and HT, but not KO, mice indicating an interplay between BTBD3 expression and fluoxetine-specific reversal of barbering. In summary, decreased BTBD3 expression reduces exploratory behaviors including digging and rearing, and increases repetitive behaviors such as barbering. The reduction of barbering behavior by chronic fluoxetine, but not desipramine, treatment lends predictive validity to this phenotype as OCD-like. In sum, BTBD3 expression plays a role in behaviors relevant to OCD in mice. We are currently assessing the neurobiological mechanisms of the role of BTBD3 in these behaviors.

Disclosures: S.L. Thompson: None. **E.V. Ho:** None. **M.E. Klinger:** None. **J.A. Knowles:** None. **S.C. Dulawa:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.10

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: DARPA Grant W911NF1420045

Title: Understanding the dynamics of decision making through the multi-source interference task

Authors: *D. I. VALLEJO[1], N. NOSSESON[1], A. C. PAULK[2], K. K. ELLARD[4,3], S. SOROWITZ[4,3], T. DECKERSBACH[4,3], E. ESKANDAR[2], A. WIDGE[3], D. DOUGHERTY[3], S. CASH[1];
[1]Neurol., Massachusetts Gen. Hospital, Harvard Med. Sc, Boston, MA; [2]Neurosurg., [3]Psychiatry, Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA; [4]Massachusetts Gen. Hospital, Athinoula A. Martinos Ctr., Boston, MA

Abstract: Decision making depends on how humans adapt to task difficulty, informing how we adapt to social and environmental challenges. The neural correlates of this flexibility has been associated with activity in the cingulo-frontal-parietal cognitive/ attention network (CFP). The CFP has demonstrated to be involved in higher order cognitive processes, including decision making of various types, and has also been implicated in neuropsychiatric diseases.

Understanding the physiology of such diseases is fundamental to create novel and targeted therapeutic approaches. The Multi-Source Interference task (MSIT) was developed as a functional neuroimaging assessment in an attempt to better understand normal human cognition and psychiatric pathophysiology. This task is a validated fMRI task that reliably activates the CFP network. To this end, we sought to use this task to explore the neurophysiology underlying decision processes, particularly when the task changes from easy to difficult and vice versa. We asked patients who had been implanted with intracranial electrodes as part of their clinically indicated evaluation for intractable epilepsy to perform the task. Participants were asked to identify via button-press the number that differs from the other two in a set of three numbers with distractors. Participants performed this task twice- prior to surgery during fMRI scanning and while implanted with electrodes. BOLD activation patterns on fMRI data was compared to the subsequent intracranial electrophysiology during the experiment. These techniques allowed us to identify the activated cortical and subcortical regions and record the neural (local field potentials) in multiple electrode locations. Nine epileptic patients who were implanted with electrodes performed 300 trials of the MSIT task while in the epilepsy monitoring unit (EMU). Three of these patients also underwent fMRI study. This task evoked ERPs in multiple regions including dorsomedial prefrontal cortex (dmPFC), dorsolateral prefrontal cortex (dlPFC), amygdala and hippocampus with peak deflections at ~500 ms after stimulus. Differences in ERP amplitude were sometimes present in the dmPFC and dlPFC between congruent (easy) and incongruent (hard) trials. In patients who had undergone fMRI these same general regions showed differential activation during the task. Results showed that during MSIT brain regions which are activated in fMRI are also observed to change activity physiologically during ERPs. Further investigations of spatiotemporal dynamics could help to better understand the changes and processes within psychiatric pathophysiology, informing future clinical innovations.

Disclosures: **D.I. Vallejo:** None. **N. Nosseson:** None. **A.C. Paulk:** None. **K.K. Ellard:** None. **S. Sorowitz:** None. **T. Deckersbach:** None. **E. Eskandar:** None. **A. Widge:** None. **D. Dougherty:** None. **S. Cash:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.11

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: National Natural Science Foundation of China (81371489)

Title: Witnessing stress induced susceptibility in individuals with intimate relationship

Authors: *W. ZHU[1], R. ZHANG[1], Y. ZHANG[1], Z. DING[1], J. SHI[1], L. LU[2];
[1]Peking Univ., Natl. Inst. On Drug Dependence, Beijing, China; [2]Peking Univ., Inst. of Mental Health/Peking Univ. Sixth Hosp. and Key Lab. of Mental Health, Ministry of Hlth., Beijing, China

Abstract: Repeated exposure to stress increases the risk of developing depression. The psychological effects of direct stressors have been well documented. However, stress-induced emotional disorder can not only occur in persons who experienced direct stress, but also in those who become indirectly affected by their close contact with individuals. Such indirect experience of stress, also named witnessing stress, can precipitate a more depression-like syndrome. However, very little is known about the neuronal architecture and mechanisms underlying the depressive behavior induced by witnessing stress.The main reason is that animal models of such witnessing emotional stress are scarce. In the current study, we used a modified social defeat stress paradigm in male C57BL/6 mice to investigate the depression-like behavioral abnormalities. Subsequently, the neuronal activity in mesolimbic dopamine pathway, composed of dopaminergic neurons in the nucleus accumbens (NAc), was monitored. The results showed that two C57BL/6 mice stayed together in one cage for 10 days spending more time in interaction zone, named as intimate partners. However, two mice stayed in different cages spending less time in interaction zone, named as stranger. C57BL/6 mice were defeated by an aggressive male retired CD1 mouse for 5 min per day, during which another C57BL/6 mouse with intimate or alienated relationship (partner or stranger) was forced to observe this defeated process. This witnessing stress in C57BL/6 mice lasted for 10 days. The behavioral tests were carried out on day 11. We found that intimacy with the defeated individual increased the sensitivity to witnessing stress and the following occurrence of social avoidance in C57BL/6 mice. Additionally, witnessing partners being defeated significantly increased serum corticosterone compared with control mice. However, witnessing strangers being defeated did not alter serum corticosterone levels. Moreover, neuronal activity in the NAc was inhibited by witnessing stress in partners but not in strangers. Finally, witnessing stress of social defeat in partners significantly reduced dopamine D2R but not D1R proteins in NAc. Our findings suggested that witnessing stress involves the transfer and acquisition of negative affective and dysfunctional cognitive states due to prolonged and extended contact with others, such as family members, who have been directly exposed to stress. Future elucidation of underlying neuronal mechanisms is critically important as they underlie witnessing stress between individuals who have close contact each other and allow adaptive behavior in uncertain social environments.

Disclosures: **W. Zhu:** None. **R. Zhang:** None. **Y. Zhang:** None. **Z. Ding:** None. **J. Shi:** None. **L. Lu:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.12

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: European Union/ERANET

Italian Ministry of University and Research (PRIN 20107MSMA4)

Fondazione CARIPLO (grant n. 20120503)

Title: Epigenetic changes of miR-30a in the prenatal stress model: implications for psychiatric disorders

Authors: *M. A. RIVA[1], A. LUONI[1], R. MASSART[2], F. CIRULLI[3], M. SZYF[2];
[1]Univ. of Milan, Milan, Italy; [2]McGill Univ., Montreal, QC, Canada; [3]Inst. Superiore di Sanità, Rome, Italy

Abstract: Early life exposure to stressful events produces widespread changes on brain function that may predispose individuals to develop a wide range of psychopathologies. This may occur through epigenetic regulation of gene expression involving changes in DNA methylation as well as miRNAs. Animal models are very useful to characterize the molecular and functional mechanisms that may be persistently affected after exposure to early-life stressors (ELS). On these bases, we performed genome-wide methylation analyses in the hippocampus and prefrontal cortex of adult rats exposed to stress during gestation (PNS), a model that is associated with persistent behavioral and molecular alterations relevant for psychiatric disorders. We found that a large number of gene promoters were differentially methylated in the prefrontal cortex and hippocampus of adult male and female rats exposed to stress during gestation. An overlap of 138 differentially methylated genes around the transcription start site (-2000 to +500) was observed among the two brain regions and genders. Ingenuity Pathway Analysis showed significant enrichment in molecules involved in neurological disease, molecular transport, nervous system development and function as well as psychiatric disorders. By restricting the overlap to genes that were modulated in the same direction, we identified miR-30a as being less methylated in PNS rats. Accordingly, the expression of miR-30a was significantly increased in adult rats that were exposed to stress *in utero*. Using miRWalk database, we determined predicted mRNA targets of miR-30a. Among these, a number of genes previously associated with mental illness were identified, including Bdnf and GAD-67, whose expression was indeed reduced as a consequence of the prenatal manipulation. In summary, our genome-wide approach allowed us to identify miR-30a as being persistently affected by prenatal stress through epigenetic changes,

suggesting that this miRNA may represent a master regulator for the increased susceptibility to psychiatric disorders as long-lasting consequence of early life stress exposure.

Disclosures: **M.A. Riva:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sunovion. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Eli Lilly; Lundbeck; Otzuka; Sumitomo Dainippon Pharma; Sunovion. F. Consulting Fees (e.g., advisory boards); Eli Lilly; Lundbeck. **A. Luoni:** None. **R. Massart:** None. **F. Cirulli:** None. **M. Szyf:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.13

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIMH MH070727

NIMH MH066198

NINDS T32 NS069562-04

Brain and Behavior Research Foundation

International Mental Health Research Organization

Title: Are eEF2 kinase and BDNF expression necessary for lithium's effects?

Authors: ***E. S. GIDEONS**, E. T. KAVALALI, L. M. MONTEGGIA;
Neurosci., UT-Southwestern Med. Ctr., Dallas, TX

Abstract: Lithium is a mood stabilizer that is used to treat manic episodes and depression in patients with Bipolar disorder. While lithium is effective as a mood stabilizer, the mechanisms that underlie its therapeutic effect are unclear. Lithium treatment is known to inhibit GSK3 in rodents as shown by increased phosphorylation of N-terminal serines in the alpha and beta isoforms of GSK3. Lithium also decreases the overall phosphorylation status of eEF2, which increases protein translation at the synapse of multiple mRNA transcripts including BDNF. Phosphorylation of eEF2 by eEF2K is necessary for the fast-acting antidepressant effects of

ketamine. In addition, lithium increases BDNF mRNA and protein in human patients and preclinical rodent models. BDNF mRNA and protein expression are necessary for the behavioral effects of monoaminergic antidepressants such as fluoxetine and citalopram and the rapid antidepressant ketamine. Data has also demonstrated that clinically effective concentrations of lithium decrease AMPAR-mEPSC amplitude acutely in dissociated hippocampal cultures and decrease AMPARs on the membrane following chronic treatment *in vivo*. The goal of this project is to investigate whether eEF2-K activity and BDNF/TrkB expression are necessary for the behavioral and electrophysiological effects of lithium. We are able to show that clinically effective doses of lithium results in antidepressant and anti-manic like effects in mice. In preliminary experiments using eEF2-K constitutive null mice and conditional forebrain specific BDNF knockout mice, we find that neither eEF2 kinase nor BDNF appear necessary for the antidepressant effects of lithium. However, our preliminary data suggest that BDNF is necessary for lithium's anti-manic actions, with altered levels of GSK3 phosphorylation occurring in conditional BDNF knockout mice. Experiments are currently underway to examine the contribution of eEF2 kinase on the anti-manic effects of lithium. To try to elucidate the mechanism for lithium's action, we are performing whole cell voltage clamp electrophysiology experiments using dissociated hippocampal cultures. Our current data suggests that chronic lithium treatment at physiological concentrations causes a significant decrease in AMPAR-mEPSC amplitude with no change in frequency, which requires the high affinity BDNF receptor, TrkB. Data will be presented highlighting our ongoing efforts to examine the role of eEF2 signaling and BDNF-TrkB signaling in the effects of lithium.

Disclosures: E.S. Gideons: None. **E.T. Kavalali:** None. **L.M. Monteggia:** None.

Nanosymposium

559. Mood Disorders: Preclinical Models and Therapeutic Approaches

Location: S403

Time: Tuesday, October 20, 2015, 1:00 PM - 4:30 PM

Presentation Number: 559.14

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIH Grant UL1 RR024153

NIH Grant HD062864

NIH Grant HD062618

Title: Optimization and validation of a standard clinical algorithm to accurately measure sleep in non-human primates from actigraphy data

Authors: *J. L. CAMERON[1], T. GAUGHAN[2], M. RAGOZA[2], M. PONGIBOVE[3], D. KAY[1], B. KREIDER[2], T. LIU[2], D. PYRDEK[1], N. ROCKCASTLE[1], D. BUYSSE[1], N. RYAN[1]; [1]Psychiatry, Univ. Pittsburgh Sch. Med., Pittsburgh, PA; [2]Neurosci., [3]Engin., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Sleep has been implicated in a variety of psychiatric disorders including those related to anxiety, and a number of approaches have been taken to measure sleep to examine this relationship. Activity monitoring devices provide a popular, noninvasive means of measuring activity in people and animals and algorithms have been developed using human data to classify sleep, with less success in primate models. The goal of this study was to optimize a standard clinical algorithm for reliable identification of sleep from actigraphic data in nonhuman primates. Twenty one adult cynomolgus monkeys wore collar-mounted activity monitors (Actical, Philips Respironics Inc., Bend, OR). During one continuous 18-hour period for each monkey, behavior was also recorded by infrared videography. The activity data was processed through the algorithm, and its efficacy was judged using a "Gold Standard" of videography. To optimize for monkeys, a series of alternate activity thresholds were tested and the one that performed best was used for further analysis. A standardized anxiety measure, the Human Intruder Test (HIT), was performed to begin physiological validation of the new threshold. Using the original threshold developed for use with human actigraphy, the sensitivity to detect videography-defined sleep was 94.4% but the specificity was only 39.3%. Optimization decreased the sensitivity to 76.2%, but specificity increased to 66.6%. In HIT, monkeys with low reactivity (a trait associated with anxious characteristics) showed significantly earlier morning waking ($R=-0.484$, $p=0.019$) and a trend toward falling asleep later ($R=-0.385$, $p=0.07$). Thus, threshold optimization allowed an increase in specificity that increased the usability of actigraphy-measured sleep in primates and kept sensitivity at an allowable level. Validation of the physiological use of the algorithm revealed that more anxious monkeys had a delay in nighttime sleep and earlier wake time. These findings will allow further detailed study of sleep patterns in nonhuman primates in carefully controlled models of psychiatric disorders.

Disclosures: J.L. Cameron: None. **T. Gaughan:** None. **M. Ragoza:** None. **M. Pongibove:** None. **D. Kay:** None. **B. Kreider:** None. **T. Liu:** None. **D. Pyrdek:** None. **N. Rockcastle:** None. **D. Buysse:** None. **N. Ryan:** None.

Nanosymposium

560. Stroke Recovery

Location: S404

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 560.01

Topic: C.21.Stroke Recovery

Support: NIH Grant NS062097

NIH Grant NS058710

NIH Grant NS085568

Title: Recombinant pyruvate kinase M2 improves angiogenesis and functional recovery after ischemic stroke in mice

Authors: D. CHEN[1], X. GU[1], L. WEI[1,2], *S. YU[1];
[1]Anesthesiol., [2]Neurol., Emory Univ., Atlanta, GA

Abstract: Ischemic stroke remains a serious threat to human life and health. The regeneration of microvessels (angiogenesis) and blood flow restoration in the peri-infarct region promotes the functional recovery after stroke. Pyruvate kinase isoform M2 (PKM2), an enzyme to catabolize glucose, has been recognized to promote cell proliferation. It was shown that recombinant PKM2 (rPKM2) promotes angiogenesis by increasing the proliferation of endothelial cells in tumor tissue, mediated by activation of STAT3 signaling. In this study, we tested the hypothesis that rPKM2 could increase angiogenesis and promote functional recovery after ischemic stroke, via the underlying mechanism of activation of STAT3 pathway. In a mouse focal ischemic stroke model, rPKM2 (160 μg/kg, intranasal administration) was administered every other day starting 24 hours after stroke, with or without the STAT3 Inhibitor XVIII, BP-1-102 (3 mg/kg, o.g., daily). To label proliferating cells, 5-Bromo-2'-deoxyuridine (BrdU, 50 mg/kg, i.p.) was injected every day starting 3 day after stroke. At 14 days after stroke, we assessed the angiogenesis by the immunohistochemistry staining of BrdU+/Glut-1+ co-labeled cells. The rPKM2 treatment increased angiogenesis in the peri-infarct region. Further, laser Doppler imaging revealed that rPKM2 enhanced the restoration of local cerebral blood flow (LCBF) in the peri-infarct region. rPKM2 also improved the sensorimotor function recovery measured by adhesive removal test at 14 days after stroke. In Western blot analysis, rPKM2 increased Tie-2 and STAT3 expression at 7 days after stroke. Inhibiting STAT3 activation by BP-1-102 abolished the beneficial effects of rPKM2 on angiogenic activities and behavioral recovery after stroke. Taken together, this study revealed that rPKM2 can enhance angiogenesis and improve functional recovery after ischemic stroke, and its underlying mechanism may involve in the activation of STAT3 signaling pathway.

Disclosures: D. Chen: None. **X. Gu:** None. **L. Wei:** None. **S. Yu:** None.

Nanosymposium

560. Stroke Recovery

Location: S404

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 560.02

Topic: C.21.Stroke Recovery

Support: NIH Grant DA016765

NIH Grant DA023555

NASA Grant NNX12AB55G

NIH Grant DA007290

NIH Grant 5R01NS088555

AHA Grant AHA 14SDG18410020

Title: B-cell mediated recovery of motor function and hippocampal neurogenesis in a murine model of stroke

Authors: *S. E. LATCHNEY[1], I. Z. NOORBHAI[2], S. B. ORTEGA[2], U. M. SELVARAJ[2], N. L. MONSON[2], E. J. PLAUTZ[2], M. P. GOLDBERG[2], A. J. EISCH[3], A. M. STOWE[2];
[1]Dept. of Psychiatry, [2]Neurol. and Neurotherapeutics, [3]Psychiatry, UT Southwestern Med. Ctr., Dallas, TX

Abstract: According to the American Heart Association, approximately 795,000 people each year will experience a new or recurrent stroke, leaving stroke the leading contributor to long-term adult disability. In the past few years, increasing evidence shows a link between the central nervous system and the immune system in mediating damage, as well as regeneration and repair, following stroke. Previous work in our lab demonstrates a protective role of B-cells in motor recovery following experimental stroke. In addition to motor dysfunction, stroke also stimulates neurogenesis in the adult hippocampal dentate gyrus. Our current study extends our previous work by hypothesizing that B-cell depletion with Rituximab - a pharmacologic that targets human CD20-expressing B-cells - prior to stroke will exacerbate motor deficits and dampen stroke-induced hippocampal neurogenesis. To test this hypothesis, adult male human CD20+ (hCD20+) transgenic mice or wild-type (WT) littermate controls were trained on an accelerating rotorod for 2 weeks. Following training, all mice were administered Rituximab (50μg i.p.) daily for 3 days and weekly thereafter. Stroke was induced by a 60-minute transient middle cerebral artery occlusion (tMCAo), with functional recovery evaluated over 2 weeks. B-cell depletion by Rituximab in hCD20+ mice induced significant motor deficits in rotorod performance through 14 days post-tMCAo, relative to deficits in WT mice that resolved by 4 days post-tMCAo. The hippocampal dentate gyrus was then examined at 2 weeks post-tMCAo for measures of neurogenesis, including quantification of doublecortin (DCX)-immunoreactive(+) neuroblasts/immature neurons. In WT mice - as expected - stroke induced a significant increase

in DCX+ cell number in the dentate gyrus granule cell layer (GCL) of the ipsilateral hemisphere vs. the contralateral hemisphere. This stroke-induced increase in DCX+ cell number was not present in B-cell depleted (CD20+) mice. GCL volume was not changed in either WT or hCD20+ mice. Taken together, B-cell depletion with Rituximab inhibits functional recovery and dampens the stroke-induced increase in neurogenesis. Our results indicate a potential therapeutic role for B-cells in enhancing motor recovery while supporting hippocampal neurogenesis following transient stroke.

Disclosures: **S.E. Latchney:** None. **I.Z. Noorbhai:** None. **S.B. Ortega:** None. **U.M. Selvaraj:** None. **N.L. Monson:** None. **E.J. Plautz:** None. **M.P. Goldberg:** None. **A.J. Eisch:** None. **A.M. Stowe:** None.

Nanosymposium

560. Stroke Recovery

Location: S404

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 560.03

Topic: C.21.Stroke Recovery

Title: Increasing self-directed training in neurorehabilitation patients by motivational enhancement

Authors: *B. STUDER[1,2], S. KNECHT[1,3];
[1]St Mauritius Therapieklinik, Meerbusch, Germany; [2]Med. Dept., [3]Univ. of Düsseldorf, Düsseldorf, Germany

Abstract: Re-acquisition of cognitive and physical functions following brain injury requires repetitive, high-intensive training. The more neurorehabilitative training patients undergo, the better the functional recovery. One strategy to maximise training intensity during neurorehabilitation is to complement therapist-directed training with self-directed training. A major challenge of this approach is that self-directed training particularly hinges on the patient's motivation, drive and persistence, which in turn are frequently diminished following brain injury. Indeed, adherence to self-directed training schedules observed in clinical practice is very low. Novel approaches targeting training motivation, effort and persistence are thus warranted. The goal of the current study was to test whether self-directed training during in-patient neurorehabilitation could be boosted by competition. Controlled competition has previously been shown to enhance motivation and performance in healthy adults. However, whether competition can also be used as motivator in therapeutic applications has never been explored. We recorded the amount and intensity of self-directed cardiovascular training on a cycle ergometer performed

by stroke patients undergoing in-patient neurorehabilitation (preliminary n = 16). Self-directed training took place under three experimental conditions: Baseline (unmonitored), Feedback (monitored) and Competition (training activity compared to that of a well-matched opponent). The order of conditions was randomised across patients, and each condition was completed (at least) twice by each patient. Within-subject comparisons of the average training activity in each experimental condition were computed. We also tested whether candidate personality traits could predict effectiveness of competition across patients. Our main finding was that, on average, patients' training activity under competition was increased by 22% compared to baseline (p=.04). Thus, competition significantly enhanced the amount of voluntarily conducted self-directed training. In conclusion, the amount of self-directed training performed by neurorehabilitation patients can be increased by adding motivation-boosting features to the training programme.

Disclosures: B. Studer: None. **S. Knecht:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NAVIGATE ESUS.

Nanosymposium

560. Stroke Recovery

Location: S404

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 560.04

Topic: C.21.Stroke Recovery

Support: NIH Grant R01NS060774

Title: The effect of startling acoustic stimulus (SAS) on voluntary elbow flexion in stroke survivors

Authors: M. BHADANE[1], F. GAO[2], P. ZHOU[1], *S. LI[3];
[1]Physical Med. and Rehab, UTHealth, Houston, TX; [2]UT Southwest, Dallas, TX; [3]Physical Med. and Rehabil., Univ. of Texas Hlth. Sci. Ctr. - Houston, Houston, TX

Abstract: Objective: Startling acoustic stimuli (SAS), via activation of reticulospinal pathways, has shown to improve muscle strength in healthy subjects. We hypothesized that there is reticulospinal hyperexcitability in stroke survivors, and SAS could improve muscle strength in stroke survivors. Objective was to quantify the effect of SAS on maximal and submaximal voluntary elbow flexion. Design: Thirteen hemiparetic stroke survivors and twelve healthy subjects volunteered for this investigation. The effect of acoustic stimuli was evaluated at rest,

for ballistic tasks and during submaximal isometric elbow contractions, using low (80 dB) and high intensity sound (105 dB). Results: Averaged occurrence frequency of acoustic startle reflex was more on the impaired side. A significant effect of SAS on reaction time and peak torque was observed across all subjects. The torque response during submaximal contractions increased 3-4 times on impaired side of stroke survivors compared to the healthy subjects. Also there was significant level dependence which suggests that contribution of reticulospinal pathway is greater at higher baseline voluntary activation. Conclusion: The findings of significantly greater SAS-induced effects in stroke survivors support reticulospinal hyperexcitability in stroke survivors. However, its implication for stroke rehabilitation remains unclear.

Disclosures: **M. Bhadane:** None. **F. Gao:** None. **P. Zhou:** None. **S. Li:** None.

Nanosymposium

560. Stroke Recovery

Location: S404

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 560.05

Topic: C.21.Stroke Recovery

Support: CTSC Grant RPC2014-1067 to DC

NIH Grant 1K01HD069504 to EP

AHA Grant 13BGIA17120055 to EP

Title: Bilateral vs. unilateral therapy for chronic stroke patients with varying degrees of motor impairment: A crossover repeated-measures design of neurophysiologic response

Authors: *D. A. CUNNINGHAM[1,3], J. KNUTSON[4], K. POTTER-BAKER[1], V. SANKARASUBRAMANIAN[1], N. VARNERIN[1], C. BONNETT[1], T. ASARE[1], A. MACHADO[2], E. PLOW[1];
[1]Biomed. Engin., [2]Ctr. for Neurolog. Restoration, Cleveland Clin., Cleveland, OH; [3]Kent State Univ., Kent, OH; [4]Dept of Phys Med. & Rehab, Case Western Reserve Sch. of Med., Cleveland, OH

Abstract: INTRODUCTION: For patients with chronic stroke, it is believed excitation of the primary cortex of the non-lesioned hemisphere (NLH) exacerbates motor deficits by exaggerating transcallosal inhibitory interactions (TCI) upon the lesioned hemisphere (LH). However, recent evidence suggests the NLH may play a compensatory role in recovery for patients with greater motor impairment. If true, then therapies recruiting the NLH would elicit a

more adaptive role for recovery of patients with greater impairment. Therefore, we tested the hypothesis that therapy involving the NLH (bilateral) would lower TCI exerted upon the LH compared to therapy only involving the LH (unilateral); an effect that would become more pronounced with increasing impairment. METHODS: In a crossover repeated-measures design, six chronic stroke patients with varying degrees of motor impairment (Fugl-Meyer [clinical measure of motor impairment]: 15 [more impaired] to 59 [less impaired]) underwent a single session each of unilateral and bilateral therapy. We measured excitation of the NLH and TCI it exerts upon the LH using transcranial magnetic stimulation. TMS uses electromagnetic induction to depolarize neurons in the cortex and assesses recruitment of hemispheric output to the muscle as motor evoked potentials and the transcallosal inhibition imposed upon the primary motor cortex. RESULTS: Overall, bilateral therapy resulted in greater increases in NLH excitability when compared to unilateral therapy (15.35 ± 33% vs. -6.81 ± 20.2%, $p < .05$). Further, bilateral therapy resulted in a greater reduction of TCI (-27.9 ± 18.6% vs. -5.16 ± 10.2%, $p < .05$), where the effect was more pronounced in the more impaired patients ($r = .829$, $p < .05$). CONCLUSION: Our preliminary results show that bilateral therapy may invoke an adaptive rather than inhibitory influence of the NLH with greater motor impairment, where the reduced TCI may free up surviving corticospinal neurons in the affected hemisphere and greater excitability of the unaffected hemisphere may trigger ipsilateral neurons devoted to the paretic limb, particularly in the more impaired patients. Still, it remains to be seen whether the neurophysiologic changes translate to recovery of motor impairment. Future work will test whether behavioral outcomes following bilateral therapy are superior to unilateral for patients with greater motor impairment.

Disclosures: **D.A. Cunningham:** None. **J. Knutson:** None. **K. Potter-Baker:** None. **V. Sankarasubramanian:** None. **N. Varnerin:** None. **C. Bonnett:** None. **T. Asare:** None. **A. Machado:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ATI, Enspire and Cardionomics. F. Consulting Fees (e.g., advisory boards); Spinal Modulation and Functional Neurostimulation. **E. Plow:** None.

Nanosymposium

560. Stroke Recovery

Location: S404

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 560.06

Topic: C.21.Stroke Recovery

Support: NIH K01HD069504 (EP)

AHA (13BGIA17120055)

RPC2014-1067 (DC)

Title: Re-thinking brain stimulation in stroke rehabilitation: Why higher-motor areas might be better alternatives for patients with greater disability

Authors: *E. B. PLOW[1], N. VARNERIN[1], V. SANKARASUBRAMANIAN[1], D. CUNNINGHAM[1], K. POTTER-BAKER[1], K. SAKAIE[1], G. H. YUE[3], A. CONFORTO[4], A. MACHADO[2];
[1]Biomed. Engin., [2]Ctr. for Neurolog. Restoration, Cleveland Clin., Cleveland, OH; [3]Kessler Fndn., West Orange, NJ; [4]Neurol. Department, São Paulo University,, Neurol. Clin. Division, Hosp. das Clinicas,, São Paulo Brazil, Brazil

Abstract: Stimulating the brain is one of the most popular yet controversial advents to boost plasticity in stroke rehabilitation. The idea is stimulating ipsilesional (stroke-affected) primary motor cortex (M1) would most impact upper limb recovery since M1 controls dexterity via corticospinal tracts (CST). However, CST from M1 are damaged commonly, which generates inconsistencies and controversies. For instance, outcomes of stimulation are weak and variable in patients with greater damage and disability. With incrementally greater damage, alternate areas, such as ipsilesional higher motor cortices, vicariate to assume the role of M1 in recovery. As such, how can stimulating M1 consistently boost rehabilitative plasticity? Here, across two independent studies, we tested the premise that stimulating ipsilesional higher motor areas would instead benefit patients with greater damage and disability. The first study used a clinical trial design to establish causality. We asked when matched for initial disability, do patients with serious damage and disability benefit more with transcranial direct current stimulation of ipsilesional higher motor areas in rehabilitative recovery? Our second study used a repeated measures crossover design to test comparative efficacy, asking whether repetitive transcranial magnetic stimulation of ipsilesional higher motor areas than M1 most benefits those with serious damage and disability? In both studies, injury to CST quantified baseline damage, while disability was noted as upper limb impairment. We studied outcomes of recovery and expressions of plasticity. Our clinical trial demonstrates that with incrementally greater injury and disability, stimulating ipsilesional higher motor areas elicits greater recovery. Our cross-sectional study confirms -stimulating ipsilesional M1 is best only in those with minimal damage and disability. While our findings from two studies confirm our premise, we note alternate expressions of plasticity. Stimulating ipsilesional higher motor areas boosts plasticity of the contralesional (intact) hemisphere. We find greater cooperation between ipsilesional and contralesional cortices and concomitant rise in excitability of contralesional CST that predicts paretic limb recovery. Therefore, with incrementally greater damage to CST from M1, ipsilesional higher motor areas can vicariate but by recruiting intact cortices and their CST. Since stimulating M1 shares diametrically opposite relationship with injury and disability than

stimulating higher motor areas, we can define threshold where outcomes of M1 weaken, but higher motor areas instead boost rehabilitative plasticity.

Disclosures: **E.B. Plow:** None. **N. Varnerin:** None. **V. Sankarasubramanian:** None. **D. Cunningham:** None. **K. Potter-baker:** None. **K. Sakaie:** None. **G.H. Yue:** None. **A. Conforto:** None. **A. Machado:** Other; AM has the following conflicts of interest to disclose: ATI, Enspire and Cardionomics (distribution rights from intellectual property), Spinal Modulation and Functional Neurostimulation (consultant)..

Nanosymposium

560. Stroke Recovery

Location: S404

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 560.07

Topic: C.21.Stroke Recovery

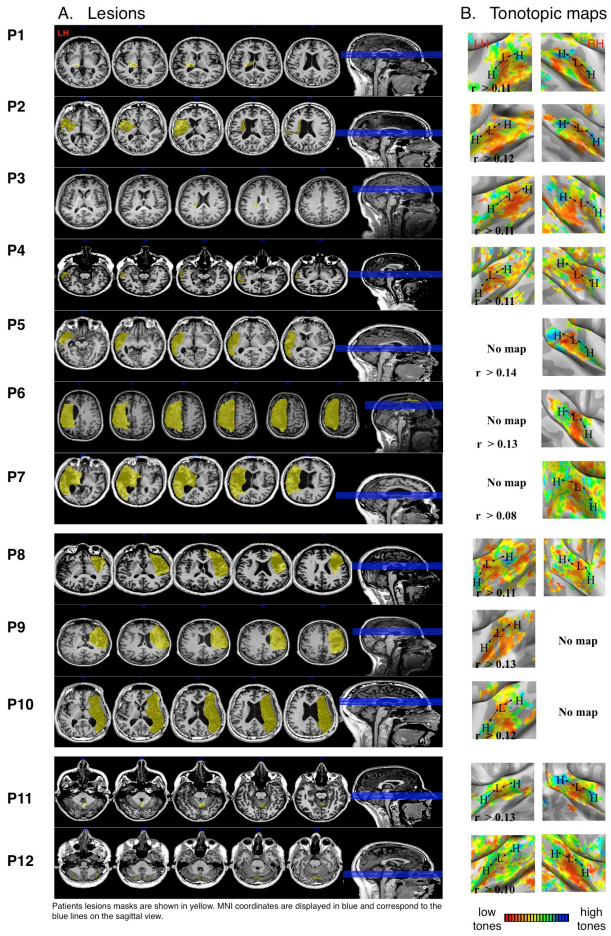
Support: SNF Grant 320030B-141177

Title: Unilateral brain lesions modulate human tonotopic mappings

Authors: *S. DA COSTA[1,4], S. CROTTAZ-HERBETTE[2], W. VAN DER ZWAAG[5], R. MEULI[3], P.-A. RAPIN[6], S. CLARKE[2];
[2]Dept. of Clin. Neurosciences, [3]Dept. of Radiology, [1]Lausanne Univ. Hosp., Lausanne, Switzerland; [4]Dept. of Hearing and Speech, Vanderbilt Med. Ctr., Nashville, TN; [5]Ctr. d'Imagerie Biomedicale, Ecole Polytechnique Feferale de Lausanne, Lausanne, Switzerland; [6]Inst. de Lavigny, Lavigny, Switzerland

Abstract: The primary auditory cortex (PAC) is essential to human auditory abilities. Previous fMRI studies have measured two large tonotopic primary subfields with mirror symmetric progressions of preferred frequency. In humans, brain lesions induce plasticity in brain regions belonging to the same network, a phenomenon defined as diaschisis. Here, we acquired fMRI tonotopic mappings in unilateral brain lesion patients and quantified how these lesions affected the contralesional tonotopic map. We hypothesised that diaschisis-like effects should cause functional reorganisation of PAC if the lesion site involved areas belonging to the auditory pathway. We scanned 12 healthy controls and 12 patients with unilateral lesion (Fig1.A) in the left hemisphere, right hemisphere and the right cerebellum. Each participant attended to progressive cycles of pure tone bursts (88 - 8000 Hz) presented in 32s-blocks during two 8min runs. PAC was functionally defined as the largest cluster containing the mirror-symmetric gradients in each individual hemisphere. Tonotopic maps were quantified as percentage of

preferred frequency within the total amount of voxels in PAC - the frequency distribution- and as signal variations for each frequency bin within PAC - the percent signal change (PSC) distributions. Mirror-symmetric gradients were maintained in both hemispheres, despite variations in frequency representations depending on the lesion site (Fig1.B). Frequency distributions and PSC variations in patients were outside normal range in contralesional and ipsilesional hemispheres, with lesion closer or within PAC inducing larger effects, such as an increased in low frequencies representations in contralesional PAC. Our results demonstrated that (1) tonotopic maps could be easily measured in stroke patients, (2) frequency mappings are preserved only if primary and non-primary auditory areas are not part of the lesion site, and (3) both contralesional and ipsilesional tonotopic maps are highly influenced by its own reciprocal maps, possibly reflecting some degrees of diaschisis-like effects.



Disclosures: **S. Da Costa:** None. **S. Crottaz-Herbette:** None. **W. Van der Zwaag:** None. **R. Meuli:** None. **P. Rapin:** None. **S. Clarke:** None.

Nanosymposium

560. Stroke Recovery

Location: S404

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 560.08

Topic: C.21.Stroke Recovery

Support: NIH R01 NS085167

Title: Vagus nerve stimulation paired with rehabilitative training improves recovery in multiple models of brain injury

Authors: *S. A. HAYS;
Bioengineering, Univ. of Texas At Dallas, Richardson, TX

Abstract: Stroke is a leading cause of disability in the US. Despite extensive rehabilitative training, many stroke patients are left with some degree of impairment in the upper limb. The development of methods that can enhance recovery after brain injury is critical to reduce disability. Recent, vagus nerve stimulation (VNS) paired with rehabilitative training has emerged as a potential method to improve post-stroke recovery. VNS paired with rehabilitative training enhances recovery of multiple quantitative measures of forelimb strength and speed compared to equivalent rehabilitative training without VNS in models of ischemic stroke and hemorrhagic stroke in rats. To further investigate that translational potential of VNS, we tested VNS paired with rehabilitative training in models of advanced age and of chronic stroke. In the first cohort, aged rats (16 months old) were trained to perform the isometric force task, which provides automated, quantitative measures of forelimb strength. Once proficient, rats received an ischemic lesion in the motor cortex to impair use of the trained limb. One week after stroke, rats were assigned to receive VNS paired with forelimb use doing rehabilitative training, or equivalent rehabilitative training without VNS for 6 weeks. We find that VNS paired with rehabilitative training results in significant, lasting increases recovery of forelimb strength compared to rehabilitative training without VNS. To investigate VNS efficacy in chronic stroke, a second cohort of rats underwent similar training and lesion. Seven weeks after lesion, rats received rehabilitative training with paired VNS, rehabilitative training with delayed VNS, or rehabilitative training without VNS. We find that VNS paired with rehabilitative training enhances recovery compared to rehabilitative training without VNS even when initiated many weeks after stroke. Additionally, we find that VNS must be paired with rehabilitative training to promote recovery, consistent with a role in enhancing neuroplasticity to support recovery. We are currently investigating the neuronal mechanisms that may underlie VNS-dependent recovery. These findings provide additional support that VNS paired with rehabilitative training may be useful as a post-stroke therapy.

Disclosures: S.A. Hays: None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.01

Topic: D.01. Chemical Senses

Title: Feedback from network states affects perception of odor in *C. elegans*

Authors: *A. GORDUS, C. BARGMANN;
The Rockefeller Univ., New York, NY

Abstract: Variability is a prominent feature of behavior, and an active element of certain behavioral strategies. To understand how neuronal circuits control variability, we examined the propagation of sensory information in a chemotaxis circuit of *C. elegans* where discrete sensory inputs can drive a probabilistic behavioral response. Olfactory neurons respond to odor stimuli with rapid and reliable changes in activity, but downstream AIB interneurons respond with a probabilistic delay. The interneuron response to odor depends on the collective activity of multiple neurons - AIB, RIM, and AVA -- when the odor stimulus arrives. These three neurons participate in an ongoing synchronously fluctuating internal state that has a very probabilistic response to odor. However, certain activity states that are less synchronous respond to odor more reliably. Artificially generating these activity states by modifying neuronal activity increases the reliability of odor responses in interneurons and the reliability of the behavioral response to odor. The integration of sensory information with network state may represent a general mechanism for generating variability in behavior.

Disclosures: A. Gordus: None. **C. Bargmann:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.02

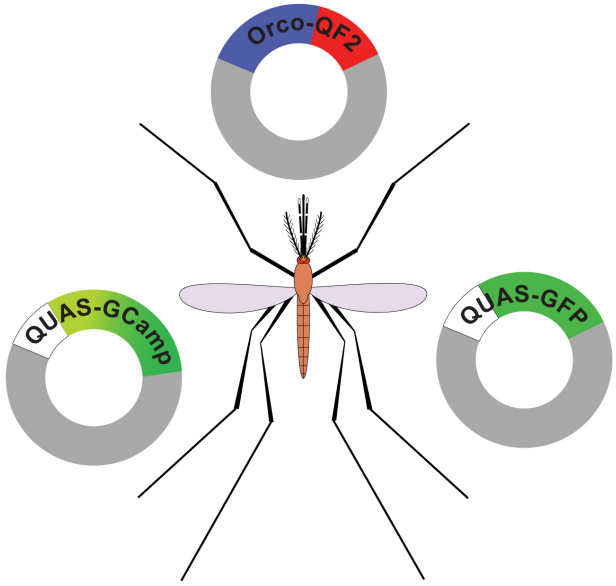
Topic: D.01. Chemical Senses

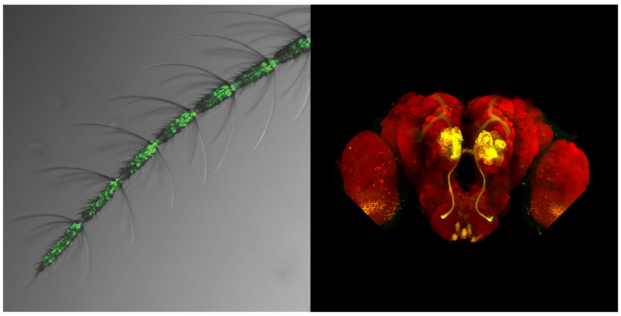
Support: Synergy Grant Award (to C.J.P)

Title: Genetic dissection and characterization of the malaria mosquito Anopheles gambiae olfactory system

Authors: *O. RIABININA[1], E. MARR[1], C.-C. LIN[1], M. JACOBS-LORENA[2], D. A. O'BROCHTA[3,4], C. J. POTTER[1];
[1]Dep of Neuroscience, SOM, Johns Hopkins Univ., Baltimore, MD; [2]Dept. of Mol. Microbiology and Immunology, Malaria Res. Inst., Johns Hopkins Bloomberg Sch. of Publ. Hlth., Baltimore, MD; [3]Inst. for Biosci. and Biotech. Res., Rockville, MD; [4]Dept. of Entomology, The Inst. for Biosci. and Biotech. Res., Univ. of Maryland, College Park, MD

Abstract: Mosquitoes are a major threat to human health as vectors for infectious diseases like malaria, dengue and yellow fever. Mosquitoes find humans by detecting olfactory (body odor and CO2) and temperature cues (McMeniman et al, 2014; DeGennaro et al, 2013). Targeting the olfactory system of mosquitoes is therefore a promising approach for interfering with the transmission of infectious diseases. We have adapted the binary expression Q-system, originally developed for *Drosophila* (Potter et al, 2010; Riabinina et al, 2015), to genetically target olfactory neurons of the mosquito Anopheles gambiae. The OR7 (Orco) gene of A. gambiae codes for an olfactory co-receptor that is co-expressed with 79 olfactory receptor genes in about 60% of all olfactory sensory neurons (OSNs). By using piggyBac transposable vectors, we created multiple Orco-QF2 driver lines that express the transcriptional activator QF2 in Orco-positive OSNs. We have also generated QUAS-mCD8-GFP reporter lines to visualize OSNs, and QUAS-CGamp6f reporter lines for functional calcium imaging. The transgenic Orco-QF2/QUAS-mCD8-GFP mosquitoes exhibit strong labelling of OSNs in the antennae, maxillary palps and proboscis, in the primary olfactory brain centre, the antennal lobes, and the primary gustatory brain centre, the suboesophageal ganglion. There are marked sexual dimorphisms in the distribution and numbers of Orco-positive cells. We developed a novel live imaging method that allows for the rapid assessment of antennal OSN population responses to essential components of human body odor and to other biologically relevant odorants. The new transgenic lines also allow for *in vivo* imaging of neuronal activity in the brain. To the best of our knowledge, this is the first successful attempt to specifically label the olfactory system of mosquitoes. These results demonstrate the feasibility of using the Q-system in A. gambiae, and dramatically enhance our abilities to characterize, decipher, and interfere with sensory processing in disease vectors.





Disclosures: **O. Riabinina:** None. **E. Marr:** None. **C. Lin:** None. **M. Jacobs-Lorena:** None. **D.A. O'Brochta:** None. **C.J. Potter:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.03

Topic: D.01. Chemical Senses

Title: Odor coding with random maps

Authors: ***S. SRINIVASAN**[1,3], C. F. STEVENS[2,3];
[2]Kavli Inst. for Brain and Mind, [1]Univ. California, San Diego, CA; [3]Mnl-s, Salk Inst., La Jolla, CA

Abstract: Since the discovery of olfactory receptors, researchers have elucidated the olfactory circuit from the epithelium to the bulb to the cortex in increasing detail. How odors are coded in the olfactory cortex, however, remains elusive. In large part because odors evoke activity within a sparse and random neuronal ensemble in the cortex, and it is unclear how this ensemble can represent an odor code. Remarkably, the 3 part circuit architecture of olfactory systems is conserved across species including flies, where olfactory circuitry and function are better understood. We take advantage of the smaller fly system to examine odor representation in the antennal lobe (bulb) and mushroom body (cortex). Experiments suggest that the antennal lobe employs a maximum entropy code to represent odors, ensuring that for any odorant only a few selective glomeruli are strongly activated. This representation is aided by gain control through lateral inhibition networks. We use random matrix theory to show how the glomerular odor code is represented in the mushroom body. We then transform theory into a specific model to quantitatively compare discrimination and generalization predictions with experimental data. We also extend this model to explain odor coding in the more complex olfactory cortex, and discuss how the two systems are designed to suit the performance objectives of their differing ecological niches.

Disclosures: S. Srinivasan: None. **C.F. Stevens:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.04

Topic: F.02. Animal Cognition and Behavior

Support: Howard Hughes Medical Institute

Title: Electron microscopy reconstruction of *Drosophila* melanogaster mushroom body synaptic architectures reveals repeating network motifs in the γ1 lobe

Authors: *J. S. LAURITZEN[1], Z. ZHENG[1], C. B. FISHER[1], J. M. RATLIFF[1,2], B. M. HARRISON[1,2], A. E. ADESINA[1,2], C. G. ROBINSON[1], J. PRICE[3], D. MILKIE[4], O. TORRENS[4], B. KARSH[1], E. T. TRAUTMAN[1], K. KHAIRY[1], E. PERLMAN[1], M. KAZHDAN[5], A. CARDONA[1], S. SAALFELD[1], D. BOCK[1];
[1]Howard Hughes Med. Inst., Janelia Res. Campus, Ashburn, VA; [2]Biol. - Behavioral Neurosci. Program, Northeastern Univ., Boston, MA; [3]Hudson Price Designs, LLC, San Diego, CA; [4]Coleman Technologies, Inc., Newtown Square, PA; [5]Johns Hopkins Univ., Baltimore, MD

Abstract: Purpose: Dopaminergic afferent neurons (DANs) attribute value to olfactory representations in the mushroom body (MB) Kenyon cells (KC) of fruit flies, and these assignments likely occur via synaptic plasticity in functional compartments defined by the co-innervation of mushroom body output neuron (MBON) dendrites and dopaminergic neuron (DAN) axons in the MB lobes (Aso et al. eLife 2014a,b). The compartments imply design elements such as coincidence detection (Hige & Turner Neuron 2015), but the synaptic architectures for any MB compartment have never been mapped, and we do not understand how dopamine acts to attribute behavioral valence within the lobes. To this end we reconstructed neural networks defining the γ1 compartment, evidenced by the co-innervation of gamma KC (γ KC) axons, MBON γ1-pedc>a/β dendrites, and axons from their cognate DANs, the PPL1-γ1 pedc cells. We then examined the KC-DAN-MBON synaptic interface in this compartment. **Methods:** Cells in an 863 serial section transmission electron microscopy volume through the horizontal lobes of an adult female *Drosophila melanogaster* brain were annotated, explored via graph visualization of connectivity, and 3D rendered using CATMAID software (Saalfeld et al. Bioinformatics 2009). Morphological reconstruction, cytoarchitectures, and connectivity analysis enabled robust cell classification. We mapped 102 γ KCs, MBON γ1-pedc>a/β dendrites, and PPL1-γ1 pedc axons until classifiable. We traced 32/102 γ KCs to completion in the volume. **Results:** The MBON γ1-pedc>a/β is postsynaptic at 9,325 sites, but never presynaptic. All 32 complete γ KCs are presynaptic to the MBON via 367 highly convergent synapses that are often spatially coincident, consistent with observations in the MB α-lobe by a parallel effort at Janelia (Janelia Fly EM Project, unpublished). PPL1-γ1 pedc cells are routinely presynaptic to the MBON, and form axo-axonal pre- and postsynaptic connections with γ KCs. Interestingly, the MBON is postsynaptic at 75% of the DAN > γ KC synapses, and 93% of the γ KC > DAN synapses, forming divergent motifs at the KC-DAN-MBON interface. **Conclusions:** γ KC-MBON convergence could support coincidence detection. The PPL1-γ1 pedc neurons act both pre- and postsynaptically to the KC-MBON interface in the γ1 lobe. Dopaminergic networks form γ1-local feedback and feedforward motifs that could modulate odor representations upstream of the DAN dendrites outside the MB. The results reveal a routinely cospatial KC-DAN-MBON synaptic architecture in the γ1 compartment, and establish an initial framework for synaptic-level understanding of MB associational compartments.

Disclosures: J.S. Lauritzen: None. **Z. Zheng:** None. **C.B. Fisher:** None. **J.M. Ratliff:** None. **B.M. Harrison:** None. **A.E. Adesina:** None. **C.G. Robinson:** None. **J. Price:** None. **D. Milkie:** None. **O. Torrens:** None. **B. Karsh:** None. **E.T. Trautman:** None. **K. Khairy:** None. **E. Perlman:** None. **M. Kazhdan:** None. **A. Cardona:** None. **S. Saalfeld:** None. **D. Bock:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.05

Topic: D.01. Chemical Senses

Support: NIH Grant F32DC012004

NIH Grant R01DC009640

NIH Grant R01DC009640

NIH Grant R01DC013576

DFG CI 222/1-1

Title: The role of trace amine-associated receptors in olfaction

Authors: *A. K. DEWAN[1], A. CICHY[1], J. ZHANG[1], D. RINBERG[2], T. BOZZA[1];
[1]Dept. of Neurobio., Northwestern Univ., Evanston, IL; [2]Neurosci. and Physiol., NYU Neurosci. Inst., New York, NY

Abstract: The Trace Amine-Associated Receptors (TAARs) are a small subset of evolutionarily conserved main olfactory receptors whose contribution to chemosensory function is not known. Our previous data have shown that the majority of TAARs are mapped to a discrete group of broadly-tuned, amine-selective glomeruli in the dorsal olfactory bulb of the mouse. Amines are key components of several social cues and/or predator-derived chemosignals in rodents as well as protein decomposition (e.g. rotting fish). We have shown that TAARs are necessary for the behavioral response to these odorants as genetic deletions of all olfactory TAARs, or even a single TAAR, eliminates the attraction or aversion to amines in a ligand dependent manner. However, it is not clear to what degree amine valence is influenced by potential detection deficits in TAAR deletion mice. Using a combination of gene targeting, electrophysiology, *in vivo* imaging, and behavior in mice, we are examining how TAAR gene deletions affect amine sensitivity. Mice lacking all olfactory TAAR genes exhibit a pronounced decrease (10-50-fold) in behavioral sensitivity to isopentylamine and phenylethylamine. Similarly, mice lacking a single TAAR gene (TAAR4) show a 10-fold decrease in sensitivity to phenylethylamine, a preferred TAAR4 ligand. These findings indicate that single TAARs can set the behavioral detection thresholds to specific amines and that TAARs may be the most sensitive amine receptors in mice. We also show that TAAR4 deletion mice fail to avoid phenylethylamine at concentrations that they can still detect. These data, along with our thresholding data, demonstrate that the loss of amine aversion in TAAR deletion mice cannot be attributed to amine anosmia. Thus, the TAAR inputs may also be crucial for encoding the perceived valence of

amines. The importance of TAARs in amine detection and valence may help explain the conservation of these receptors in a wide range of vertebrates.

Disclosures: **A.K. Dewan:** None. **A. Cichy:** None. **J. Zhang:** None. **D. Rinberg:** None. **T. Bozza:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.06

Topic: D.01. Chemical Senses

Support: NIH Grant DC00566

NIH Grant DC04657

NSFC 31100799

Title: Mitral cell responses are strongly dependent on trial-to-trial anticipatory variability in the basal firing rate

Authors: *D. RESTREPO[1], E. M. GUTHMAN[2], A. LI[1];
[1]Cell & Dev. Biology, Neurosci. Program, Univ. of Colorado Anschutz Med. Campus, Denver, CO; [2]Neurosci. Program, Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: In fundamental olfactory studies Lord Adrian found development of irregular intrinsic activity in the olfactory bulb (OB) as the animal awoke from anesthesia. Interestingly, he observed that this increase in basal activity made it difficult to detect responses to odor by mitral/tufted (M/T) cells, the second order neurons in the OB, and he hypothesized that this effect of intrinsic activity could be altered by changes in attention1. Indeed, in the awake animal the basal activity and responsiveness of these M/T cells is irregular and modulated by sniff. Here we studied the trial-to-trial variability of M/T cell baseline firing rate (BFR) before stimulus addition in awake behaving mice, and asked the question whether the response to sensory stimuli depends on this intrinsic activity and whether this activity reflects anticipatory status of the animal. Using tetrode recordings we find that BFRs vary widely on a trial-to-trial basis in M/T cell ensembles of awake mice. Importantly, the rate responses to stimulus display a negative correlation with BFR in the majority (70%) of M/T cells. Interestingly, when mice learned to associate one odor with lack of reward there was a decrease of excitatory responses and an increase in inhibitory responses in low BFR trials. Finally, in a substantial number of units when

the animal responded to the unrewarded odor incorrectly (false alarm) the mean BFR was lower compared to correct rejection suggesting that intrinsic activity reflects the anticipatory status of the animal. Thus, in this sensory modality that receives massive parallel input through ~1,200 olfactory receptors ensembles of second order neurons exhibit changes, that are modulated by the animal's behavioral state, in BFR-dependent responsiveness on a trial-to-trial basis. This variation in BFR likely reflects trial-to-trial changes in processes such as attention, motivation or arousal.

Disclosures: D. Restrepo: None. **E.M. Guthman:** None. **A. Li:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.07

Topic: D.01. Chemical Senses

Title: Lateral inhibition differences between mitral and tufted cells: causes and consequences

Authors: *M. A. GERAMITA[1], S. D. BURTON[2], N. N. URBAN[2];
[1]Biol. Sci., Univ. of Pittsburgh, Pittsburgh, PA; [2]Biol., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Mitral cells (MCs) and tufted cells (TCs) are the principal output neurons of the olfactory bulb. Although recent evidence suggests that MCs and TCs encode distinct features of olfactory information, the circuit mechanisms that lead to the functional differences are unknown. We hypothesize that these functional differences are mediated in part by differences in lateral inhibition (LI), the circuit motif that allows M/TCs to indirectly inhibit one another and that enhances contrast between similar odors. We measured LI in olfactory bulb slices from M72-ChR2-YFP mice that express ChR2 in a single type of olfactory sensory neuron. Photoactivation of the M72 glomerulus evoked LI onto M/TCs projecting to glomeruli adjacent to the M72. We measured the strength of LI by recording IPSCs evoked by stimulating the M72 glomerulus with 10ms light pulses. We found that the peak amplitude of IPSCs onto MCs (38 + 18 pA, n=12) was significantly larger than LI onto TCs (25+12 pA, n=11). We assessed the impact of LI on MC and TC spiking by constructing FI curves for each M/TC via somatic current injections of increasing amplitudes. At each current step, we recorded the number of action potentials evoked with and without M72 photostimulation. We found that LI affects MCs at intermediate firing rates (25-75 Hz) and TCs at low firing rates (5-40 Hz). We hypothesized that this difference in the range of firing rates affected by LI was due to differences in the intrinsic excitability between superficial granule cells (sGCs) and deep granule cells (dGCs). We

confirmed this hypothesis in 2 ways. First, whole-cell *in vitro* recordings from sGCs and dGCs indicated that sGCs have increased input resistance, lower rheobase, and steeper FI curves compared to dGCs. Second, artificially increasing the excitability of GCs by bath applying an mGluR agonist, DHPG, shifted the range of firing rates affected by LI in MCs to lower rates. To gain insight into how these differences in LI between MCs and TC affect odor coding, we used computer simulations to model how well olfactory bulbs composed of only MCs or TCs discriminate between similar odors. We found that TCs outperform MC when odors are presented at low concentrations while MCs outperform TCs at high concentrations. Additionally, we showed that odor discrimination across a large concentration range is optimal with a combination of MCs and TCs as opposed to using only MCs or TCs. Together, these findings indicate that LI differentially affects MCs and TCs and may underlie the functional differences between them. Future work will build on these findings to better understand the types of olfactory tasks that each cell is best suited to perform.

Disclosures: M.A. Geramita: None. **S.D. Burton:** None. **N.N. Urban:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.08

Topic: D.01. Chemical Senses

Support: NIH Grant R01DC011286

NIH Grant R01DC009994

NIH Grant R01DC009977

NIH Grant T15LM007056

NIH Grant T32NS007224

Title: Circuit models identify mechanisms of respiration driven lateral inhibition underlying mitral activity

Authors: *S. M. SHORT[1,2], T. S. MCTAVISH[1], T. M. MORSE[1], G. M. SHEPHERD[1], J. V. VERHAGEN[1,2];
[1]Neurobio., Yale Univ., New Haven, CT; [2]John B. Pierce Lab., New Haven, CT

Abstract: In the bulbar network, unique and functionally relevant interactions occur between spontaneous respiration-evoked and odor-evoked glomerular inputs. The responses that reach the mitral and tufted cell (MTC) somas backpropagate into the lateral dendrites, where they are balanced by feedback and lateral inhibition from granule cells. While recent modeling studies emphasize the importance of lateral inhibition in shaping bulbar responses to odors, how temporal and spatial glomerular input patterns influence the firing of a single MTC, the main output of the olfactory bulb, has not been fully characterized. Consistent with previous studies examining MTC responses to odor stimuli across the respiratory cycle, we find phase shifts in peak MTC activity following optical stimulation in the glomerular layer. MTCs display spontaneous respiration-mediated burst firing during the transition from exhalation to inhalation. This activity is followed by synchronized lateral inhibition that results in a quieting of MTC activity. *In vivo* optogenetic stimulation of excitatory glomerular inputs results in a significant shift in peak firing towards the exhalation phase. We are developing a model to investigate mechanisms of lateral inhibition that may underlie such respiration mediated tuning of sensory inputs. We examine the individual and combined roles of periglomerular and granule cell mediated lateral inhibition. Similar to our *in vivo* optogenetic experiments, our model simulated activation of excitatory glomerular inputs shifts MTC activity into the exhalation phase. Additionally, both our *in vivo* and modeling studies indicate that stimulation of glomerular inputs during the transition between exhalation and inhalation commonly results in a decrease in burst firing. Preliminary data indicate both layers of inhibition are important for shaping respiration mediated tuning of sensory inputs, but each may underlie unique aspects of glomerular input processing. Our data highlight the importance of temporal coding, and show how spontaneous respiration driven activity, associated with specific phases of the respiration cycle, influences the efficacy of glomerular input patterns. Using a combination of *in vivo* experiments and neural network modeling, we provide mechanistic explanations of how the bulb may process discrete dorsal glomerular inputs.

Disclosures: **S.M. Short:** None. **T.S. McTavish:** None. **T.M. Morse:** None. **G.M. Shepherd:** None. **J.V. Verhagen:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.09

Topic: D.01. Chemical Senses

Support: Swiss National Science Foundation

Title: Neuronal pattern separation in the olfactory bulb improves odor discrimination learning

Authors: *A. CARLETON[1], O. GSCHWEND[1], N. ABRAHAM[1], S. LAGIER[1], F. BEGNAUD[2], I. RODRIGUEZ[1];
[1]Univ. of Geneva, Geneva, Switzerland; [2]Firmenich, Geneva, Switzerland

Abstract: Neuronal pattern separation is thought to enable the brain to disambiguate sensory stimuli with overlapping features thereby extracting valuable information. In the olfactory system, it remains unknown whether pattern separation acts as a driving force for sensory discrimination and the learning thereof. Here we show that overlapping odor-evoked input patterns to the mouse olfactory bulb (OB) are dynamically reformatted in the network at the timescale of a single breath, giving rise to separated patterns of activity in ensemble of output neurons (mitral/tufted cells; M/T). Strikingly, the extent of pattern separation in M/T assemblies predicts behavioral discrimination performance during the learning phase. Furthermore, exciting or inhibiting GABAergic OB interneurons, using optogenetics or pharmacogenetics, altered pattern separation and thereby odor discrimination learning in a bidirectional way. In conclusion, we propose that the OB network can act as a pattern separator facilitating olfactory stimuli distinction, a process that is sculpted by synaptic inhibition.

Disclosures: A. Carleton: None. **O. Gschwend:** None. **N. Abraham:** None. **S. lagier:** None. **F. Begnaud:** None. **I. rodriguez:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.10

Topic: D.01. Chemical Senses

Title: Figure background separation in the mouse olfactory bulb

Authors: *A. VINOGRAD[1], Y. LIVNEH[2], A. MIZRAHI[2];
[1]The Edmond and Lily Safra Ctr. for Brain Sci., The Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]The hebrew university, Jerusalem, Israel

Abstract: Natural scenes are comprised of salient as well as background information. The brain separates the salient from the background by a computation known as figure-background separation (FBS). Where and how neural circuits compute FBS remain open questions. In an attempt to answer these questions in the olfactory system we used in-vivo two-photon calcium

imaging of mitral cells (MCs) in the mouse olfactory bulb (OB). We used a three-odor based protocol where one odor is presented as background (a 50 sec stimulus) and one as figure-over background (a 2 sec stimulus during the background presentation). We compared between MCs responses to the figure alone versus the figure over background. Our data show that FBS is evident both at the single cell level, as well as at the population level. To test whether FBS is shaped by plasticity we used a 1-week odor enrichment protocol prior to testing FBS. In enriched mice, single MCs responses as well as population responses to the figure over background were significantly reduced. Additionally, FBS was stronger in the awake vs the anesthetized state. These data show that FBS already occurs at the level of the OB and that this computation undergoes experience-dependent plasticity.

Disclosures: **A. Vinograd:** None. **Y. Livneh:** None. **A. Mizrahi:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.11

Topic: D.01. Chemical Senses

Support: NIH K99 MH101634-01

NARSAD Young Investigator Award

Crick-Jacobs Junior Fellowship

Japan Society for the Promotion of Science

the Kanae Foundation for the Promotion of Medical Science

the Uehara Memorial Foundation

the Naito Foundation and the Pioneer Fund

Title: Origin and identity of feedback projecting neurons to the main olfactory bulb revealed through retrograde viral tracing

Authors: *K. PADMANABHAN[1], F. OSAKADA[2], E. CALLAWAY[3], F. GAGE[3], T. J. SEJNOWSKI[3];
[1]Salk Inst. CNL-S, La Jolla, CA; [2]Nagoya Univ., Nagoya, Japan; [3]Salk Inst., La Jolla, CA

Abstract: Although feedback projections from higher processing areas can constitute the majority of synaptic inputs to primary sensory regions, and play a role in shaping perception, principles of their anatomical organization remain largely unknown. Using a viral based strategy, we mapped feedback from the whole mouse brain to the granule cell layer (GCL) in the main olfactory bulb. Projections originated from a number of areas including from olfactory regions, neuromodulatory areas, and the ventral arm of CA1 hippocampus. Additionally, we identified asymmetries in the organization of feedback depending on the area of origin. For instance, spatially clustered feedback from the piriform contrasted with the distributed organization observed in feedforward projections to the piriform. Additionally, we found biases in the input from the ventral arm of the contralateral anterior olfactory nucleus (AON) as compared to the uniform distribution of feedback observed in ipsilateral projections to the bulb. The identity and organization of feedback projecting cells revealed through our viral tracing methods suggests higher olfactory processing centers and areas involved in stress, anxiety, learning and memory can all influence olfactory neuronal responses at the earliest stages, 2 synapses away from the where chemical compounds are first detected.

Disclosures: K. Padmanabhan: None. **F. Osakada:** None. **E. Callaway:** None. **F. Gage:** None. **T.J. Sejnowski:** None.

Nanosymposium

561. Olfactory Processing

Location: N226

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 561.12

Topic: D.01. Chemical Senses

Support: HHMI

Title: Neural circuits in the cortical amygdala mediate innate, odor-driven behavior

Authors: *C. M. ROOT, A. ZARDINA, Y. WANG, K. LAWLOR, R. AXEL;
Neurosci., Columbia Univ., New York, NY

Abstract: Innate behaviors are observed in naïve animals without prior learning or experience, suggesting that the neural circuits that mediate these behaviors are genetically determined and stereotyped. The neural circuits that convey olfactory information from the sense organ to the cortical and subcortical olfactory centers have been anatomically defined but the specific pathways responsible for innate responses to volatile odors have not been identified. We have demonstrated that a stereotyped neural circuit that transmits information from the olfactory bulb

to cortical amygdala is necessary for innate aversive and appetitive behaviors. Moreover, we have employed the promoter of the activity-dependent gene, arc, to express the photosensitive ion channel, channelrhodopsin, in neurons of the cortical amygdala activated by odors that elicit innate behaviors. Optical activation of these neurons leads to appropriate behaviors that recapitulate the responses to innate odors. We observe that aversive and appetitive odors activate distinct populations of neurons with unique projections to downstream targets. Furthermore, within the posterorlateral cortical amygdala we have identified an aversive domain that mediates avoidance behavior. Expression of channelrhodopsin in random ensembles of neurons in this region, and subsequent optical activation, is sufficient to elicit aversive behavior. Lastly, we have begun to characterize odor representation in cortical amygdala by endoscopic imaging of neuronal calcium activity using GRIN lens coupled 2-photon microscopy. Preliminary evidence suggests that neurons in this brain region may be tuned to odor valence. These data indicate that the cortical amygdala plays a critical role in the generation of innate odor-driven behaviors.

Disclosures: **C.M. Root:** None. **A. Zardina:** None. **Y. Wang:** None. **K. Lawlor:** None. **R. Axel:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.01

Topic: D.17. Voluntary Movements

Support: CIHR Grant MOP84293

CIHR Grant MOP126158

Title: Movement intention modulates neural responses in visual cortex

Authors: *J. P. GALLIVAN[1], C. S. CHAPMAN[2], D. A. MCLEAN[3], J. R. FLANAGAN[1], J. C. CULHAM[3];
[1]Queen's Univ., Kingston, ON, Canada; [2]Univ. of Alberta, Alberta, ON, Canada; [3]Univ. of Western Ontario, London, ON, Canada

Abstract: The primate visual system contains myriad feedback projections from higher- to lower-order cortical areas, an organization that, across several theories and models, has been frequently implicated in sharpening or facilitating perceptual processing. The role of these feedback projections in action planning, by contrast, has received considerably less attention and

it remains largely unexplored how movement preparation impacts neural responses in the early visual system. Here we show, by combining data across several human functional MRI studies, that pre-movement activity patterns in early visual cortex can be used to reliably predict which movements--from the effectors used (e.g., limbs, eyes) to the particular actions performed (e.g., grasping vs. reaching)--will be executed mere moments later. All the fMRI studies examined used event-related delayed movement tasks in which participants were first instructed about which object-directed movement to make and then, following a delay period, executed the movement. Multivoxel pattern analyses revealed that the representation of movement-related information in visual cortex during the delay epoch, rather than being object position-invariant, was primarily restricted to regions corresponding to the retinotopic position(s) of the object(s) to be acted upon. The only exception to this observation was during eye movement preparation, whereby we found that foveal retinotopic cortex contained information about saccades to be performed to objects located in the visual periphery. Together, these findings show that, prior to movement execution, the intention to act influences visual cortex activity patterns in an effector-specific, goal-dependent manner and provide evidence for a modulation of early visual processing in accordance with the sensory consequences of upcoming movement.

Disclosures: J.P. Gallivan: None. **C.S. Chapman:** None. **D.A. McLean:** None. **J.R. Flanagan:** None. **J.C. Culham:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.02

Topic: D.17. Voluntary Movements

Support: NIH Grant P01-NS44393

Institute for Collaborative Biotechnologies Grant W911NF-09-0001 from the U.S. Army Research Office

NSF Grant DGER1144085

Title: Decoding the cortical dynamics of continuous manual tracking from fMRI

Authors: *D. A. BARANY[1], S. VISWANATHAN[2], M. CIESLAK[1], E. CADDIGAN[1], S. T. GRAFTON[1];
[1]UC Santa Barbara, Santa Barbara, CA; [2]Univ. Hosp. of Cologne, Jülich, Germany

Abstract: Many everyday actions require the fluid performance of smoothly changing, multidirectional movements. How can we map these complex behaviors in terms of their underlying movement representations? Motor regions in humans and non-human primates have neural populations that show tuning to multiple movement-related variables during goal-oriented hand movements. In humans, such neural populations have been identified with fMRI for discrete pointing movements along single fixed directions. To identify the neural populations involved in continuous movements, we implemented a simple manual-tracking task with systematically changing movement variables to probe the dynamics of population-level tuning, as revealed by BOLD fMRI signals measured at high spatial and temporal resolution. Participants continuously tracked a visual stimulus moving in a circle (16 s period) for blocks of three minutes. In each block, participants tracked the stimulus as smoothly as possible in one of three ways: (1) moving their right hand along a circular grooved board placed horizontally on their abdomen (Hand-only), (2) moving their eyes (Eyes-only), or (3) moving their hand and eyes concurrently (Hand-and-eyes). Movements in different blocks were either clockwise or counterclockwise. fMRI data were obtained on a 3T Siemans Prisma scanner, with a multiband accelerated pulse sequence that provided a full-brain scan with a 2x2x2 mm resolution and a 720 ms repetition time. We sought to map movement representations from the multivoxel responses evoked by each of these three types of movements. We used multivariate regression to relate the time-varying conjoint activity of voxels in regions of interest to the instantaneous angular position and movement direction of the stimulus. This regression model was then used to decode these corresponding variables on data from separate movement blocks. We found accurate decoding of hand movements in primary motor and premotor regions that reflected the current movement direction, whereas parietal and visual areas showed accurate decoding of the stimulus and hand positions. The superior parietal lobule showed generalization across effectors, suggesting distinct mappings for both hand and eye movements. Interestingly, decoding performance was highest at the fundamental frequency of the stimulus, and did not generalize across movement rotation blocks. Together, these results highlight the possibility of mapping the representations of dynamically changing movement variables across the motor system, and provide a promising framework for disentangling movement representations during complex visuomotor behavior.

Disclosures: D.A. Barany: None. **S. Viswanathan:** None. **M. Cieslak:** None. **E. Caddigan:** None. **S.T. Grafton:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.03

Topic: D.17. Voluntary Movements

Support: DFG Grant SCHE 1575/1-1

Title: Grasping with and without motor preparation

Authors: *J. A. MICHAELS[1], B. DANN[1], R. W. INTVELD[1], R. EPPINGER[1], H. SCHERBERGER[1,2];
[1]German Primate Ctr., Göttingen, Germany; [2]Biol., Univ. of Göttingen, Göttingen, Germany

Abstract: Neural networks of the brain involved in the planning and execution of grasping movements are not fully understood. The network formed by macaque anterior intraparietal area (AIP) and hand area of the ventral premotor cortex (F5) is strongly implicated in the generation of grasping movements. However, it is not clear how these areas encode the preparation and execution of grasping movements at the neural population level. To examine how preparation is represented, we recorded spiking activity from many electrodes in parallel in F5 and AIP while two macaque monkeys performed a delayed or non-delayed grasping task. Six individual recording sessions were collected for each animal. By visualizing the neural trajectories of delayed vs. non-delayed grasps, it was clear that a distinct preparation state was achieved in the population of F5 and AIP units. Furthermore, this preparation state seemed to be bypassed during non-delayed grasps. During catch trials, in which no action was performed, activity in F5 begins to return to baseline after it is clear that no action will be required, while activity in AIP lingers near the preparation state until a reward is received. In order to quantify the existence of a unique preparation state statistically, the distance between the delayed and non-delayed neural trajectory was analyzed in the full space of all simultaneously recorded units. At the instant of cue presentation, only 1 of 24 cases (2 grip types x 12 recording sessions) showed a significant ($p < 0.01$) difference between the delayed and non-delayed trajectories, confirming that the animals could not anticipate the task conditions. This pattern was maintained at 200 ms after cue presentation (2/24 and 3/24 cases in F5 and AIP), implying that the initial response to the cue is not modified by the command to move immediately. Crucially, at the time of go cue, 20/24 and 17/24 of cases showed a significant difference between the trajectories in F5 and AIP, respectively. This suggests that this state is only achieved when an action must be withheld. Interestingly, delayed and non-delayed grasps occasionally elicited differential activity during movement (14/24 and 8/24 of cases in F5 and AIP), and after movement was completed (5/24 and 6/24 of data sets in F5 and AIP), even when the action performed was identical. Taken together, these results re-enforce the essential role of F5 and AIP in the preparation of grasping movements, while endorsing the notion that the withholding of an action represents a unique state in both F5 and AIP. Moreover, variability in activity during movement may hint at a surprisingly flexible encoding scheme for grasp execution in this fronto-parietal network.

Disclosures: **J.A. Michaels:** None. **B. Dann:** None. **R.W. Intveld:** None. **R. Eppinger:** None. **H. Scherberger:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.04

Topic: D.17. Voluntary Movements

Support: MIUR

FIRB 2013,RBFR132BKP

Title: Effect of visual feedback on grasping activity in monkey dorsomedial visual stream

Authors: ***R. BREVEGLIERI**, A. BOSCO, C. GALLETTI, P. FATTORI;
Univ. Di Bologna, Bologna, Italy

Abstract: The medial posterior parietal area V6A is sensitive to visual stimulation as well as to grasping arm movements performed in darkness. The aim of this work was to assess whether, and to what extent, visual feedback affects grasp-related activity of V6A cells. Two trained Macaca fascicularis performed an instructed-delayed reach-to-grasp task in darkness and in light. Our hypothesis was that in light the neural activity would reflect motor efferent signals as well as proprioceptive and visual afferent feedbacks, whereas in dark it would reflect only the motor efferent copy and proprioceptive feedback. The object to be grasped in the task was an handle that could have, in different blocks, different orientations, so to require hand movements with different wrist orientations. We tested 150 V6A neurons. In half of the cell population, grasp-related activity was excited by visual input and in the other half it was inhibited. The most prominent influence on cell activity was exerted by visual condition and wrist orientation jointly. About 40% of cells were modulated during grasping preparation and 60% during grasping execution, and handle pulling (ANOVA, factor 1: wrist orientation; factor 2: visual environment, $p<0.05$). Cells were classified as "motor," "visual," and "visuomotor" neurons. Motor cells, discharging equally well in light and in dark, represented 14% of cell population. Visual cells, discharging only in light, represented the 17% of cell population. The majority of cells (69%) were of visuomotor type, discharging both in light and in dark but with a different strenght. These findings suggest a multimodal representation of grasping action in V6A and strengthen the role of V6A in integrating visual and motor signals to monitor grasping actions.

Disclosures: **R. Breveglieri:** None. **A. Bosco:** None. **C. Galletti:** None. **P. Fattori:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.05

Topic: D.17. Voluntary Movements

Title: Shared representations for delayed and non-delayed movement plans

Authors: ***G. ARIANI**, A. LINGNAU;
CIMeC - Ctr. for Mind/Brain Sci., Rovereto, Italy

Abstract: Previous human functional magnetic resonance imaging (fMRI) studies on the neural basis of movement planning typically used delayed-movement paradigms to isolate planning from execution (e.g. Toni et al., 2001; Mars et al., 2008; Gallivan et al., 2011a, 2011b, 2013). Although well established, this approach introduces artificially long planning delays that include brain activity unrelated to movement planning, making it difficult to disentangle the processes co-occurring with movement preparation during the delay period. Consequently it remains unclear to which degree delay-related brain signals 1) specifically reflect movement preparation, 2) can be generalized to contexts without a delay (see Ames et al., 2014). To address these questions, we directly compared delayed and non-delayed arm movements (reach-to-touch vs. reach-to-grasp) towards a central target object. To examine if and where brain activity shared between delayed and non-delayed movement planning carries information about the planned movements, we used univariate as well as multivariate analysis of fMRI data. The univariate contrast [Planning > Baseline] revealed a bilateral network of premotor (dorsal premotor cortex, PMd - ventral premotor cortex, PMv), parietal (posterior intraparietal sulcus, pIPS - superior parieto-occipital cortex, SPOC), prefrontal (dorsolateral prefrontal cortex, dlPFC) and temporal (superior temporal sulcus, STS) regions, as well as the left supplementary motor area (SMA). A conjunction analysis confirmed that, with the exception of the left dlPFC, the same brain regions are recruited during the planning of both delayed and non-delayed movements. Moreover, multivariate cross-condition decoding showed substantial overlap with the univariate conjunction in the left PMd, PMv, SMA, the right STS, and bilateral pIPS, SPOC regions, but not in the dlPFC. These results suggest that frontal (PMd, PMv, SMA) and parietal (pIPS, SPOC) regions involved in movement planning represent planned movements regardless of the presence of a delay.

Disclosures: **G. Ariani:** None. **A. Lingnau:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.06

Topic: D.17. Voluntary Movements

Support: CIHR (MOP-102662)

CFI

FRSQ

EJLB Foundation

FYSSEN Foundation

GRSNC

Title: Evidence that the globus pallidus provides an urgency signal for decision-making

Authors: *D. THURA, P. CISEK;
Dept Neurosci., Univ. Montreal, Montreal, QC, Canada

Abstract: To optimize their reward rate, animals must find the best speed-accuracy trade-off (SAT) for both their decisions and their movements. Recent analyses suggest that to optimize reward rate one should make decisions when sensory evidence reaches an accuracy criterion that decreases over time in a context-dependent manner. It has been proposed that this is accomplished by combining sensory evidence with an "urgency signal" that grows over time and sets the animal's SAT policy. While recent neurophysiological studies have shown the effect of the urgency signal in several decision-related regions, the origin of this signal is unknown. We recently observed that urgency of decisions appears related to the vigor of movements produced after the decision is made. This suggests that SATs for deciding and acting are influenced by a shared urgency/vigor signal, possibly originating from the basal ganglia. Here, we test this hypothesis by recording activity in the BG output nucleus, the globus pallidus (GP). A monkey performed a reaching decision task in which sensory evidence continuously evolves during the time course of a trial. In different blocks, the temporal properties of the task were varied to induce adjustments of monkey's speed-accuracy trade-off. Consistent with our predictions, GP activity during the decision process was not tuned to sensory evidence, but many cells showed build-up or decreasing activity during the deliberation period. Crucially, their activity often strongly varied with the context of the task: in blocks of trials favoring speed over accuracy,

build-up neurons were more active than in blocks favoring accuracy. Neurons with decreasing activity had the opposite pattern. These results support the role of GP in providing the urgency signals needed to set the monkey's SAT. To assess whether GP activity is causally involved in SAT adjustment, we interleaved control trials with trials during which GP activity was perturbed by trains of electrical pulses (100μA) delivered during deliberation. In most cases, micro-stimulation reduced the context-specific behavior of the monkey in the two blocks of trials: it tended to slow down the fast decisions performed in blocks favoring speed over accuracy, and accelerated the slower decisions performed in blocks favoring accuracy. Together, these results suggest that BG output structures provide the contextual urgency/vigor signal that influences cortical activities related to decision and action.

Disclosures: D. Thura: None. **P. Cisek:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.07

Topic: D.17. Voluntary Movements

Support: FIRB 2013 grant RBFR132BKP to LT

Title: Neural coding of action planning with and without visual feedback

Authors: *S. MONACO, E. PELLENCIN, G. MALFATTI, L. TURELLA;
Univ. of Trento, Ctr. for Mind/Brain Sci., Trento, Italy

Abstract: The fronto-parietal and occipito-temporal cortices show action-related preparatory responses for grasping and reaching movements. What remains unclear is whether the role of these areas is related to the perceptual representation of the object that is dynamically updated in the context of the upcoming action or to the anticipation of somatosensory consequences of the planned action. To answer this question, we used a slow event-related fMRI paradigm that independently manipulated vision of the object (Vision or No Vision) and action type (Grasp or Move hand). Movements consisted of either grasping the object with a whole hand grip or moving the hand beside the object without interacting with it. Sixteen right-handed human participants performed delayed movements with and without visual feedback using their dominant hand. At the beginning of each trial an auditory cue instructed participants whether or not to close their eyes and the action to be performed at the end of the trial. A delay of 10 seconds was followed by the go cue. We hypothesized that areas involved in processing visual

properties of the object that are relevant for the upcoming object manipulation would show higher activation for Grasp than Move hand actions, but only in the Vision condition. In contrast, areas involved in processing somatosensory consequences of upcoming actions would show higher activation for Grasp than Move hand actions in the Vision as well as No Vision condition. We found that bilateral Inferior Occipital Gyrus (IOG), Cuneus and posterior Intraparietal sulcus (pIPS) in the left hemisphere showed higher activation for Grasp than Move hand actions in Vision but not in No Vision conditions. In addition, the Pre-Cuneus in the left hemisphere showed higher activation for Grasp than Move hand actions in the Vision as well as No Vision condition. These results suggest that while areas in the occipital cortex process visual information about the object for the upcoming object manipulation, the parietal cortex shows visual processing as well as somatosensory anticipations for planned actions.

Disclosures: **S. Monaco:** None. **E. Pellencin:** None. **G. Malfatti:** None. **L. Turella:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.08

Topic: D.17. Voluntary Movements

Support: NIH R01EY015545

Boswell Foundation

USC Neurorestoration Center

Title: Numerical representations in electrophysiology recordings from human posterior parietal cortex

Authors: *S. KELLIS[1], C. KLAES[1], T. AFLALO[1], B. LEE[3], K. PEJSA[1], K. SHANFIELD[5], S. HAYES-JACKSON[5], B. PHILLIPS[5], M. AISEN[5,4], C. HECK[4], C. LIU[3,6,2], R. ANDERSEN[1]; [1]Div. of Biol. and Biol. Engin., [2]Biol. and Biol. Engin., Caltech, Pasadena, CA; [3]Neurosurg., [4]Neurol., Keck Hosp. of USC, Los Angeles, CA; [6]Neurosurg., [5]Rancho Los Amigos Natl. Rehabil. Ctr., Downey, CA

Abstract: The parietal cortex is centrally involved in sensorimotor transformations for motor outputs such as reaches, saccades, and grasps. These actions require computations on numerically quantifiable variables such as distance and size. This fundamental link between sensorimotor planning and execution and numerical processing may explain why, in both animal

electrophysiology and human neural imaging studies, the parietal cortex has been implicated in quantity representation during arithmetic, comparison, counting, and other number manipulations. Here, for the first time, we investigate numerical encoding in the posterior parietal cortex using electrophysiological data recorded from a human with tetraplegia. As further evidence that the posterior parietal cortex encodes aspects of numerical processing, we have identified neurons in presumed human analogues of the anterior intraparietal area and Brodmann's area 5 whose firing rates modulate during mental arithmetic calculations, while retaining numbers in memory, and while generating numerical responses. Furthermore, these neural activities are evident across representations of numbers in different modalities including language, visual symbols, and imagined actions. The involvement of the parietal cortex in numerical processing confirms an important function of this versatile brain area, and points toward potential applications in neural prosthetics where quantization could reflect speeds, forces, or other crucial aspects of action and interaction.

Disclosures: **S. Kellis:** None. **C. Klaes:** None. **T. Aflalo:** None. **B. Lee:** None. **K. Pejsa:** None. **K. Shanfield:** None. **S. Hayes-Jackson:** None. **B. Phillips:** None. **M. Aisen:** None. **C. Heck:** None. **C. Liu:** None. **R. Andersen:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.09

Topic: D.17. Voluntary Movements

Support: DFG SFB 889 C5 to A.G

BMBF 01 GQ 1005C to A.G

Title: Functional interaction between monkey premotor and posterior parietal cortex for goal-directed behavior: Spatial working memory retrieval or motor-goal selection?

Authors: *P. MARTINEZ-VAZQUEZ[1], A. GAIL[1,2,3];
[1]Deutsches Primatenzentrum (DPZ), Göttingen, Germany; [2]Bernstein Ctr. for Computat. Neurosci., Göttingen, Germany; [3]Georg-August-Universität Göttingen, Göttingen, Germany

Abstract: The parietal reach region (PRR) and the dorsal pre-motor cortex (PMd) in rhesus monkeys both encode sensory and motor-related activities during action planning, but their functional interaction during goal-directed behavior is not understood. Functional interactions

between premotor and posterior parietal areas in previous studies were assigned to either processes of motor-goal selection under uncertainty (sensorimotor decision making), or spatial working memory processes. Here we test if directed functional interactions between PMd and PRR occur selectively during reach goal selection or during spatial working memory processing. Two rhesus monkeys conducted a memory-guided center-out reach task. Depending on the context, reach goals were either directly indicated by a spatial cue (pro-reach) or had to be inferred from it (anti-reach). Space and context information was provided separately or simultaneously either before or after an instructed delay, which allowed us dissociating the motor-goal selection process (=space-context integration) from spatial working memory processes. We quantified the functional connectivity between PMd and PRR with the spectro-temporal directed transfer function (DTF) from simultaneously recorded local field potentials (LFP) in PRR and PMd. We identified consistent Granger-causal functional interactions between PMd and PRR in two frequency bands. During trial periods which required the monkeys to hold a current state (fixation, memory, or target-hold period), a significant directed interaction from PRR to PMd in the beta-band (12-32 Hz) predominated, but was independent of both the motor goal and the spatial working memory state of the animals. In contrast, low-frequency (2-10 Hz) functional interactions (DTF-LF) from PMd to PRR occurred selectively during motor initiation, but not during selection of instructed motor goals, and were particularly strong when the spatial cue was provided prior to the instructed delay, i.e., when motor initiation required retrieval of preliminary motor goal information from spatial working memory. The DTF-LF magnitude correlated with the monkeys' reaction times. Our results support the existence of directed functional interactions between PMd and PRR during goal-directed behavior, consistent with a combined role in motor-goal confirmation or initiation and spatial working memory retrieval of preliminary motor goals, but independent of motor-goal selection.

Disclosures: P. Martinez-Vazquez: None. **A. Gail:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.10

Topic: D.17. Voluntary Movements

Support: Radboud Excellence Fellowship

Title: Neurocomputational correlates of swiping movements

Authors: *S. FABBRI, L. SELEN, I. TONI, P. MEDENDORP;
Radboud Univ., Nijmegen, Netherlands

Abstract: With the advent of touchscreen technologies we can interact with objects in a virtual environment. Thus far, the neural computations underlying these virtual interaction have remained unexplored. Here, we measured hand kinematics during object manipulation on a touch screen during a swiping task. In this task, participants were asked to lock to a target object by placing their index finger anywhere on the touch screen and subsequently drag the target into the goal area (much like manipulating a map on your tablet). As a control we used a reaching task, in which they had to move the target by putting their finger onto its actual location before dragging it to the goal. We manipulated task difficulty by varying the size of the goal area and the distance between the goal and the target. During the swiping task, participants locked to the target by positioning their index finger in between the target location and the goal area, and not on the target itself. The locking distance to the target depended on both the target-to-goal distance and size of the goal area. These behavioral results show that object manipulation during swiping elicits different interactions with the target compared to direct reaching movements. We are currently measuring the neuronal correlates of this behavior collecting functional magnetic resonance imaging (fMRI) data while participants execute visually-guided swiping movements on a touch screen in the scanner. Preliminary imaging results show spatially-tuned activity in the sensorimotor network during both swiping and reaching. Maltivariate fMRI analyses are applied to decode this activity in terms of differences and commonalities in the neurocomputational mechanisms of these types of interactions.

Disclosures: S. Fabbri: None. **L. Selen:** None. **I. Toni:** None. **P. Medendorp:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.11

Topic: D.17. Voluntary Movements

Support: FIRB 2013, project RBFR132BKP

Title: Hierarchical action coding within the human brain

Authors: *L. TURELLA[1], R. RUMIATI[2], A. LINGNAU[1,3];
[1]Ctr. For Mind/Brain Sci. (CIMeC), Univ. of Trento, Trento, Italy; [2]2.Scuola Internazionale

Superiore di Studi Avanzati (SISSA), Trieste, Italy; [3]3.Department of Psychology and Cognitive Science, Univ. of Trento, Trento, Italy

Abstract: In daily life, we continuously interact with objects within our environment. These interactions require the specification of specific muscular patterns for smoothly executing an appropriate action. At the same time, the same action needs to be represented also in terms of its more general aim irrespective of how it will be achieved. This more abstract level of action representation should allow, when necessary, a flexible remapping of the aim of an intended behavior through a different motor output, e.g. comprising a different muscular pattern or even adopting another effector. Recent studies support the idea that actions might be represented at different levels of abstraction, i.e. generalizing across different motor features. This type of more "abstract" action representations have been described for movements performed with a specific effector (effector-dependent level), and even at an effector-independent level. Here we investigated within the same experimental paradigm how these different effector-dependent and independent "abstract" action representations are encoded within the human brain. Participants were instructed to perform non-visually guided object-directed actions within the MR scanner. We used a 2 (grip type: precision grip, whole hand grip) x 2 (hand orientation: 0°, 90°) x 2 (effector: left hand, right hand) experimental design. A whole brain volume-based MVPA searchlight approach was adopted to investigate the encoding of different action representations. We used cross-decoding to test for the generalization of specific action features (i.e. across hand orientation and/or effector). Our results support the view of a hierarchical organization of action representations within the fronto-parietal "prehension" network during movement execution. Within this network, there was a widespread encoding of specific effector-dependent actions (within effector and hand orientation), but several regions were also encoding effector-specific actions irrespective of the adopted hand orientation. Effector-independent action encoding was evident within posterior parietal regions, such as the IPS and SPL, and within the lateral occipitotemporal cortex, a region considered fundamental for coding action semantic. Our data widen previous investigations on motor control by demonstrating that actions are represented at different levels of abstraction, possibly following a hierarchical organization, which might be at the basis of the extreme flexibility of our daily behavior.

Disclosures: L. Turella: None. **R. Rumiati:** None. **A. Lingnau:** None.

Nanosymposium

562. Cortical Planning and Execution: Neurophysiology

Location: S402

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 562.12

Topic: D.17. Voluntary Movements

Support: NIH

Boswell Foundation

Title: When is freewill?

Authors: ***T. AFLALO**[1], B. REVECHKIS[1], C. ZHANG[1], E. ROSARIO[2], S. KELLIS[1], C. KLAES[1], D. OUELLETTE[2], C. LIU[3], K. PEJSA[1], N. POURATIAN[4], R. A. ANDERSEN[1]; [1]Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA; [2]Casa Colina Hosp. and Centers for Healthcare, Pomona, CA; [3]USC, Los Angeles, CA; [4]Sch. of Med., UCLA, Los Angeles, CA

Abstract: We investigated the relationship between single neurons recorded in the posterior parietal cortex (PPC) of two human participants and the subjective experience of the will to initiate movement. To determine the timing between neural activity and awareness of motor intent we used several variants of the method introduced by Libet and colleagues. Previous reports that have used this paradigm generally concluded that conscious intent results from unconscious neural processes that ramp up in anticipation of movement. The implication is that freewill as traditionally understood is untenable. Our results suggest a different interpretation. When aligned to the time of reported awareness, neurons in PPC showed a mixture of responses. Some neurons show significant modulation from baseline after the time of conscious intent, while others become active well beforehand. Some neurons showed a high degree of effector specificity, becoming active only for a preferred action, while others became active independent of the performed action. Application of dimensionality reduction techniques indicate network dynamics that begin to evolve in anticipation of awareness. One major component has linearly separable effector specificity (consistent with the representation of an evolving motor plan) and the other major component is effector general (perhaps reflecting a global urgency signal). These results are consistent with previous reports and indicate that PPC encodes not only the "what" of motor intentions (e.g. move the shoulder upward) but also the "when" of movements in the temporal evolution of the network dynamics. To better understand the nature of these dynamics, we realigned neural data with respect to trial onset. We found that the majority of units showing modulation in anticipation of movement began modulating, in an effector specific manner, at trial onset. In a modified version of the task, the subject chose whether to participate in the task on a trial to trial basis. The network dynamics observed when the subject chose to perform the trial were absent when the subject chose to skip the trial. It seems that a motor plan in the form of a dynamically evolving network is immediately initiated when the subject chooses to participate in a trial. The finding that neural activity ramps up in anticipation of the subject's report of the urge to move questions the notion of freewill based on the logic that an effect cannot precede its cause. However, our data suggests that the "ramping" neural activity preceding the time of awareness at the end of the trial is actually the consequence of a decision that is made at trial onset. This raises the basic question: when is freewill?

Disclosures: **T. Aflalo:** None. **B. Revechkis:** None. **C. Zhang:** None. **E. Rosario:** None. **S. Kellis:** None. **C. Klaes:** None. **D. Ouellette:** None. **C. Liu:** None. **K. Pejsa:** None. **N. Pouratian:** None. **R.A. Andersen:** None.

Nanosymposium

563. Comparative Anatomy and Evolution

Location: S401

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 563.01

Topic: D.19. Comparative Anatomy and Evolution

Title: Energy dissipation model of natural selection for the evolution of brain and behavior

Authors: *L. N. IRWIN[1], C. BECK[2];
[1]Univ. Texas at El Paso, Denver, CO; [2]Psychology, Univ. of Alberta, Edmonton, AB, Canada

Abstract: Behavior is an energy consuming process. Like all energy transformations in the abiotic and biotic realms, those brought about by behavioral and brain evolution conform to the Second Law of Thermodynamics (SLT) and the Principal of Least Action (PLA). Natural selection favors those behavioral uses of energy that consume it most efficiently and most completely, since energy is commonly a limiting resource. Those organisms that can make energy "go further," or that can extract the maximum energy obtainable from their environments, are more likely to survive and reproduce than competitors that use energy less efficiently or completely. Therefore, the proximate end of survival, and the ultimate end of minimizing effort mandated by the PLA, are distinct but complimentary facets of the role behavior plays in the evolutionary process. Brains have evolved to subserve those behavioral requirements. This has resulted over time in a net but not inevitable increase in brain size in relation to body mass, and in more highly integrated connectional complexity. These trends are well illustrated in the evolution of brains in the line leading to modern humans. In all probability, tool use, control of fire, cooking and increased caloric consumption, co-ordinated social activity, and language interacted and co-evolved in a synergistic way, leading to brain enlargement and new connectivity, as humans dealt with the challenges of oscillating climate cycles both in Africa and Eurasia during the Pleistocene. Given that the human brain requires an inordinate proportion of the body's available energy, it has to perform efficiently. The neural networks of the human brain have evolved to yield maximum communication effectiveness while minimizing connection cost (maximizing efficiency). Both effectiveness and efficiency of energy use or entropy generation have been selected for. The importance of this analysis is shown by the fact that degradation in effectiveness of this optimally functioning connectivity is a characteristic of

autism and an early predictor of schizophrenic pathology. Conceptually the model affirms the ultimate directionality of the evolution of the brain and behavior.

Disclosures: L.N. Irwin: None. **C. Beck:** None.

Nanosymposium

563. Comparative Anatomy and Evolution

Location: S401

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 563.02

Topic: D.19. Comparative Anatomy and Evolution

Title: The convergence of cortical structure and network topography

Authors: *D. S. MARGULIES[1], S. S. GHOSH[2], G. LANGS[3], M. PETRIDES[4];
[1]Max Planck Inst. For Human Cognitive and Brain Sci., Leipzig, Germany; [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [3]CIR Lab, Dept. of Radiology, Med. Univ. of Vienna, Vienna, Austria; [4]McGill Univ., Montreal, QC, Canada

Abstract: The cerebral cortex is composed of various areas that are characterized by unique cyto- and myeloarchitectonic features. Although the delineation of borders between such areas continues to be debated, specifically with respect to the sharpness and specific locations of transitions, the existence and relative spatial arrangement of these areas is well-established. Various attempts have been made to uncover an overarching organizational principle both for the architectonic differences and for the connectivity between these areas. One suggestion is that all cortical areas are the result of waves of differentiation originating from two distinct limbic sources: the paleocortex (piriform) and the archicortex (hippocampus). Here we aimed to describe the topography of connectivity patterns in the human cerebral cortex, and to relate those patterns to morphological features of cortical structure. Cortical surfaces and preprocessed resting-state fMRI data from the Human Connectome Project were analyzed. The connectivity matrix from each hemisphere was created separately, and included all cortical nodes, excluding the medial wall. Topographic patterns of connectivity were assessed on two spatial scales: In the first analysis, spectral clustering was applied to the connectivity matrix. The resultant spatially distributed network clusters were transformed into a graph where nodes represent networks and edges the probability of spatial adjacency. Spectral decomposition of the graph Laplacian was then used to derive an ordering of the network clusters. Results were visualized using a novel software that displays arrows superimposed on the cortical surface to depict the cluster ordering. In the second analysis, spectral decomposition was applied to the full connectivity matrix, thus providing a high resolution map of connectivity ordering. To relate connectivity organization to

spatial distance along the cortical surface, geodesic distance was measured from peak areas of the topography maps. Connectivity patterns were ordered along a spectrum with the primary sensory/motor regions at one end and the heteromodal association and paralimbic areas at the other. The geodesic distance analysis revealed that peak areas of association cortex were equidistant from morphological landmarks of primary sensory/motor regions (central and calcarine sulci). These finding suggest a basic topographic organization that is consistent with theories of progressive differentiation of cortical areas based on cyto- and myeloarchitectonic studies. Further work will compare these findings in the human to connectivity topography in the brains of other mammalian species.

Disclosures: **D.S. Margulies:** None. **S.S. Ghosh:** None. **G. Langs:** None. **M. Petrides:** None.

Nanosymposium

563. Comparative Anatomy and Evolution

Location: S401

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 563.03

Topic: D.19. Comparative Anatomy and Evolution

Title: Cortical folding universality and local measures of gyrification

Authors: ***B. MOTA**[1], Y. WANG[2];
[1]Univ. Federal Do Rio De Janeiro, Rio de Janeiro, Brazil; [2]Dynamic Connectome Lab., Sch. of Computing Science, Newcastle Univ., Newcastle, UK, United Kingdom

Abstract: The expansion of the cerebral cortex is the most obvious feature of mammalian brain evolution, and is generally accompanied by increasing degrees of folding of the cortical surface. However, the mechanisms that drive gyrification remain undetermined. This has been an area of intense research interest lately, with a number of proposals being put forward to explain it. Most such studies [1,2] focus on human cortices, and make use of detailed MRI data to postulate folding as driven by the (possibly differential or multi-layered) expansion of the cortical surface. In contrast, inspired by the Van Essen's axonal tension-based hypothesis [3] and the statistical physics of membranes, we have recently [4] proposed a model in which folding is a consequence of the dynamics of white matter axon elongation coupled with surface expansion and self-avoidance. This model predicts a power-law relation between cortical average thickness, exposed and total areas. Using coarse-grained data from dozens of different mammalian species, we have verified that the predicted relation holds true for both gyrified and lysencephalic cortices. Cortical folding that scales universally across clades, species implies that a single mechanism exists throughout cortical development and evolution - one that is based on the physics of

minimizing the effective free energy of a growing surface subject to inhomogeneous bulk stresses. In the present work, we attempt to: (i) Apply and extend our model to fine-grained human cortical surface reconstructions from MRI data, and examine its applicability over variations across different human subjects; (ii) extend our understanding of the relevant morphological variables beyond global means towards local parameters such as cortical thickness and local gyrification, and verify if a similar scaling law can be obtained for variations in folding patterns across different areas of a given cortex. Of particular interest, it has been postulated that a range of genetic, environmental and pathogenic factors can contribute certain congenital brain formation disorders in which cortices are less (lissencephaly) or more (polymicrogyria) gyrified than normal. Do these cases also conform to the universal folding relation? This last question may be of some significance, as the answer may shed light upon the mechanisms through which these brain disorders operate, and even allow differentiating between their various putative causes. [1] Tallinen et al (2014) PNAS 111:12667-12672. [2] Ronan, L. et al. (2013) Cerebral Cortex 24:2219-2228 [3] Van Essen DC (1997) Nature 385: 313-318. [4] Mota, M, Herculano-Houzel (2015), Accepted for publication

Disclosures: **B. Mota:** None. **Y. Wang:** None.

Nanosymposium

563. Comparative Anatomy and Evolution

Location: S401

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 563.04

Topic: D.19. Comparative Anatomy and Evolution

Support: VENI (# 451-12-001) grant from the Netherlands Organization for Scientific Research (NWO)

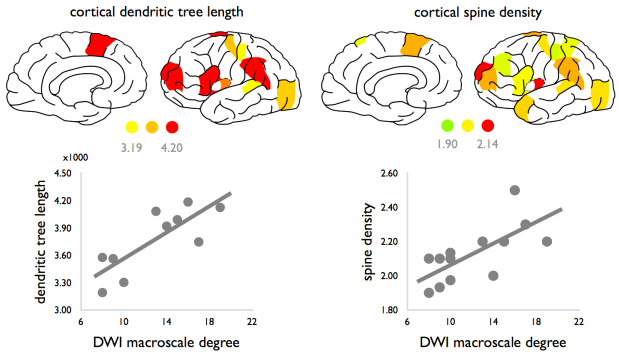
Fellowship of the Brain Center Rudolf Magnus

Title: Bridging the smallest and the biggest of the human brain: interplay between cytoarchitectonics and macroscale connectomics in human cortex

Authors: *M. P. VAN DEN HEUVEL, L. SCHOLTENS, M. DE REUS;
Rudolf Magnus Inst. of Neuroscience, Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: The human brain comprises a complex network of neural interactions at both the micro and macroscale. Studies examining connectivity on the microscale have reported a rich variety in cytoarchitecture with associative areas noted to display more complex neurons. In

addition, -but predominantly coming from a different field of neuroscience- Magnetic Resonance Imaging has reported features of cortico-cortical white matter wiring to be related to brain functioning, with for example association regions showing elaborate global wiring. Here, we started to explore the interplay been microscale and macroscale connectivity of human cerebral cortex. Data on neuronal complexity was collated from histology studies, providing detailed information on cortical variation in dendritic branching, spine density etc. Next, we used ultra-high resolution DWI data of the Human Connectome Project to reconstruct macroscale connectivity of cortical areas. Cross-modal micro-to-macro analysis revealed a clear link between cortical variation in neuronal complexity of pyramidal neurons of layer 3 -a layer known for its role in cortico-cortical communication- and macroscale connectivity. Areas with more and stronger macroscale white matter projections (i.e. a higher connectome degree) were found to display more elaborate ($p=0.005$, $r=0.80$), longer ($p=0.002$, $r=0.70$), and more spinous layer 3 pyramidal neurons ($p=0.007$, $r=0.70$) (Fig). Macroscale hubs -and their construction of a central rich club- were found to display more complex neuronal architecture as compared to peripheral regions ($p=0.003$). Furthermore, network attributes (e.g. path length, intermodular participation) significantly related to cytoarchitectonic features of cortical areas ($p<0.01$). We show our findings to be consistent across multiple datasets, including early histology work and other mammalian species (macaque, mouse). Taken together, our findings are supportive of the notion of the smallest and the biggest organizational aspects of neural connectivity of the human brain to be linked, and possibly interacting.



Disclosures: **M.P. Van den Heuvel:** None. **L. Scholtens:** None. **M. de Reus:** None.

Nanosymposium

563. Comparative Anatomy and Evolution

Location: S401

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 563.05

Topic: D.19. Comparative Anatomy and Evolution

Title: Biodiversity of mammalian claustrums

Authors: *J. I. JOHNSON[1,2,3], M. A. SUPANICH[1], E. J. SUCHER[1], J. M. TIERNEY[1], M. HANNA[1], C. R. DASBACH[1], A. S. JASWA[1], B. A. FENSKE[1], H. T. YORK[2], R. C. SWITZER, III[2], J. A. MORRIS[3];
[1]RADIOLOGY: ANATOMY, Michigan State Univ., East Lansing, MI; [2]NeuroScience Associates, Knoxville, TN; [3]SNBL, Everett, WA

Abstract: Claustrums come in a wide variety of shapes, unlike other components of the brain. We here survey a sampling of this variation, one feature of which is to serve as a guide for selecting species for doing certain types of contemporary investigation that require at least a certain volume of contiguous tissue in order to obtain meaningful data while being certain of the locus of origin of the data. We used consistent and complete series, of claustrum-containing, stained sections of the brains of several mammals, to reconstruct in three dimensions the shapes of claustrums in specific taxa. Programs used for reconstructing include Photoshop, FIJI (ImageJ), TrakEm 2 plugin for FIJI and MeshLab. These 3-D reconstructions are then used for comparison to provide instances of unique morphological features in certain species. The chalice shaped claustrum of anthropoid primates rests on a columnar base. In humans, a ring near the base of the cup exhibits scallops and points reaching into suprajacent gyral cores. In pigs a sturdy backpack projects prominently adding to the extent of the claustrum. Dolphin claustrums show three curved branches reaching around the anterior limit of the insula well into the frontal cortex. Some marsupial and xenarthran claustrums resemble a forward-streaking comet trailing scattered cells behind. The claustrum of the red fox shows an elegant thin long stem stretching straight up beside the putamen capped at the top by a flower-like pyramid. In cats and dogs the topping appears more like a backward leaning club ending. The posterior part of this club contains maps of the visual, auditory and somatic sensory cerebral cortical regions with which they connect. Afrotherian hyraxes exhibit a robust thick claustrum in boomerang shaped parentheses on either side of the basal ganglia. In the highly evolved brains of murine rodents, the possibly vestigial tiny claustrum almost vanishes inside the cerebral cortical layers. Conclusions that can be drawn include: 1)identification of insular cortex as claustrocortex is mistaken, since many claustrums exist in the absence of, or in a different location than, insular cortex, and many regions of insular cortex have no adjacent claustrum. 2) claustral function cannot depend on spatial relationships of intraclaustral regions, otherwise there would be a standard shape for all claustrums. 3) claustrums take positions to fill available spaces, rather than imposing their spatial needs upon neighboring structures 4). there are many regions where local enlargements, here called puddles, are available for the conduct of a variety of modern investigative methods requiring a particular volume of contiguous claustral tissue.

Disclosures: **J.I. Johnson:** None. **M.A. Supanich:** None. **E.J. Sucher:** None. **J.M. Tierney:** None. **M. Hanna:** None. **C.R. Dasbach:** None. **A.S. Jaswa:** None. **B.A. Fenske:** None. **H.T. York:** None. **R.C. Switzer:** None. **J.A. Morris:** None.

Nanosymposium

563. Comparative Anatomy and Evolution

Location: S401

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 563.06

Topic: D.19. Comparative Anatomy and Evolution

Support: NHMRC Project Grant 1068140

Title: Claustrum connections with hubs of the default mode, salience, and frontoparietal networks in the common marmoset

Authors: ***D. H. RESER**[1], P. MAJKA[1,2], J. M. H. CHAN[1], X. PHAM[1], K. J. WATKINS[1], S. SNELL[1], K. RICHARDSON[1], M. G. P. ROSA[1,3];
[1]Monash Univ., Clayton, Australia; [2]Nencki Inst. of Exptl. Biol. PAS, Warsaw, Poland; [3]ARC Ctr. of Excellence in Integrative Brain Function, Melbourne, Australia

Abstract: Although it was first described over 250 years ago, the function(s) of the claustrum are as yet almost completely unknown. We have recently hypothesized that one possible function of the primate claustrum may be to modulate the activity of resting state brain networks (RSN). These networks exhibit synchronous changes in blood flow, glucose metabolism, and/or postsynaptic activation during periods of task negativity or idleness, and the degree of functional connectivity is modulated as new tasks or external stimuli arise. Although the functional connectivity of the major RSN (default mode network-DMN; salience network- SN; frontoparietal network- FN) is well described, the structural connectivity presumed to underpin them is poorly understood. In this study, we examined claustrum connections with presumed network hubs in medial prefrontal (MPFC), anterior (ACC) and posterior cingulate (PCC), and posterior parietal cortex (PPC), using microinjections of fluorescent and biotinylated tracers. Eight injections in six adult marmosets were made into cortical areas 32 (MPFC), 24 (ACC), 23 (PCC) and PFG (PPC) using procedures approved by the Monash Animal Ethics Committee. Claustrum connections were present in all cases, with marked variability between cortical areas. The densest claustrum connectivity was observed in PCC and MPFC, which are hubs of the marmoset DMN, while lighter connections were evident between hubs of the SN (ACC) and FN (PPC). Although the precise homology of cortical areas between primate species is still

somewhat controversial, our data suggest that the claustrum is differentially connected to the hubs of the major cortical RSN.

Disclosures: **D.H. Reser:** None. **P. Majka:** None. **J.M.H. Chan:** None. **X. Pham:** None. **K.J. Watkins:** None. **S. Snell:** None. **K. Richardson:** None. **M.G.P. Rosa:** None.

Nanosymposium

563. Comparative Anatomy and Evolution

Location: S401

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 563.07

Topic: D.19. Comparative Anatomy and Evolution

Support: NIH Grant 5R21MH099458

NIH Grant 5R01MH080116-05

Brain and Behavior Foundation

Title: Anatomy and function of serotonin 2A receptor neurons in claustro-cortical circuits

Authors: ***E. Y. DEMIREVA**[1], C. E. MCOMISH[1,2], K. K. DEONARAINE[3], J. A. GINGRICH[1,4];
[1]Developmental Neurosci., New York State Psychiatric Institute, Columbia Uni, New York, NY; [2]Florey Inst. of Neurosci. and Mental Health, Univ. of Melbourne, Melbourne, Australia; [3]Dept. of Neurosci. and Behavior, Barnard Col., New York, NY; [4]Sackler Inst. for Developmental Psychobiology, New York, NY

Abstract: The serotonin 2A receptor (5-HT2AR) has been implicated in multiple neuropsychiatric disorders, including schizophrenia, anxiety and depression. Furthermore, 5-HT2AR signaling mediates the behavioral responses to hallucinogenic compounds. Detailed examination of 5-HT2AR mRNA expression revealed that this receptor is highly enriched in the mouse claustrum (CL). Specifically, we show that 5-HT2AR is expressed in the glutamatergic projection CL neurons from the Emx1 lineage. The CL is a subcortical structure that gives rise to extensive claustro-cortical loops, and has been hypothesized to play a role in time perception and integration of multi-sensory information to generate unified experiences and conscious states. In this context, the CL is an intriguing candidate as a neural substrate involved in complex psychiatric syndromes such as autism spectrum disorders, schizophrenia, obsessive-compulsive disorder, and mood disorders. The dense innervation of the CL by serotonergic fibers and its high level of 5-HT2AR expression led us to hypothesize that 5-HT2AR defined claustro-cortical

circuits may be important in the regulation of cognitive and emotional behaviors disrupted in psychiatric disease. We explored whether CL-cortical circuits expressing 5-HT2AR are part of the signaling responsible for behavioral response to hallucinogens, by restoring expression in the CL and/or cortex in a null background using conditional rescue 5-HT2AR mice and stereotactic injection of AAV2-Cre-ires-GFP into CL and cortex. We found a partial restoration of the head twitch response to the hallucinogen DOI when we restored expression of 5-HT2AR in both CL and adjacent cortex. Understanding CL circuits has been hindered by the ribbon-like anatomy and the position of the CL, making surgical access to the structure in mice difficult. To test hypotheses about the activity and function of 5-HT2AR CL neurons, a genetic strategy for CL manipulation is needed. To target the CL genetically we identified two CL-specific markers, Gnb4 and Gng2, that show high degree of overlap with the 5-HT2AR population, making them ideal candidates for genetic manipulation of the CL. We have designed a strategy to target Gng2 and Gnb4 using CRISPR technology in order to insert gene expression cassettes into the start site of both loci, with the goal of rapid generation of genetic tools to study the function of the 5-HT2A CL neurons.

Disclosures: E.Y. Demireva: None. **C.E. McOmish:** None. **K.K. Deonaraine:** None. **J.A. Gingrich:** None.

Nanosymposium

563. Comparative Anatomy and Evolution

Location: S401

Time: Tuesday, October 20, 2015, 1:00 PM - 3:00 PM

Presentation Number: 563.08

Topic: D.19. Comparative Anatomy and Evolution

Title: Exploring fruit bat cortical and subcortical neurophysiology: optimizing planes of section

Authors: *R. ORMAN;
Physiology&Pharmacology, SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: The focus of our studies is cortical and subcortical neuronal circuit physiology of the Short-Tailed Fruit Bat, Carollia Perspicillata. Bats are the only truly flying mammals. Unlike rats and mice, where most studies of navigation have been done to date, and where these studies demonstrate an essential role for hippocampus, bats provide an opportunity to study the physiology of hippocampus and other structures involved in an animal navigating in 3 dimensions. In this study, we explored planes of section that preserve the best connectivity of neuronal circuits in the limbic system, neocortex, and their subcortical partners in the fruit bat. Bats were deeply anesthetized with isoflourane. Bat's brains were fixed in 4% paraformaldehyde

and sectioned on a freezing microtome at 40-micron thickness. Fixed brain sections were processed immunohistochemically (stained with a variety of primary antibodies) to reveal the morphology that is most likely to preserve functional connectivity. This provides us with a guideline for preparing acute brain slices for electrophysiological studies of neuronal connectivity in the bat's brains. Connectivity within individual hippocampal and neocortical regions as well as between cortical and subcortical partners is assessed in brain slices using a multi-electrode array system with and without focal stimulation.

Disclosures: R. Orman: None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.01

Topic: F.03. Motivation and Emotion

Support: 1KL2RR031974-01 Georgetown-Howard Universities Center for Clinical and Translational Science

Title: Priming emotions to dissociate affective contributions to decision making in the ultimatum game

Authors: *S. EL DAMATY, L. WAHEDI, J. VAN METER;
Georgetown Univ., Washington, DC

Abstract: Previous studies have explored the effects of fairness and uncertainty on cooperative behavior in the Ultimatum Game (UG). Fairness is an abstract concept and is poorly identified in the UG literature. We investigate the effects of valence priming on decision-making in the UG. We find no support for uncertainty hypotheses. We find that negative valence primes predicts lower generosity, while positive valence primes predict higher generosity. We also find that the neural correlates of decision-making after exposure to a negative prime are the same as the neural correlates of decision-making in response to an unfair offer in the UG context. This suggests that the fairness preference reported in the literature may operate through the same mechanism as affect. We also make a methodological contribution, showing that sub-threshold primes affect decision-making, and that constructs using the offering player in UG can be used to examine more divers treatments than those using the receiving player.

Disclosures: S. El Damaty: None. **L. Wahedi:** None. **J. Van Meter:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.02

Topic: F.03. Motivation and Emotion

Support: National Science Fund for Distinguished Young Scholars (no. 81225009)

Title: Engagement in a relationship tunes romantic jealousy: behavioral and neural correlates

Authors: Y. SUN[1], H. YU[2], J. CHEN[1], J. LIANG[1], L. LU[1,3,4], X. ZHOU[2,4,5], *J. SHI[1];
[1]Natl. Inst. On Drug Dependence of Peking Univ., Beijing, China; [2]Ctr. for Brain and Cognitive Sci. and Dept. of Psychology, Peking Univ., Beijing, China; [3]Inst. of Mental Health/Peking Univ. Sixth Hosp. and Key Lab. of Mental Health, Peking Univ., Beijing, China; [4]Peking-Tsinghua Ctr. for Life Sci. and PKU-IDG/McGovern Inst. for Brain Research, Peking Univ., Beijing, China; [5]Key Lab. of Machine Perception (Ministry of Education), Peking Univ., Beijing, China

Abstract: Background: Romantic jealousy is not only a way of experiencing love but also acts to stabilize romantic relationships. However, morbid romantic jealousy is maladaptive. Romantic jealousy might arise from violation of romantic expectancy and can appear in two different stages: before and after being in a formal romantic relationship. We hypothesized that being engaged in a relationship can tune one's romantic jealousy to the relationship partner. Here, we investigated the behavioral and neural correlates of romantic jealousy and their evolution across stages. Methods: The protagonist scenarios which base on romantic relationships in a campus setting were used to measure the imagined romantic jealousy and romantic happiness in forty heterosexual undergraduate students. The subjects underwent two MRI scanning runs (Stage 1-before being in a relationship; Stage 2-after being in a relationship). Besides, all subjects were assessed by a set of self-report instruments, mainly including the Love Attitude Scale, Self-report Jealousy Scale and Modified Overt Aggression Scale. Results: We found that across stages, romantic jealousy produced activations mainly in the basal ganglia. Romantic jealousy was significantly higher after the relationship was established, and this increased jealousy was associated with a higher tendency toward aggression. Moreover, romantic jealousy was predicted by romantic expectancy (as reflected by romantic happiness). Conclusion: This neural representation, along with the subjective feeling of jealousy, is modulated by romantic expectancy and the stage of the romantic relationship. Such sharpening effect not only influences jealousy, but also has bearing on violence and aggressive behavior in romantic relationships.

These results suggest that the essence of romantic jealousy is an expectancy violation, and may shed light on the neural underpinning of human monogamy.

Disclosures: **Y. Sun:** None. **H. Yu:** None. **J. Chen:** None. **J. Liang:** None. **L. Lu:** None. **X. Zhou:** None. **J. Shi:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.03

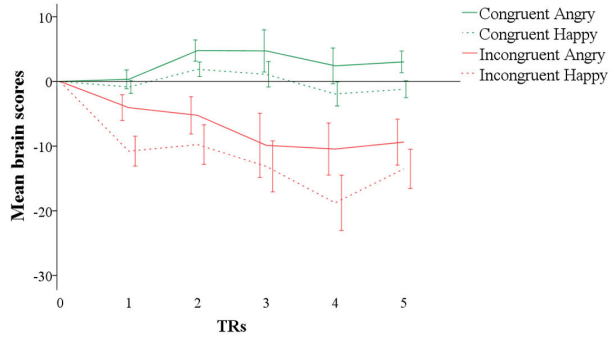
Topic: F.01. Human Cognition and Behavior

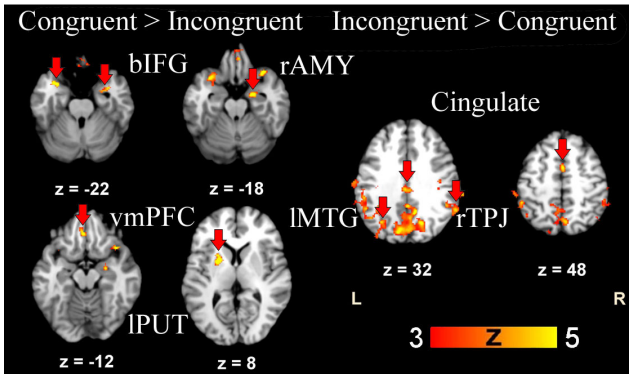
Title: Dynamic emotion perception and prior expectancy: a novel fMRI paradigm and multivariate analysis

Authors: ***I. DZAFIC**[1], A. K. MARTIN[1], J. HOCKING[3], B. MOWRY[1,4], H. BURIANOVÁ[2,5]; [1]Queensland Brain Inst., [2]Ctr. for Advanced Imaging, The Univ. of Queensland, Brisbane, Australia; [3]Inst. of Hlth. Biomed. Innovation, Queensland Univ. of Technol., Brisbane, Australia; [4]Queensland Ctr. for Mental Hlth. Res., Brisbane, Australia; [5]Dept. of Cognitive Sci., Macquarie Univ., Sydney, Australia

Abstract: Complex social interactions require the ability to rapidly perceive and interpret dynamic, multisensory emotional cues. Emotion perception is facilitated by prior expectations, which prioritize attention to cues that are aligned with what is expected. Findings show that prior expectations influence emotion perception both at the behavioural and neural level. However, studies to date have investigated prior expectations using static emotional images, despite the fact that dynamic stimuli would represent greater ecological validity. The objective of the study was to create a novel and ecologically valid fMRI paradigm to examine the influence of prior expectations on naturalistic emotion perception. For this purpose, we developed a dynamic emotion task, which consists of audio-visual videos that carry emotional information congruent or incongruent with the preceding emotional cues. The results show that emotional congruency was associated with activity in prefrontal regions, amygdala and putamen, whereas emotional incongruency was associated with activity in occipitoparietal regions, temporoparietal junction, and cingulate gyrus. Supported by the behavioural results, our findings suggest that, in a real world, perception of congruent emotion is facilitated by greater top-down influence, whereas incongruent emotion may rely more on rapid bottom-up processes. The results from the current study are compatible with the notion that the ability to automatically detect and turn attention

towards unexpected events in complex dynamic environments allows for adaptive behaviours in potentially dangerous situations.





Disclosures: I. Dzafic: None. **A.K. Martin:** None. **J. Hocking:** None. **B. Mowry:** None. **H. Burianová:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.04

Topic: F.03. Motivation and Emotion

Support: RSA Grant

Title: An fMRI study of impulsivity in 'risky' and 'safe' male drivers

Authors: *G. O'CALLAGHAN, C. KELLY, M. GORMLEY;
Trinity Col. Dublin, Dublin, Ireland

Abstract: Adolescence and young adulthood are developmental stages associated with an increase in impulsive and risk taking behaviors. Studies have posited a link between this developmental impulsivity and risky driving, with ‘risky’ drivers displaying higher psychometric and cognitive impulsivity than ‘safe’ drivers. However, these studies have not explicitly examined the neural bases of the links between impulsivity and risky driving. The current study utilised fMRI to examine the relationship between impulsivity, risky driving behaviors, and impulsivity-related functional activation in 40 ‘risky’ (individuals who had accrued “penalty points” on their license and/or reported being collision culpable) and 40 ‘safe’ male drivers, in two age groups: younger (18-24, M=20.5, SD=1.8) and older (29-56, M=38.5, SD=8.1). Participants completed three tasks designed to assess different facets of cognitive impulsivity whilst being scanned in a Philips Achieva 3T MR system: the Iowa Gambling Task (IGT), a Monetary Incentive Delay task (MID) and a Go/No Go task. They also completed psychometric measures of impulsivity and driving risk: Barratt’s Impulsiveness Scale, Kirby’s Delay Discounting Task and the Manchester Driver Behavior Questionnaire. Small volume correction analyses of *a priori* regions of interest were conducted with the WFU Pickatals toolbox of SPM8 and corrected for multiple comparisons using FWE correction in combination with cluster extent thresholds identified using Monte Carlo simulations. Psychometric measures of impulsivity and driver behavior successfully differentiated between ‘risky’ and ‘safe’ drivers, with ‘risky’ drivers scoring significantly higher than ‘safe’ on many of the subscales. Despite minimal differences in performance on the tasks, the BOLD responses of ‘risky’ and ‘safe’ male drivers were found to be significantly different in several regions implicated in impulsivity and cognitive control, such as the ACC and SMA in the MID and the OFC, IFG and the ventral and dorsal striatum in the IGT, regardless of age. Furthermore, Go/No Go-related activation in the ACC, SMA, VMPFC and DLPFC differed between younger ‘safe’ and ‘risky’ male drivers. In most cases, ‘safe’ drivers demonstrated greater activation in these regions, with the exception of the SMA and the ACC, in which ‘risky’ drivers exhibited greater activation than ‘safe’ drivers in the MID. These findings indicate that there may be age-related as well as age-independent neural correlates of impulsivity that relate to risk taking tendencies while driving that may be relevant for the development of preventative initiatives aimed at both novice and more experienced drivers.

Disclosures: **G. O'Callaghan:** None. **C. Kelly:** None. **M. Gormley:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.05

Topic: F.03. Motivation and Emotion

Support: NIH HD047520

NIH HD059205

NIH HD057610

NSF DRL-0750340

Title: Behavioral and neurobiological correlates of a positive mindset in children

Authors: *L. CHEN, S. BAE, C. BATTISTA, T. M. EVANS, V. MENON;
Stanford Univ., Palo Alto, CA

Abstract: Positive mindset, defined as favorable self-perceptions of people's feeling and competence on learning, has been recently shown to play an important role in raising task and academic achievement (Broomhead et al., 2012; Paunesku et al., 2015). Little is known, however, about the brain mechanisms underlying positive mindset. One cognitive domain in which mindset has been extensively investigated behaviorally is math. Crucially, given the importance of math competence for academic and professional success, it is important to identify the behavioral and neurobiological correlates of a positive mindset towards math in children. We recruited 243 children (115 girls; Age M=8.17 years, SD=0.66) from the San Francisco Bay Area. Each child completed neuropsychological assessments for IQ, math (numerical operations; NO and math reasoning; MR), reading abilities, working memory (WM), and math anxiety. A Positive Mindset Scale for Math (PMSM) was used to assess children's attitudes towards math (e.g. 'Are you having fun with math?', 'Are you good at math?' etc.). Of these children, 48 (25 girls; Age M=8.28 years, SD = 0.72) participated in the fMRI study. In the fMRI scanner, children were asked to verify addition problems (e.g., "3+6=9") or passively view fixation point (baseline). Behaviorally, multivariate regression revealed that PMSM scores of children predicted their math competence even when IQ, age, WM, reading skills, and math anxiety were controlled for: NO (β=0.24, t=3.25, p=.001) and MR (β=0.14, t=2.49, p=.01). At the neurobiological level, whole-brain regression analysis revealed that higher PMSM scores were associated with increased activation in left hippocampus (-28 -10 -24), left dorsomedial prefrontal cortex (DMPFC,-6 26 62), left supplementary motor area (SMA,-12 6 68), right lingual gyrus (rLG,16 -56 -6), and dorsal cerebellum (10 -62 -32) (voxel-wise height: p<.01, FWE correction: p<.05, k=100 voxels). Higher PMSM scores were also associated with increased functional connectivity of left hippocampus with SMA and rLG. Interestingly, increased functional connectivity of left hippocampus with DMPFC, SMA and cerebellum was related to better in-scanner performance on the addition task. Our findings provide strong evidence that a positive mindset contributes to children's math competence. Crucially, a positive mindset is associated with greater engagement of the hippocampus and its functional circuits with DMPFC, SMA and rLG, highlighting distributed memory, cognitive control and visual

processing processes (Menon, 2014) by which a positive mindset can contribute to children's learning and growth for academic success.

Disclosures: L. Chen: None. **S. Bae:** None. **C. Battista:** None. **T.M. Evans:** None. **V. Menon:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.06

Topic: F.03. Motivation and Emotion

Support: Grant-in-Aid for Scientific Research (S) no.21220005.

''Development of biomarker candidates for social behavior'', carried out under the Strategic Research Program for Brain Sciences by the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Title: A rewarding nature of conversation: an fMRI study on the contingency between own actions and positive outcome

Authors: *M. SUMIYA[1,2], T. KOIKE[1], S. OKAZAKI[1], N. SADATO[1,2];
[1]Natl. Inst. For Physiological Sci., Okazaki / Aichi, Japan; [2]SOKENDAI (THE GRADUATE UNIVERSITY FOR ADVANCED STUDIES), Hayama / Kanagawa, Japan

Abstract: Why can the everyday conversation last so long? Infants develop a motivation to communicate with others through proto-conversation consisted of a contingency, an event whose outcome depends on individual's action (Benson et al., 2014), between their actions and their mother's feedbacks (Treverthen and Aitken, 2001). Thereby, the contingency may generate the intrinsic driving-force for conversation. Previous neuroimaging studies have found that actively earning rather than passively received monetary reward activates the reward-related brain areas such as striatum (Tricomi et al., 2004; Zink et al., 2004). These results indicate that positive outcome contingent on own action is a reward within an activity. In this study, we investigates the role of contingency as a reward which may drive people into conversation, in relation to pleasure. We hypothesized that the listener's contingent positive feedback makes the speaker pleasant, and that pleasure within a conversation is related to the reward system. Thus we expected higher activation when the listener's positive feedback is contingent on own action. To test these hypotheses, we developed a pseudo-interactive humor task which simplified a

conversational interaction to a form making a listener laugh with funny humors, and conducted on functional MRI with 38 participants. In the task, a participant in the scanner uttered the punch line of the humor toward the listener outside the scanner, whose laughter was fed back to the participant (SELF-condition). There were three patterns of listener's feedback; group laugh, single laugh, and no laugh. As a control condition of speaker's action, the punch line was read aloud by the computer (PC-condition). Participants rated their pleasure after listener's feedbacks. In addition, to identify the reward system, participants were required to perform the gamble task (Izuma et al., 2008). Subjective pleasure was higher when the laughter was contingent on the own utterance compared to PC conditions. For the analyses of neural data, first we identified bilateral ventral striatum as monetary reward related regions of interest on the gamble task (peak-FWE $p < .05$, $k > 10$). These regions were responded to social reward and correlated with subjective pleasure in the humor task ($p < .05$, Bonferroni corrected). Furthermore, right ventral striatum was strongly activated by the laughter contingent on own utterance ($p < .05$, Bonferroni corrected). These results indicate that outcome-related activity in the ventral striatum reflects succession of own action. Our study showed that a contingency within a conversation have an important role to drive a conversation.

Disclosures: **M. Sumiya:** None. **T. Koike:** None. **S. Okazaki:** None. **N. Sadato:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.07

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant MH080833

Title: Emotional regulation strategy use relates to multivariate patterns in cortical thickness in young and older adults

Authors: ***C. R. MADAN**[1], D. LINSLEY[1], C. M. LECLERC[2], E. A. KENSINGER[1]; [1]Psychology, Boston Col., Chestnut Hill, MA; [2]Psychology, State Univ. of New York at Oswego, Oswego, NY

Abstract: INTRODUCTION: In daily life, we sometimes experience strong emotions that need to be deliberately regulated, such as feeling nervous during a first date or angry after getting cut off in traffic. One form of emotion regulation is cognitive reappraisal, where an individual reframes the emotional experience within a different context. Another form of emotional

regulation is expressive suppression, where an individual prevents the emotion from overtly manifesting. While prior studies have found relationships between emotional regulation strategy use and gray matter volume in frontal regions in young adults, here we asked how cortical thickness, across all of the cortex, may relate to inter-individual differences in the use of reappraisal and suppression strategies in both younger and older adults. METHODS: We collected Emotion Regulation Questionnaire (ERQ) responses and structural brain images from 75 adults (38 young [age=18-35] and 37 older [age=60-82]). Cortical thickness estimates for parcellated regions of cortex were calculated using FreeSurfer. Multivariate analyses were used to determine which regions were differentially related to cognitive reappraisal vs. expressive suppression emotional regulation strategies. RESULTS: Age-related cortical thinning was observed throughout the cortex, and age-related differences were particularly predictive of cortical thinning in frontal and temporal cortices. After accounting for age-related effects, we observed regions related to the use of reappraisal vs. suppression, with the former being particularly related to higher cortical thickness in frontal and temporal cortices. We also observed that several regions were more generally related to emotional regulation use (i.e., mean ERQ scores, averaging across the two subscales), including right inferior frontal gyrus and several visual processing regions. DISCUSSION: Here we examined the relative preference in strategy use, unlike prior studies which used the subscales directly, allowing us to more directly assess how structural differences relate to inter-individual variability in preferred emotional regulation strategy. Additionally, a whole-brain multivariate approach allows us to isolate regions that are individually important in predicting patterns, while penalizing against groups of regions that co-vary together. Our results demonstrate that the two emotional regulation strategies are related to brain morphometry.

Disclosures: **C.R. Madan:** None. **D. Linsley:** None. **C.M. Leclerc:** None. **E.A. Kensinger:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.08

Topic: F.03. Motivation and Emotion

Support: UCL Grand Challenge studentship to CJC

Title: Emotional modulation of loss and risk aversion in clinical anxiety

Authors: *C. J. CHARPENTIER, O. J. ROBINSON, T. SHAROT, J. P. ROISER;
Univ. Col. London, London, United Kingdom

Abstract: Influential theories in cognitive neuroscience and behavioral economics suggest that emotions determine the choices we make. This implies that manipulating an individual's emotions should impact their decisions. Anxiety disorders are associated with both disrupted emotional processing and decision-making, but how emotions influence economic decisions and whether this interaction is altered in anxiety remain unresolved questions. To address these questions, patients with Generalized Anxiety Disorder (GAD) and matched healthy controls completed a gambling task, featuring a decision between a gamble and a safe (certain) option on every trial. Each decision was preceded by happy, fearful, or neutral faces, or object primes. One type of gamble featured only wins ("win-only"), allowing us to assess risk aversion; the other type involved weighing a potential win against a potential loss ("mixed"), allowing us to assess loss aversion. Preliminary results (N=19 patients, N=16 healthy controls) revealed that fearful faces, relative to object primes, induced an overall increase in risk-taking across both groups, with more gambles chosen under threat. Neutral faces, relative to objects, only affected clinically anxious individuals, resulting in more choices of potentially harmful (mixed) gambles, consistent with decreased loss aversion. By contrast, happy faces, relative to object primes, only affected healthy controls, increasing their propensity to choose win-only gambles, consistent with decreased risk aversion. These findings suggest that emotions influence people's decisions in a mood-congruent manner. GAD individuals appeared to exhibit a specific increase in risk-taking involving potential losses under ambiguity, possibly reflecting an impaired ability to deploy harm-avoidance processes.

Disclosures: C.J. Charpentier: None. **O.J. Robinson:** None. **T. Sharot:** None. **J.P. Roiser:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.09

Topic: F.01. Human Cognition and Behavior

Title: The dynamics of continuous self control

Authors: *P. SOKOL-HESSNER[1], N. D. DAW[2];
[1]Dept. of Psychology, [2]Psychology/CNS, New York Univ., New York, NY

Abstract: In recent years, substantial advances have been made in understanding the behavioral and neural bases of self control in discrete choices (e.g. a choice to order healthy or unhealthy food off a menu). However, we must often exercise self control over longer timescales, in a continuous fashion (e.g. resisting eating cake in your kitchen all afternoon). Very little is known about the processes supporting continuous self control, let alone the temporal dynamics of such behavior, but clues may come from a recent movement toward "rational self control" models. These models reconceptualize self control as trading off between multiple sources of utility under constraints (like limited attentional capacity, or limited time). The question of how self control is exercised then becomes a question of identifying utility sources, their characteristics, and quantifying the constraints involved. We designed a novel task to examine continuous self control in an environment with known temporal and reward structures. Twenty-seven heterosexual males completed a task pitting a boring, but monetarily rewarding task against distracting images for 60 uninterrupted minutes. On half of a participant's screen was a white circle with a "clock hand" that ticked in roughly 1/100 increments every second. Rarely ($p = 0.01$), the hand would move twice as far (~2/100th). Participants received $1 for every correctly identified double-sized movement, but lost a dollar for every false alarm. The other half of the screen displayed the subset of IAPS images rated positively by males, with images changing every 1 or 2 seconds (synchronized with clock hand movements). We recorded eye tracking data throughout the session, allowing us to examine when participants were "on-task" (watching the clock hand) versus "off-task" (looking anywhere else), as a function of clock hand movements, image content, and image changes. We created a computational model based on the tradeoff between the known expected utility of clock hand movements and the "consumption utility" of the images, under constraints including the subjective estimation of the passage of time. The model fit gaze behavior well, and allowed the inference, from gaze alone, of the consumption utility of a given image for a given participant, as well as changes in that value over time. Critically, consumption utility was not reducible to ratings of valence or arousal. This combination of a novel task and computational models of how limited agents seek and consume utility over time holds the potential to provide new insights into the processes underlying continuous self control in both healthy and clinically-disordered populations.

Disclosures: P. Sokol-Hessner: None. **N.D. Daw:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.10

Topic: F.01. Human Cognition and Behavior

Support: R01MH101194

Title: The integrative process of reading emotional expressions from a crowd of faces

Authors: *H. IM[1], D. ALBOHN[3], R. B. ADAMS, Jr[3], K. KVERAGA[2];
[1]Harvard Med. Sch. / Massachusetts Gen. Hos, Somerville, MA; [2]Harvard Med. Sch. / Massachusetts Gen. Hos, Charlestown, MA; [3]The Pennsylvania State Univ., University Park, PA

Abstract: The vast majority of affective perception research has employed single faces as stimuli. Yet, when we face a crowd of strangers, we may need to rapidly evaluate the crowd's collective mood and decide whether to approach or avoid it. One efficient way to do this is to read facial expressions in the crowd. Here we tested how humans extract emotion from groups of faces (termed "crowd emotion") with average crowd emotion ranging from happy to angry. We created 'morphed' faces from emotionally extreme faces of 6 different identities (3 female/3 male). In Study 1, two crowds of 4 or 6 morphed faces of a single identity were presented in the left and right visual fields for 1 sec. Subjects (N = 18) were asked to indicate via a key press whether the group on the left or right looked more approachable. We found that overall accuracy (63.7%) was significantly higher than chance, suggesting they could reliably extract the average emotion from two crowds of faces. The accuracy increased with the average emotional distance between the two face crowds (60.97% for ±5 and 67.22% for ±9 emotional units). We also found the tendency towards faster RTs for angrier crowds than happier crowds indicating more rapid processing of potential threat. There was no set size effect on accuracy or RT, suggesting that crowd emotion can be extracted without requiring serial processing. Finally, happy female crowds were identified more accurately than happy male crowds, while the opposite was true for angry male vs. angry female crowds. This suggests that crowd emotion perception is modulated by sex-specific identity cues (masculinity or femininity of a crowd), an effect also found for processing individual faces (Adams, Hess, & Kleck, 2015). In Study 2, we tested the effect of facial identity on perceived crowd emotion with a new cohort (N=18). The same morphed faces were intermixed to create crowds of 4 or 6 different identities. Although there was a slight drop in overall accuracy (60.31%) compared to Study 1, indicating interference of identity cues with emotion cues, we replicated the findings from Study 1: increased accuracy with average emotional distance, faster RTs for angrier vs. happier crowds, and no set size effects. In Study 3, we tracked subjects' eye movements and found that the first saccade was made to the happiest face in the crowd more frequently than to any other faces, indicating that the eye movement system prioritizes extreme expressions in evaluating crowd emotion. In conclusion, average crowd emotion can be reliably extracted from crowds with varying emotional expressions, and its perception is modulated by identity cues and emotional valence.

Disclosures: **H. Im:** None. **D. Albohn:** None. **R.B. Adams:** None. **K. Kveraga:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.11

Topic: F.03. Motivation and Emotion

Support: COI HIROSHIMA

Title: Detecting emotional component from EEG waveforms using ICA decomposition

Authors: *N. KANAYAMA, K. MAKITA, R. KOZUMA, M. MACHIZAWA, T. SASAOKA, G. OKADA, S. YAMAWAKI;
Hiroshima Univ., Hiroshima-Shi, Japan

Abstract: If we have any biological marker to objectively estimate our emotional state in real time, we can more effecctively exploit the emotion to facilitate our social communication. To achieve this, it is fundamental to detect neural responses reflecting emotional states. Real time recording of EEG can be of a tool as a brain emotion interface. EEG signals are, however, a composit of activities from different cortical sources, making it difficult to identify our complex emotional states. Independent component analysis (ICA) is a solution of this problem, which enables us to separate the superimposed EEG components into independent cortical responses [1]. Here, we recorded scalp EEGs from 64 electrodes of 13 undergraduate students while they perform an emotional evaluation task. An emotion-driving picture selected from IAPS was presented on a monitor for each trial. Participant was asked to fixate at the center of the picture, and they reported their emotional responses. Valence, arousal, luminance and spatial frequency power of the pictures were controlled across the pictures. EEG data was segmented into epochs from 1000 ms pre-stimulus to 4000 ms post-stimulus relative to the onset of the picture. The extended Infomax ICA was performed to obtain 64 independent components (ICs) from each participant.ICs were clustered into 16 clusters. Of these clusters, 2 clusters were found to be relevant to index features of presented pictures. A cluster localized in occipital area showed a significant effect of luminance and spatial frequency power ($p < .05$, bootstrap test, FDR-corrected), while emotional valance and arousal had no influence on this cluster. In contrast, the other cluster of activities from posterior cingulate had a significant effect of emotional valence and arousal ($p < .05$, bootstrap test, FDR-corrected). As in the case of the first cluster in the occipital area, luminance and spatial frequency as physical features of the presented picture had no effect on this component. The posterior cingulate cortex is found to be related to evaluation emotional status [2, 3]. Our results not only support the role of the posterior cingulate on emotional evaluation but also demonstrate possibility of detecting pure emotional responses from

the posterior cingulate using ICA. [1] Makeig, S. et al.. (2004). Trends in Cognitive Sciences. doi:10.1016/j.tics.2004.03.008 [2] Maddock, R. J. et al. (2003). Human Brain Mapping, 18(1), 30-41. [3] Mantani, T. et al. (2005). Biological Psychiatry, 57(9), 982-90.

Disclosures: **N. Kanayama:** None. **K. Makita:** None. **R. Kozuma:** None. **M. Machizawa:** None. **T. Sasaoka:** None. **G. Okada:** None. **S. Yamawaki:** None.

Nanosymposium

564. Emotional Processing and Regulation

Location: N228

Time: Tuesday, October 20, 2015, 1:00 PM - 4:00 PM

Presentation Number: 564.12

Topic: F.03. Motivation and Emotion

Support: National Basic Research Program of China 2010CB833904

Title: Neural correlates of guilt-induced self-punishment

Authors: ***H. YU**, B. SHEN, Y. CAO, X. ZHOU;
Peking Univ., Beijing, China

Abstract: Compensation/reparation following interpersonal transgression has been shown to have the function of reducing the unpleasant feeling of guilt. However, when actual compensation is not possible (i.e., the victim cannot benefit from the transgressors), the transgressors still tend to take effort or punish themselves, both in front of their victims and in complete privacy. In this study, we addressed the question how the effectiveness of self-punishment and the presence of the victim influence guilt-related brain processes and self-punishment behavior. The participants were playing a dot-estimation task with an anonymous partner. In some trials, the participants took the responsibility of estimation, while in others the partner did. The participants were told that an intensive painful stimulation will be delivered to their partner if the estimation, either by the participants or by the partner, was incorrect. Before pain delivery, participants were asked to choose the level of pain they would be willing to take. In separate blocks, the consequences of participants' taking pain (i.e., self-punishment) were manipulated. In the Reparable block, the level of pain taken by the participants anti-correlated with the level inflicted on the partner. In the Open block, the pain stimulation inflicted on the partner was not affected by the participants' choice but the partner could see the participants' choice. In the Private block, the participants' self-punishment could neither alleviate the partner's pain, nor be conveyed to the partner. Self-report of guilt was lower in the Reparable block, confirming the guilt-reduction effect of compensation. We defined the behavioral agency

effect as the allocation difference between self-error and the partner-error conditions. Such effect was positive in all three blocks but decreased linearly from the Reparable to the Open and the Private blocks. The agency effect of brain activation (self-error > partner-error) in the brain structures previously associated with interpersonal guilt, such as the anterior middle cingulate and the anterior insula, were modulated by the effectiveness of self-punishment and the presence of the victim: the agency effect was higher when the self-punishment could not reduce partner's pain and the partner could observe the participants' choice (Open block). To our knowledge, these findings provided the first evidence that compensation could reduce the neural activations in the brain structures associated with affective processes and suggested that guilt-induced self-punishment may be driven by such processes.

Disclosures: H. Yu: None. **B. Shen:** None. **Y. Cao:** None. **X. Zhou:** None.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.01

Topic: G.04. Physiological Methods

Support: NIH Grant 5 F32 NS073422-03

Title: Impact of soft interfaces on neural recordings

Authors: *A. SRIDHARAN, J. MUTHUSWAMY;
Sch. of Biol. & Hlth. Systems Engin., Arizona State Univ., Tempe, AZ

Abstract: Soft materials have shown promise in improving the biocompatibility of neural interface devices and have been hypothesized to reduce interfacial, mechanical strain. However, the impact of soft materials on neuronal recording performance has not yet been carefully studied. We have developed a novel, mechanically soft, brain-like interface to assess whether minimizing the mechanical mismatch between the brain-electrode interface would improve the reliability of long-term neural recordings. A brain-like, soft (elastic modulus ~5-8 kPa) material with conductive properties was coated on a total of 9 tungsten electrodes. Six other uncoated tungsten electrodes were used as negative controls (n=5 rats). The coated and uncoated electrodes were implanted in the somatosensory cortex of the rat brain and neural recordings from awake animals were taken and analyzed for signal-to-noise ratio (SNR), firing rate, unit amplitude and neural activity characteristics. Electrochemical impedance spectroscopy measurements were used to test for changes in impedance due to tissue remodeling at the

electrode-tissue interface. Soft neural interfaces whose elastic moduli were matched with that of the surrounding brain tissue showed relatively stable electrical impedance characteristics over 6 months compared to the uncoated control electrodes. Peak-to-peak amplitudes (Vpp) for 6 sorted units each from coated and uncoated electrodes were tracked for 4 weeks. Coated electrodes showed negligible change in Vpp for 3 units and significantly increased amplitudes for 3 units, while 4 of 6 uncoated electrodes showed a decrease in amplitude. We conclude that soft, brain-like coatings enable neural interfaces with relatively stable electrical impedances over 6 months *in vivo* compared to conventional microelectrodes. However, the soft, brain-like coatings did not by themselves guarantee high quality neural recordings due to several other contributing factors.

Disclosures: A. Sridharan: None. **J. Muthuswamy:** None.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.02

Topic: G.04. Physiological Methods

Title: A method for integration of ECoG data from mutliple individuals: validation in the language network

Authors: *R. A. VAN DER SPEK, N. F. RAMSEY, Z. V. FREUDENBURG;
Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: Electrocorticography is one of the latest additions to the neuroscience toolbox. It has limitations due to the fact that patients are involved with pathologies that dictate the position, spacing and extent of coverage of electrodes. In most patients electrodes only cover part of a functional network such as the language system. The limited agreement in coverage and the resulting variability across subjects causes problems for research on mechanisms underlying functions that are served by neural networks. Here we present a data driven clustering approach for grouping data across individuals. Results are obtained for the language system, and are compared to known spatiotemporal activity patterns. Fifteen subjects with coverage over parts of their left hemisphere performed a verb generation task in which they had to covertly read a noun and overtly respond with a matching verb. Electrodes over all subjects were clustered based on the broadband gamma (40-125Hz) time-locked amplitude response to the task, regardless of the anatomical location of the electrodes. For the clustering we used the affinity propagation algorithm [Frey and Dueck, 2007]. The clusters represent the most common activation patterns among subjects over the entire left hemisphere. Cluster membership was spatially evaluated by

means of heatmaps representing electrodes belonging to a single cluster. The cluster-specific gamma response waveform indicated timing of signal increase and decline. Clusters were surprisingly coherent in space, suggesting an anatomical agreement between function and our clustering method. The cluster waveforms indicated a sequence of events that followed a meaningful path: a distinct pattern of increased broadband gamma activity was observed starting at the occipital cortex, and followed by the left fusiform gyrus. Next, the dorsolateral prefrontal cortex (DLPFC) shows double activation peaks. In between the double peaks we see a peak in Broca. This is followed by a simultaneous peak in both the DLPFC and Broca. This might indicate task specific computation correlating the noun concept to the chosen verb concept. The sensory-motor cortex (SMC) peaks just prior to the recorded verb onset time and is likely involved in the generation of primary motor commands for speech. Prior to auditory feedback in the superior temporal gyrus, evidence for an internal control loop has been found involving Broca, the orbitofrontal prefrontal cortex and SMC. These results provide an initial high spatiotemporal overview of cortical activation patterns involved in language processing. Furthermore, this study has attempted to provide initial steps in performing group analysis in ECoG.

Disclosures: **R.A. Van Der Spek:** None. **N.F. Ramsey:** None. **Z.V. Freudenburg:** None.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.03

Topic: G.04. Physiological Methods

Support: DARPA REPAIR Program N66001-10-C-2010

NSF CBET-1402803 and CBET-1264816

NSF EFRI Grant 0937848

The Ministry of Science, Korea, CISS-2012366054204

Title: Development of fully transparent micro-optoelectrode array for simultaneous optical, electrical interface to the brain and its applications

Authors: ***J. LEE**[1], I. OZDEN[1], Y.-K. SONG[2], A. NURMIKKO[1];
[1]Sch. of Engin., Brown Univ., Providence, RI; [2]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Optogenetics, a technique of selective controlling neural activity by light, has become a powerful method for studying various field of the neuroscience. However, related device technology for broad in-vivo applications was still hindered mainly by light-induced electrical artifact. Here, we report a fully transparent micro-optoelectrode array (MOA) made from a single crystal of semiconductor zinc oxide (ZnO) and demonstrate its multiple functionality of multisite optical stimulation and simultaneous electrical recording of neural activity in in-vivo mouse model. New fabrication techniques were developed for processing 2 mm-thick bulk ZnO to 2D array of optoelectrodes, scalable to >100 channels, with precision dicing and wet chemical etch. Its physical foam factor is targeted Utah/Blackrock Si microelectrode array, > 1 mm long shanks with 400 μm pitch. And flexible optical/electrical interconnections for independent electrical and optical access to each optoelectrode were fabricated and integrated onto MOA afterwards. We performed optogenetic stimulation and electrical recording from Thy1-ChR2 transgenic mice with 4×4 version of MOA. A focused 473 nm laser pulses were sequentially delivered onto pre-determined position of each optoelectrode by computer-controlled laser scanning system. High optical transparency of ZnO allowed us to monitor neural activities from multiple channels without apparent photoelectrical artifact while light was delivered through optoelectrodes to the same recording location, from microwatt to milliwatt levels of optical input power. Other additional capabilities, benefited from unique material choices, such as optical fluorescence detection and electrical neural stimulation was also demonstrated. Currently, we're preparing a light source-integrated fully implantable ZnO MOA system integrated for expanded applicability in freely-moving animal model, while improving device performances such as recording quality, biocompatibility, and lager size of array for employing in non-human primates.

Disclosures: **J. Lee:** None. **I. Ozden:** None. **Y. Song:** None. **A. Nurmikko:** None.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.04

Topic: G.04. Physiological Methods

Support: European Community's Seventh Framework Programme (FP7) under grant agreement n° 280433 (NEUROCARE project)

French Agence Nationale de la Recherche (ANR) through the project MEDINAS (ANR07TECSAN014)

Title: Nanostructured diamond microelectrode arrays for neural interfacing

Authors: G. PIRET[1], C. HÉBERT[2], J.-P. MAZELLIER[3], L. ROUSSEAU[4], E. SCORSONE[2], M. COTTANCE[4], G. LISSORGUES[4], M. O. HEUSCHKEL[5], S. PICAUD[6], P. BERGONZO[2], *B. YVERT[1];
[1]Clinatec UA01, INSERM, Grenoble Cedex 9, France; [2]CEA-LIST, Gif sur Yvette, France; [3]Thalès Res. and Technol., Palaiseau, France; [4]ESIEE-Paris, Noisy le Grand, France; [5]Qwane Biosci., Lausanne, Switzerland; [6]INSERM/UPMC, Paris, France

Abstract: Current development of neural implants and interfacing systems requires highly stable and biocompatible microelectrode arrays (MEAs) offering large numbers of small-diameter microelectrodes. However, such high-density integration cannot be achieved with conventional materials, for which microelectrodes have then high impedances, high intrinsic noise level, and small charge injection capacity. These issues can be overcome by nanostructuration of the electrode surface. In this context, 3-µm-long carbon nanotubes (CNTs) embedded into conductive boron-doped diamond (BDD/CNTs/BDD) has recently been proposed as a new 3D nanostructured BDD electrode material with very promising electrochemical properties. Here, we build MEAs made of either conventional BDD or 3D nanostructured BDD and tested these devices for neural recordings. The two types of MEAs were processed on glass substrates using micro-fabrication steps. Conventional BDD resulted in a macro-structured surface, while 3D nanostructured BDD displayed a high-aspect ratio nanostructured surface and a very large surface area. This innovative material allows for neural cell attachment, survival and neurite extension. 3D-nanostructured BDD microelectrodes have much lower impedances compared to conventional BDD microelectrodes. CV measurements show that 3D nanostructured BDD microelectrodes have an increased double layer capacitance compared to the conventional BDD ones, exhibit a large theoretical charge storage capacity (10 mC.cm-2 for 20-µm diameter electrodes), and have a much lower noise level compared to the conventional BDD ones. Further direct experimental measurement of charge injection capacity of these electrodes confirmed their better efficacy in stimulation as compared to conventional BDD. These 3D nanostructured BDD microelectrodes allowed both low amplitude signal recording and electrical stimulation in hippocampal cell cultures and whole acute embryonic mouse hindbrain spinal cord preparations. In conclusion, 3D nanostructured BDD is a promising new material for neural interfacing and the development of neural prosthesis or implants for rehabilitation.

Disclosures: G. Piret: None. **C. Hébert:** None. **J. Mazellier:** None. **L. Rousseau:** None. **E. Scorsone:** None. **M. Cottance:** None. **G. Lissorgues:** None. **M.O. Heuschkel:** None. **S. Picaud:** None. **P. Bergonzo:** None. **B. Yvert:** None.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.05

Topic: G.04. Physiological Methods

Support: EC-FP7 NAMASEN ITN

FP7-NMP MERIDIAN

Title: Protruding nanocrystalline diamond microelectrode arrays for 'in-cell' recording and stimulation

Authors: ***M. MCDONALD**[1], F. VAHIDPOUR[1], M. SPIRA[2], M. NESLADEK[1];
[1]IMO-MEC, Hasselt Univ., Diepenbeek, Belgium; [2]The Life Sci. Inst., The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: We report here on the design and fabrication of microelectrode arrays that use diamond mushroom-shaped microelectrodes (dMμEs) with an NCD passivation layer to deliver 'in-cell' neural recordings. Microelectrodes have undergone rapid development recently with advances in both the interface materials and electrode geometries to bridge the gap between patch-clamp electrodes and planar microelectrode arrays. Protruding mushroom-shaped geometry can be used to elicit spontaneous engulfment by neurons, as shown by Spira et al., to reduce the junctional resistance and allow for 'in-cell' recordings; describing extracellular recordings with signal quality of intracellular single-cell recordings1. This gives the combined benefits from both patch-clamping and microelectrode arrays, to allow highly parallelized long-term recordings with optimal signal quality and single-cell resolution. Electrode material is important for the electrical properties of the interface as well as the stability and biocompatibility. Advantages of diamond as an electrode material include biocompatibility, chemical and mechanical robustness, and a large potential window. Boron-doped nanocrystalline diamond (BNCD) has been shown to be an excellent material for both recording and stimulation of neural cells2. Additonally, intrinsic nanocrystalline diamond (NCD) is insulating and has been shown to work well as a passivation layer for microelectrode arrays3. Mushroom electrodes were fabricated on commercial microelectrode arrays (Multi Channel Systems MCS GmbH) with 200 μm spacing and 30 μm electrode diameter (figure 1a,b). These electrodes combine advantages of mushroom-shaped geometry for cell engulfment with the interface properties of diamond electrodes. We have shown that neurons engulf dMμEs (figure 1c) and are currently performing functional testing with the described MEAs which are expected to give 'in-cell' recordings. 1 A. Hai, M.E. Spira, Jour: of Neurophys. 104, 559 (2011). 2 M. Cottance, S. Joucla, DTIP 16 (2013). 3 V. Maybeck, A. Offenhäusser, Adv. Healthcare Mat. 3, 283 (2014).

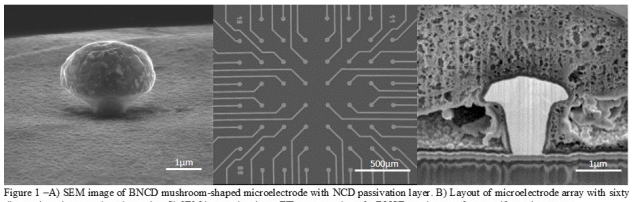


Figure 1 –A) SEM image of BNCD mushroom-shaped microelectrode with NCD passivation layer. B) Layout of microelectrode array with sixty diamond mushroom microelectrodes. C) SEM image showing a FIB cross-section of a BNCD mushroom after engulfment by neuron.

Disclosures: **M. McDonald:** None. **F. Vahidpour:** None. **M. Spira:** None. **M. Nesladek:** None.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.06

Topic: G.04. Physiological Methods

Support: DARPA W31P4Q-11-C-0134

Title: A novel elastomeric conducting microwire for improved chronic tissue integration of neural electrodes

Authors: ***Z. DU**[1,2,3], C. L. KOLARCIK[1,2,3,4], S. SAPP[6], S. LUEBBEN[6], T. D. Y. KOZAI[1,2,3], N. R. SNYDER[1,2,3], C. F. LAGENAUR[5], X. T. CUI[1,2,3];
[1]Bioengineering, [2]Ctr. for Neural Basis of Cognition, [3]McGowan Inst. for Regenerative Med., [4]Systems Neurosci. Inst., [5]Neurobio., Univ. of Pittsburgh, Pittsburgh, PA; [6]TDA Research, Inc., Golden, CO

Abstract: Implantable multielectrode array (MEA) is an essential technique to understand electrical signaling of *in vivo* neural networks and modulate the adjacent neuronal activity through micro-stimulation. Chronically implanted MEAs are critical components of brain computer interface (BCI) techniques for restoring lost neural functions in patients. However, current designs of MEAs used for interfacing with the nervous system elicit a characteristic inflammatory response that ultimately lead to device failure. Traditionally, relatively stiff materials like tungsten and silicon are employed to establish an interface with the relatively soft neural tissue. The stiffness of device cause multiple aspects of problems, preventing the formation of a chronically stable neural interface. In order to minimize the disparity between neural interface device and the brain, novel soft electrodes consisting of elastomers and conducting polymers were fabricated in this study. Both the conductive and the insulation

materials were consisted of polymeric materials that aim to match the mechanical properties of the brain. To implant and characterize this soft microelectrode, an insert-and-release stainless steel shuttle was developed for the procedure. Neural recording, stimulation, immunohistochemistry and mechanical measurements of the device performance revealed satisfactory early result for this novel micro electrode. The elastic material also enabled *in situ* histology characterization of the electrode-tissue interface with the microelectrode sectioned inside the tissue block. Iba1, NF200 and GFAP markers were assessed to compare the different tissue response towards soft and stiff microwire electrodes, and cell deformation analysis indicated the soft microwire applied less strain to cells surrounding the implants. The results presented in our study substantiate the evidence in supporting of the use of soft materials for long term neural implants.

Disclosures: **Z. Du:** None. **C.L. Kolarcik:** None. **S. Sapp:** None. **S. Luebben:** None. **T.D.Y. Kozai:** None. **N.R. Snyder:** None. **C.F. Lagenaur:** None. **X.T. Cui:** None.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.07

Topic: G.04. Physiological Methods

Support: NIH:NIBIB 1R43EB018200-01A1

NSF:IGERT 0903715

Title: Parylene C-aluminum oxide bilayer encapsulation and minimal iridium oxide tip metal coverage promote neural electrode impedance stability during accelerated aging tests

Authors: *R. B. CALDWELL[1], H. MANDAL[3], R. SHARMA[2], L. RIETH[2], F. SOLZBACHER[2], P. TATHIREDDY[2];
[1]Bioengineering, [2]Univ. of Utah, Salt Lake City, UT; [3]Blackrock Microsystems, Salt Lake City, UT

Abstract: Increasing the reliability of neural interface performance is critical to develop these technologies into chronic implantable research tools and therapies. Encapsulation and electrode metal stability influence all aspects of the device performance, and aging studies have shown impedance reductions for various electrode technologies both in saline and in-vivo. In particular, the silicon-micromachined Utah Electrode Array (UEA) has shown impedance reductions of

>10x, loss of single-unit recording, and variations in results and thresholds for stimulation. We hypothesize that encapsulation damage is a key contributor to this failure, permitting electrochemical interactions at previously shielded electrode shank areas. We propose two methods to mitigate this failure mode: **(1) Use of parylene C-aluminum oxide bilayer encapsulation**, shown in previous work to be superior to parylene C alone in preserving impedances of planar test devices aged *in vitro*. UEAs were completely encapsulated (i.e. tips not deinsulated) with either parylene C alone (P-only) or parylene-alumina (PA) bilayer (N=2 each) and aged in phosphate buffered saline (PBS) at 67°C. Devices were soaked for 97 days and measured at regular intervals; typical day 0 impedances at 1 Hz and 1 kHz were 8,000 MΩ and 10 MΩ, respectively. Upon study completion both P-only devices showed median impedances of <50 MΩ and <6 MΩ at 1 Hz and 1 kHz while PA bilayer devices exhibited median final impedances of >1,000 MΩ and 10 MΩ. This indicates PA bilayer encapsulation will prevent aging-induced impedance reductions associated with P-only encapsulated UEAs. **(2) Limit coverage of iridium oxide (IrO_x) to the electrode site**, such that any encapsulation damage does not expose more IrO_x, and therefore has less impact on the electrical performance. Impedances in PBS were measured for two UEAs with 50 μm IrO_x exposure: device UEA1 had electrodes without any insulation but with tight tip metal tolerances, and device UEA2 utilized normal tip deinsulation with precise encapsulation boundaries. Average UEA1 (N=32 channels) and UEA2 (N=16 channels) impedances closely (<10% error) matched between 1 Hz and 1 kHz (1 MΩ to 6 kΩ). Impedances differentiated at 1 kHz, where UEA2 maintained constant impedance while UEA1 displayed a slope change and decreased to <1 kΩ at 100 kHz. This indicates that IrO_x exposure drives electrochemical interactions at frequencies <1 kHz, while only higher frequencies are affected by large areas of exposed silicon. Thus, by matching lengths of IrO_x and encapsulation removal during microelectrode fabrication, the possibility of aging-induced low-frequency impedance reduction is expected to be eliminated.

Disclosures: **R.B. Caldwell:** None. **H. Mandal:** A. Employment/Salary (full or part-time); Blackrock Microsystems. **R. Sharma:** None. **L. Rieth:** A. Employment/Salary (full or part-time); Blackrock Microsystems. **F. Solzbacher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackrock Microsystems. **P. Tathireddy:** A. Employment/Salary (full or part-time); Blackrock Microsystems.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.08

Topic: G.04. Physiological Methods

Support: NSF EEC0310723

Coulter

Title: *In vivo* characterizations of platinum-iridium electroplated dbs electrodes

Authors: *A. PETROSSIANS[1], J. J. WHALEN, III[1], F. MANSFELD[2], J. D. WEILAND[3]; [1]Ophthalmology, [2]Chem. Engin. and Materials Sci., [3]Biomed. Engin., USC, Los Angeles, CA

Abstract: Deep brain stimulation (DBS) therapy is a clinically accepted technique for treatment of movement disorders. Continuous electrical stimulation of certain brain regions has been shown to decrease the symptoms of movement disorders such as Parkinson's disease and essential tremor. DBS therapy is expanding to a multitude of neurological disorders. More generally, microelectronic implants are used to treat cardiac rhythm disorders, deafness, chronic pain, and depression. New targets for use of implants are obesity, memory loss, blindness, and migraine. Implants also record electrical activity from surrounding nerves inside of the brain. All these devices use electrodes to interface with excitable tissue. An improved electrode material will have a significant impact on the capabilities of these devices and the effectiveness of these treatments. A novel, ultra-low impedance electrode material, high surface-area platinum-iridium alloy (Pt-Ir), was developed and characterized. The results showed increased stimulus pulse efficiency up to 80%, which will delay or possibly eliminate the need for expensive battery replacement surgery. The Pt-Ir material will enable highly-automated flex circuit electrode fabrication processes, which will significantly reduce manufacturing costs and allow more sophisticated designs. Pt-Ir coated DBS-style electrodes were evaluated in a chronic passive in-vivo test to evaluate the effect of encapsulation on impedance and compare the effect versus a conventional platinum electrode. Pt-Ir coated DBS electrodes were implanted in rabbit brain and characterized by electrochemical impedance spectroscopy (EIS) at days 0, 30, 60 and 180 post-implantation. The EIS measured values at 1 kHz, 100 Hz and 10 Hz at day 0 of the implantation, for uncoated Pt electrodes vs Pt-Ir coated ones, were reduced from 1,346 Ohm, 2,011 Ohm and 5,540 Ohm to 673 Ohm, 742 Ohm and 966 Ohm, respectively. After 180 days post-implantation, the impedance values of the Pt-Ir coated electrode at the aforementioned frequencies were 838 Ohm, 902 Ohm, 1092 Ohm, respectively. The results showed that the enhanced impedance of the coated electrodes were nearly unchanged after 180 days of implantation. The in-vivo results suggest a superior electrode material to lower the impedance on the electrode surface to be used potentially for chronic stimulation or for brain/machine interface applications.

Disclosures: **A. Petrossians:** A. Employment/Salary (full or part-time); Platinum Group Coatings, LLC (part-time). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Platinum Group Coatings, LLC (co-founder). **J.J. Whalen:** A. Employment/Salary (full or part-time); Platinum Group Coatings, LLC (part-time). E. Ownership Interest (stock, stock options, royalty, receipt of

intellectual property rights/patent holder, excluding diversified mutual funds); Platinum Group Coatings, LLC (co-founder). **F. Mansfeld:** None. **J.D. Weiland:** A. Employment/Salary (full or part-time); University of Southern California. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Platinum Group Coatings, LLC (co-founder).

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.09

Topic: G.04. Physiological Methods

Support: NIH Grant 1-U01-NS090526-01

Title: Fiberless multicolor optoelectrodes for neural circuit analysis

Authors: *K. KAMPASI, J. SEYMOUR, K. NA, K. D. WISE, E. YOON;
Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: The number of novel opsins and solutions for cell-type specific expression has been rapidly increasing. But the existing engineering solutions available to deliver light to the brain come with limited functionality. Stimulation through light sources placed on the surface of the brain or large fibers placed in the brain parenchyma constrains animal movement and activates many un-monitored neurons. Whereas, stimulation through light sources placed directly on the probe shank or on the shank backend can result in thermal tissue damage. We report a minimally invasive fiber-less, multicolor optoelectrode that can provide spatial precision and scalability needed to enable many novel experiments such as closed loop excitation, creation of synthetic patterns to study plasticity, and control of a few to many neurons. The highly compact optical design is implemented using side-emitting injection laser diodes (ILD), coupled via gradient-index (GRIN) lenses, to 7μm thick and 30μm wide dielectric waveguides on a 22μm thick Michigan probe. This novel waveguide approach provides independent activation and inhibition of simultaneously monitored neurons by illuminating different wavelengths at a given stimulation site and can be expanded to synchronously stimulate multiple optical sites along the shank length. The waveguide mixer design and alignment tolerances of optical assembly are thoroughly simulated in Zemax to maximize optical system efficiency. We have achieved 100 to 5000 mW/mm^2 of irradiance at the waveguide tips during optical bench testing and have successfully scaled up our design to a 4-shank device with eight ILD-GRIN assemblies. Combined with varied color choices for manipulating multi-opsins expressing local neural

populations, this multi-port mixer waveguide design also offers low EMI noise and effective thermal isolation between light sources and tissue, realizing modular implantable optoelectrode array. Such versatile optogenetic tools ultimately hold a potential for allowing neuroscientists to study complex brain networks such as memory consolidation networks in hippocampus.

Disclosures: K. Kampasi: None. **J. Seymour:** None. **K. Na:** None. **K.D. Wise:** None. **E. Yoon:** None.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.10

Topic: G.04. Physiological Methods

Support: Cyberonics, Inc

Title: A wireless platform for closed-loop optogenetics

Authors: *S. LEE, Q. YUAN, P. P. IRAZOQUI;
Weldon Sch. of Biomed. Engin., Purdue Univ., West Lafayette, IN

Abstract: Wireless neural prostheses can enable the scientific community towards more clinically relevant and chronic experimental protocols. A large portion of current rodent optogenetic experiments use restrictive tethers which prohibit freely behaving experiments. Wireless devices currently available only offer optical stimulation for open-loop modulation. Closed-loop strategies have been shown to offer advantages in deep brain stimulation for Parkinson's disease and also in epilepsy by stopping seizures immediately upon seizure detection. Here, we present the optogenetic Bionode (o-BN). The o-BN provides two channels of biopotential recording and 1 channel of constant current LED-based optical stimulation in a miniature footprint (< 1cm^3). The 2 channels of differential recording (0.7 Hz - 1 kHz, 60 dB gain) can be configured to observe cardiac, respiratory, and neural activity. A microcontroller (MCU) allows feature detection algorithms and a radio enables wireless programming of stimulation parameters. The LED-based optical module is driven by a constant current stimulator and can be coupled to a 200 μm diameter optical fiber for targeting deep brain structures. The fiber irradiance can reach 10 mW/mm^2 with only 8 mA of input current (λ = 473 nm), which is sufficient to activate neurons with ChR2. Other wavelengths for optical stimulation can be implemented to be paired with the appropriate molecular probe. The o-BN consumes < 4 mW during non-stimulating conditions. The device is powered using resonantly coupled filter energy

transfer (RCFET), a magnetic resonance wireless power transfer method. The powering cage provides powering in all orientations for true, freely behaving experimental approaches.

Disclosures: **S. Lee:** None. **Q. Yuan:** None. **P.P. Irazoqui:** None.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.11

Topic: G.04. Physiological Methods

Title: A low-cost digital headstage for high channel count µECoG

Authors: ***M. TRUMPIS**[1], M. INSANALLY[2], J. ZOU[3], A. ELSHARIF[3], A. GHOMASHCHI[3], N. S. ARTAN[4], R. C. FROEMKE[2], J. VIVENTI[1];
[1]Biomed. Engin., Duke Univ., Durham, NC; [2]Skirball Inst., NYU Sch. of Med., New York, NY; [3]Electrical and Computer Engin., NYU Sch. of Engin., Brooklyn, NY; [4]Electrical and Computer Engin., NYIT Sch. of Engin. and Computer Sci., New York, NY

Abstract: There is currently a growing interest in the development of high channel-count electrode arrays that can survey cortical activity at high resolution and with broad spatial coverage (Fukushima et al. 2014, Khodagholy et al. 2014, Dimitriadis et al. 2014). The increasing quantity of recording channels requires strategies to simplify the external wire connections. We have formerly proposed a multiplexing solution integrated into the electrode array itself (Viventi et al. 2011). Here we present a headstage-level solution that provides integrated amplification, filtering and analog to digital conversion from many channels using a single commercial integrated circuit (IC). Amplification and digitization at the headstage level reduces the effect of transmission noise as compared to analog recording systems. We utilized an ultra low-noise, current-input analog to digital converter (Texas Instruments DDC232) to digitize and multiplex neural signals. The TI DDC232 combines current integration, 20-bit analog-to-digital conversion, and multiplexing with sampling rates up to 6 kS/s per channel. We validated the current-sensed signal in acute recordings from rat auditory cortex. Cortical currents from a 61-channel µECoG electrode array (Woods et al. 2015) were measured by two 32-channel ICs in a custom-built headstage. The IC dimensions are 9x9 mm, keeping the total headstage dimension to only 15x21 mm. Digital outputs were relayed by an ultra-flexible micro-HDMI cable. The measured signal was transformed by the impedance at the electrode-electrolyte interface. We successfully corrected for this transformation using a linear time-invariant filter model of the electrode impedance. We also confirmed similar results using a composition of bandpass and

integrating filters. The current-sensed recording quality was compared to that from a voltage-sensing headstage with analog multiplexing and conventional high-impedance amplification (Wang et al. 2014). We observed equal or better performance in a variety of signal and electrophysiological metrics including: evoked-response detectability; signal-to-noise and response-to-baseline ratios; rate of decay in spatial correlation; and ability to predict tone frequency from the multi-channel evoked-response. The headstage design was aligned with our ongoing efforts to leverage reliable and economical solutions made available by industrial electronics fabrication (Wang et al. 2014, Trumpis et al. 2014). The class of IC utilized can be tiled to create a digital headstage accommodating 1000s of channels with very few external wires, making it a realizable solution for novel high-density electrode designs.

Disclosures: **M. Trumpis:** None. **M. Insanally:** None. **J. Zou:** None. **A. ElSharif:** None. **A. Ghomashchi:** None. **N.S. Artan:** None. **R.C. Froemke:** None. **J. Viventi:** None.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.12

Topic: G.04. Physiological Methods

Support: DARPA/BTO N66001-15-C-4017

Title: Enhancing the recording and stimulation performance and stability of Utah electrode arrays through metallization improvements

Authors: B. BAKER[1], R. CALDWELL[2], H. MANDAL[3], R. SHARMA[1], M. GRUENHAGEN[3], P. TATHIREDDY[1,3,4], *L. RIETH[1,3];
[1]Electrical and Computer Engin., [2]Bioengineering, Univ. of Utah, Salt Lake City, UT;
[3]Blackrock Microsystems, Salt Lake City, UT; [4]Applied Biosensors, Salt Lake City, UT

Abstract: The Utah Electrode Array (UEA) is a penetrating neural interface designed to communicate with the nervous system through recording and stimulation. They are used for basic neuroscience research, and being investigated for use in treating neural disorders and controlling prosthetics. Damage to the tip metallization during chronic use or long-term soak testing of UEAs has been reported. We have found that damage to the metallization has a large impact on the impedance and charge injection capacity (CIC) of the electrodes. Characterization of the devices via electrical measurements and electron microscopy demonstrates that metal delamination, often with degradation of the silicon can occur during recording or stimulation,

and with Pt or IrOx tip metallizations. We investigated the use of three novel electrode metallizations in comparison to existing metallizations used for these arrays. All metallizations used top layers of Ir and IrOx that are 200 and 350 nm, respectively. The layer for contact and adhesion investigated included 200 nm Pt, 25 nm Pt, and cosputtered 40 nm PtSi. These layers were subjected to typical UEA annealing conditions of 375 °C in forming gas for 45 minutes for the backside metallization, followed by a 475 °C, 30 minute oxygen anneal for the tip metallization. Dual-beam Focus Ion Beam (db-FIB) and cross-sectional scanning transmission electron microscopy (STEM) analysis found significant non-uniformity in silicide reactions with the Si, and the development of Kirkendall voids between PtSi and the Ir layers for the pure Pt contact layers. Cross-sectional STEM elemental mapping of each film stack on planar substrates showed complete transformation of the platinum layer to PtSi. In addition, a 40 nm layer of iridium silicide formed at the PtSi/Ir interface. For the thicker Pt contact layer, significant levels of Kirkendall voids formed at the Pt/Ir interface. These are expected to decrease the adhesion and mechanical stability of the interface. A smaller size and concentration of Kirkendall voids were found for the thin Pt metallization, and preliminary measurements suggests the co-sputter PtSi layer mitigates the formation of the voids. In-vitro electrical characterization of these tip metallizations demonstrated impedances of ~10 kOhms and charge injection capacities of 1-2 mC/cm2. Accelerated stimulation testing was performed in-vitro to characterize the evolution of CIC, impedance, and degradation product concentrations, to investigate damage mechanisms. In addition, an improved metallization is proposed for recording and stimulation of peripheral nerve in a clinical study, and array performance metrics will be reported.

Disclosures: **B. Baker:** None. **R. Caldwell:** None. **H. Mandal:** A. Employment/Salary (full or part-time); Blackrock Microsystems. **R. Sharma:** None. **M. Gruenhagen:** A. Employment/Salary (full or part-time); Blackrock Microsystems. **P. Tathireddy:** A. Employment/Salary (full or part-time); Blackrock Microsystems, Applied Biosensors. **L. Rieth:** A. Employment/Salary (full or part-time); Blackrock Microsystems.

Nanosymposium

565. Electrode Arrays III

Location: N227

Time: Tuesday, October 20, 2015, 1:00 PM - 4:15 PM

Presentation Number: 565.13

Topic: G.04. Physiological Methods

Support: Cal Brain Grant

Title: Nanostructured electrodes for cell recording

Authors: *N. MELOSH[1], K. CHANG[2], T. BOZORG-GRAYELI[2];
[1]Materials Sci., [2]Materials Sci. and Engin., Stanford Univ., Stanford, CA

Abstract: In the past decade, substantial progress has been made in improving the sensitivity and biocompatibility of electrode arrays for massively parallel single-cell recordings within the brain. However, while recording quality depends on the coupling of cells to adjacent electrodes, this crucial interface remains relatively unexplored. Recent *in vitro* work has shown that protruding nanoelectrodes can shrink the cleft between the membrane and sensing electrode surface, exhibiting higher seal resistances than planar electrodes. The degree of coupling is significantly affected by both the geometry and the chemical functionality of these 3D structures. However, high quality recordings necessitate low impedance devices, limiting electrode design and material choices. Here we will describe our efforts to use nanostructured systems that separate the active electrode from the membrane sealing mechanism. We are developing electrodes encased in nano-ring structures whose outer ring region can be modified independently of the working electrode. This allows us to selectively vary the dimensions and surface chemistry of the outer structure without compromising electrode sensitivity. This geometry also permits chemical entrapment and release from the active electrode, enabling selective and controllable material delivery to single cells. Nano-ringed electrodes can be readily integrated onto high density electrode arrays, allowing for selective two-way communication channels with single cells.

Disclosures: **N. Melosh:** None. **K. Chang:** None. **T. Bozorg-Grayeli:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.01

Topic: C.03. Parkinson’s Disease

Support: NINDS Grant NS089622

National Parkinson Foundation

Title: Comprehensive studies of α-synuclein striatal seeding in non-transgenic and transgenic α-synuclein mice

Authors: *C. G. JANUS[1], P. CHAKRABARTY[2], M. BROOKS[2], C. HERNANDEZ[2], L. COLON-PEREZ[2], M. FEBO[2], D. BORCHELT[2], T. GOLDE[2], B. GIASSON[2];
[1]CTRND and Dept. of Neurosci., [2]Univ. of Florida, Gainesville, FL

Abstract: α-synuclein (α-syn) is an abundant brain neuronal protein predominantly localized in axon terminals being implicated in the regulation in synaptic function. α-syn is a prime suspect for contributing to Lewy pathology and clinical aspect of diseases, including Parkinson's disease, dementia with Lewy bodies, and a Lewy body variant of Alzheimer's disease. To explore the putative mechanisms underlying α-synucleinopathy pathology, we used transgenic mice overexpressing wild-type human α-syn in CNS neurons as a model of progressing nigro-striatal pathology and progressive sensorimotor abnormalities. The study followed factorial design with groups of non-transgenic (nTg) and transgenic M20 mice stereotaxically injected into striatum at 2 months (mo) of age with mouse or human pre-aggregated α-syn. PBS injected mice served as controls within each genotype, yielding 2 × 3 between subject design. Starting one month post-injection the mice were evaluated in a battery of tests including SHIRPA screen, beam crossing, wire suspension, grip strength, pole climbing, rota-rod tests and home cage burrowing behavior. The battery of behavioral tests was administered repeatedly 5 times, with the last test administered at 8 mo of age. All cohorts of mice were extensively studied for neuropathological changes and with brain imaging. Our results demonstrated that although M20 mice exhibited locomotor abnormalities in some of the tests including beam crossing, they stay longer on the accelerated rod when challenged in rota-rod test. Interestingly, the most robust treatment effect caused by the α-syn seeding was observed in the burrowing and nest building behaviors. Overall, the M20 mice showed significantly delayed burrowing activity and compromised nest building. Importantly, the M20 mice injected with aggregated human α-syn were most severely impaired in both activities and this compromised phenotype persisted throughout the experiment.

Disclosures: C.G. Janus: None. **P. Chakrabarty:** None. **M. Brooks:** None. **C. Hernandez:** None. **L. Colon-Perez:** None. **M. Febo:** None. **D. Borchelt:** None. **T. Golde:** None. **B. Giasson:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.02

Topic: C.03. Parkinson's Disease

Support: Monument Trust Discovery Award from Parkinson's UK (grant J-0901)

Medical Research Council (MRC) UK (awards U138164490, MC UU 12020/1, U138197109, MC UU 12020/5)

Joan Pitts- Tucker/Mortiz studentship

MRC studentship

Wellcome Trust Senior Research Fellowship

Title: R1441C-LRRK2 BAC transgenic rats show progressive motor impairment and neurophysiological changes in dopamine circuit function

Authors: A.-K. KAUFMANN[1,2], M. SLOAN[3,2], D. POTGIETER[3,2], J. ALEGRE-ABARRATEGUI[3,2], R. EXLEY[3,2], T. DELTHEIL[3,2], S. THRELFELL[3,2], K. BRIMBLECOMBE[3,2], M. CIOROCH[3,2], D. BANNERMAN[4], S. CRAGG[3,2], R. WADE-MARTINS[3,2], *J. BOLAM[1,2], P. J. MAGILL[1,2], P. D. DODSON[1,2];
[1]MRC Brain Network Dynamics Unit, Univ. of Oxford, Oxford, United Kingdom; [2]Oxford Parkinson's Dis. Ctr., [3]Dept. of Physiology, Anat. and Genet., [4]Dept. of Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene lead to late-onset Parkinson's disease, characterized by degeneration of dopamine neurons in the substantia nigra pars compacta (SNc) and clinical motor and non-motor symptoms. Some of the most frequent Parkinson's disease linked LRRK2 mutations (e.g. R1441C) are located in the GTPase domain of the LRRK2 gene. To better understand neurophysiological deficits of dopamine neurons and circuits which are affected in Parkinson's disease, we generated transgenic rats that express the full human wild-type LRRK2 or the R1441C-LRRK2 gene variant from a bacterial artificial chromosome insert. We examined young adult (6 months) and aged (16-22 months) rats for changes in motor behavior in a rotarod task and tested their cognitive ability in a spontaneous alternation paradigm. We found that aged R1441C-LRRK2 mutant rats show progressive motor impairments on the rotarod as well as cognitive deficits in the spontaneous alternation task. We assessed striatal dopamine release by fast-scan cyclic voltammetry and recorded the *in vivo* firing properties of identified (juxtacellularly labeled) dopamine neurons in the SNc of young adult and aged rats. We found that aged R1441C-LRRK2 rats show altered striatal dopamine release together with an age-dependent reduction in burst firing compared to non-transgenic and human wild-type LRRK2 controls. The progressive reduction in dopamine transmission and burst firing of SNc dopamine neurons are likely to result in reduced extracellular striatal dopamine levels, and may account for the observed motor impairment. Our results provide novel insights into the impact of LRRK2 mutations on dopamine neuron and circuit function which may underlie the development of Parkinson's disease.

Disclosures: **A. Kaufmann:** None. **M. Sloan:** None. **D. Potgieter:** None. **J. Alegre-Abarrategui:** None. **R. Exley:** None. **T. Deltheil:** None. **S. Threlfell:** None. **K.**

Brimblecombe: None. **M. Cioroch:** None. **D. Bannerman:** None. **S. Cragg:** None. **R. Wade-Martins:** None. **J. Bolam:** None. **P.J. Magill:** None. **P.D. Dodson:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.03

Topic: C.03. Parkinson's Disease

Support: Parkinson Society of Canada - Graduate Award

CIHR - LRRK2 Inflammation (CLINT)

Title: LRRK2 modulates phagocytic activity of microglia via phosphorylation of the actin-nucleating complex WAVE-2

Authors: *P. MARCOGLIESE[1], K.-S. KIM[1], C. WEI[1], J. YANG[1], E. ABDEL-MESSIH[1], G. KABBACH[1], R. S. SLACK[1], M. E. HAQUE[2], K. VENDEROVA[3], M. G. SCHLOSSMACHER[4], D. S. PARK[1];
[1]Cell. & Mol. Med., Univ. of Ottawa, Ottawa, ON, Canada; [2]Biochem., United Arab Emirates Univ., Al Ain, United Arab Emirates; [3]Univ. of the Pacific, Stockton, CA; [4]Ottawa Hosp. Res. Inst., OTTAWA, ON, Canada

Abstract: Mutations in leucine-rich repeat kinase 2 (LRRK2) are implicated in both familial and sporadic Parkinson's disease (PD). Determining LRRK2's function in the cell and subsequent role in dopaminergic cell death has been a challenge to elucidate. However, evidence in the field has been mounting that LRRK2 may play a robust role in immune cell function. Here we show both *in vitro* and *in vivo* that LRRK2 G2019S knock-in primary microglia and bone marrow-derived macrophages (BMDMs) display increased phagocytic activity that correlates with an increase in the ARP2/3 complex activator, WAVE-2. Conversely, LRRK2 null immune cells display impaired engulfment correlating with a decrease in WAVE-2 protein level. We also provide indirect evidence that LRRK2 may stabilize WAVE-2 via direct phosphorylation to induce increased phagocytic activity. To explore LRRK2's role only in microglia and its effect on neurons we expressed LRRK2 specifically in *Drosophila* CNS phagocytes (ensheathing cells) which leads to both age-dependant locomotor deficits and loss of dopaminergic neurons. Taken together, our data implicate microglial phagocytic hyper-activity in the pathogenesis of LRRK2-mediated Parkinson's disease.

Disclosures: **P. Marcogliese:** None. **K. Kim:** None. **C. Wei:** None. **J. Yang:** None. **E. Abdel-Messih:** None. **G. Kabbach:** None. **R.S. Slack:** None. **M.E. Haque:** None. **K. Venderova:** None. **M.G. Schlossmacher:** None. **D.S. Park:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.04

Topic: C.03. Parkinson's Disease

Support: Fondation de France grant agreement 000016819

Title: Effect of the overexpression of LRRK2 fragments containing the kinase domain: a study in rats using lentiviral and adeno-associated vectors

Authors: ***N. CRESTO**, M.-C. GAILLARD, E. DIGUET, D. BELLET, L. LEGROUX, L. KAMGUE, L. FRANCELLE, J. MITJA, G. AURÉGAN, C. JOSÉPHINE, M. GUILLERMIER, D. HOUITTE, C. JAN, F. PETIT, P. HANTRAYE, N. DÉGLON, K. CAMBON, A. BEMELMANS, E. BROUILLET;
MIRCen CEA UMR 9199, Fontenay Aux Roses Cedex, France

Abstract: Mutations in the leucine-rich repeat kinase 2 gene (LRRK2) are the most common genetic causes of autosomal dominant Parkinson's disease (PD), which is characterised by a loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) and the presence of the fibrillar cytoplasmic aggregates of α-synuclein (Lewy-bodies and neurites). We aimed at studying the neuronal consequences of an increase in the kinase activity of G2019S-LRRK2 mutation, a phenomenon that is considered to be central in the triggering of neurodegeneration. To specifically address this question, we evaluated the potential neurotoxicity of lentiviral (LV) and adeno-associated viral (AAV) vectors expressing three different fragments of the C-terminal part of wild type (WT) or G2019S mutant LRRK2: 1) the kinase domain (K), 2) the kinase domain plus its regulatory ROC-COR domain (RCK) and 3) the RCK domain with the C-terminal WD40 domain (RCK-WD40). The fragments were evaluated in kinase activity assay *in vitro* (autophosphorylation and substrate phosphorylation), showing that the mutation G2019S induced a major increase of the kinase activity of the RCK-WD40 domain. Viral vectors coding the different constructs were injected in the rat SNc. Histological evaluation showed that 20-60% of the tyrosine-hydroxylase-(TH)-positive DA neurons were transduced. Longitudinal evaluation (up to 25 weeks post transduction) of the rats injected with LVs and AAVs coding RCK-WD40 (WT) or G2019S fragments showed no performance change in motor tests, and no loss of TH-

positive DA neurons in G2019S group as compared to controls. However, overexpression of RCK-WD40-G2019S produced significant transcriptomic changes as compared to the WT fragment and a Dead-Kinase (G2019S/D1994A). These observations indicated that this Cterminal fragment of LRRK2 was functional and produced cellular disturbances *in vivo* that, however, were sub-toxic at the time points considered after infection. We hypothesized that the lack of neurotoxicity of RCK-WD40-G2019S in DA neurons in rodents may be related to the absence of intrinsic factors rendering DA neurons exquisitely vulnerable in patients with the G2019S mutatio. One possibility is that human alpha-synuclein may play a permissive or accelerating role in neurodegeneration induced by LRRK2-G2019S. To study this hypothesis, we are examining whether G2019S RCK-WD40 could increase the neurotoxicity of human alpha-synuclein in DA neurons. We will present preliminary results from ongoing experiments where rat DA neurons have been co-infected with AAV-G2019S-RCK-WD40 and AAV- A53T-alpha-synuclein.

Disclosures: **N. Cresto:** None. **M. Gaillard:** None. **E. Diguet:** None. **D. Bellet:** None. **L. Legroux:** None. **L. Kamgue:** None. **L. Francelle:** None. **J. Mitja:** None. **G. Aurégan:** None. **C. Joséphine:** None. **M. Guillermier:** None. **D. Houitte:** None. **C. Jan:** None. **F. Petit:** None. **P. Hantraye:** None. **N. Déglon:** None. **K. Cambon:** None. **A. Bemelmans:** None. **E. Brouillet:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.05

Topic: C.03. Parkinson’s Disease

Support: Parkinson's Disease Foundation (Grant No. PDF-IRG-1305)

EPFL

Van Andel Research Institute

Title: Impact of pathogenic or endogenous LRRK2 on tau metabolism, pathology and neurodegeneration in mouse brain

Authors: A. TRAN NGUYEN[1], G. DANIEL[2], P. VALDES[2], B. SCHNEIDER[2], *D. J. MOORE[1,2];

[1]Ctr. for Neurodegenerative Sci., Van Andel Res. Inst., Grand Rapids, MI; [2]EPFL, Lausanne, Switzerland

Abstract: Mutations in the leucine-rich repeat kinase 2 (LRRK2, PARK8) gene cause late-onset, autosomal dominant Parkinson's disease (PD) and represent the most common cause of familial PD. Common variation at the LRRK2 genomic locus also contributes to the risk of idiopathic PD. LRRK2 mutations typically give rise to alpha-synuclein-positive Lewy body pathology in the brains of PD subjects yet in some subjects mutations can instead precipitate tau-positive pathology characteristic of certain neurodegenerative tauopathies. Furthermore, the overexpression of mutant LRRK2 in some transgenic mouse models can produce alterations in the phosphorylation and levels of endogenous tau in the brain. These observations suggest that LRRK2 mutations can potentially regulate tau metabolism, aggregation and pathology yet the nature of this interaction is poorly defined. To further explore the interaction of LRRK2 and tau *in vivo*, we crossed a well-characterized P301S-tau transgenic mouse model with G2019S-LRRK2 transgenic and LRRK2 knockout (KO) mice. We have assessed the impact of pathogenic and endogenous LRRK2 on the steady-state levels, detergent solubility and phosphorylation of human tau in multiple brains regions at 6 months of age prior to disease-onset in the P301S-tau mice. G2019S-LRRK2 or LRRK2 deletion has minimal effects on human tau levels, solubility or phosphorylation throughout the brain. To complement these models, we have delivered AAV2/6 vectors expressing human P301S-tau to the hippocampal CA1 region of G2019S-LRRK2 transgenic and LRRK2 KO mice. At 8 weeks post-injection, P301S-tau expression induces the degeneration of CA1 pyramidal neurons and tau pathology in these mice. We are currently conducting unbiased stereological analysis of CA1 neuronal number and tau pathology to determine the impact of pathogenic and endogenous LRRK2 on tau-induced neurodegeneration. Our studies aim to clarify the role of LRRK2 in regulating tau metabolism and aggregation in the brain which could provide important insight into the pathophysiological mechanisms underlying LRRK2 mutations in PD.

Disclosures: **A. Tran Nguyen:** None. **G. Daniel:** None. **P. Valdes:** None. **B. Schneider:** None. **D.J. Moore:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.06

Topic: C.03. Parkinson's Disease

Support: CIHR Canada Graduate Scholarship - Master's Program

Title: LRRK2 modulates α-synuclein toxicity *in vitro* and *in vivo*

Authors: *S. MACISAAC[1,2], A. MILNERWOOD[1,2], M. VOLTA[1,2], S. BERGERON[1], E. MITCHELL[1], I. TATARNIKOV[1,2], M. FARRER[1,3];
[1]Neurosci., Ctr. For Applied Neurogenetics, Vancouver, BC, Canada; [2]Div. of Neurology, Fac. of Med., [3]Dept. of Med. Genetics, Fac. of Med., Univ. of British Columbia, Vancouver, ON, Canada

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder with a prevalence of between 2-5% in people over age 65. PD is pathologically defined by the death of dopaminergic nigrostriatal neurons with Lewy bodies composed primarily of misfolded a-synuclein (a-syn) in surviving neurons. The most common genetic cause of PD is mutation of the gene that encodes leucine-rich repeat kinase 2 (LRRK2), a large, multi-domain protein with functions in vesicular recycling and neurotransmitter release. The LRRK2 G2019S mutation, which increases LRRK2 kinase activity, is the most common PD-causing mutation worldwide. We are currently investigating a-syn fibril-induced pathology *in vitro* and *in vivo*, and whether LRRK2 modulates this phenotype. Addition of synthetic a-syn pre-formed fibrils (PFFs) to primary neuronal cultures has been previously shown to induce aggregation of a-syn, neuronal network dysfunction, and eventual neuronal death. We are examining differences in the response of wild type, LRRK2 knockout (LKO), and LRRK2 G2019S knockin (GKI) primary cortical neurons to PFFs to elucidate if LRRK2 is involved in cellular response to a-syn insult, and if this may be relevant to the neuropathology of genetic PD. We are concurrently examining consequences of a-syn insult *in vivo* with behavioural testing following striatal injection of PFFs in nontransgenic, LKO, and GKI mice. This information could be crucial in the characterization of early molecular disease correlates and in the design of therapeutic and neuroprotective strategies for synucleinopathies.

Disclosures: S. MacIsaac: None. **A. Milnerwood:** None. **M. Volta:** None. **S. Bergeron:** None. **E. Mitchell:** None. **I. Tatarnikov:** None. **M. Farrer:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.07

Topic: C.03. Parkinson's Disease

Support: CIHR 201109 MOP 260124

Title: Neurotransmitter receptor trafficking and synapse maintenance in the p.D620N knock-in mouse model of Parkinson's disease

Authors: C. KADGIEN[1], L. MUNSIE[1], I. TATARNIKOV[1], D. BECCANO-KELLY[2], J. KHINDA[3], S. MACISAAAC[1], M. FARRER[2], *A. J. MILNERWOOD[4];
[1]Grad. Program in Neuroscience, Ctr. for Applied Neurogenetics & Brain Res. Ctr., [2]Dept Med. Gen. Ctr. for Applied Neurogenetics & Brain Res. Ctr., [4]Neurology, Ctr. for Applied Neurogenetics & Brain Res. Ctr., [3]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The pathogenic D620N (DN) mutation in vacuolar protein sorting 35 (VPS35) is linked to late-onset, autosomal-dominant Parkinson's disease (PD). VPS35 is a core component of the retromer complex, involved in endosomal recycling and intracellular trafficking. Data from our overexpression model suggests that the mutation confers a loss of function upon AMPA-type glutamate receptor (AMPAR) recycling, resulting in aberrant synaptic connectivity. Here we explore differences in binding of known and novel retromer cargoes and early synaptic dysfunction in a novel D620N knock-in mouse model of PD. Western blot and co-immunoprecipitation were performed in tissue from wild-type and mutant mice to explore differences in binding of neurotransmitter receptors and known VPS35 interactors. We found mutation-specific alterations to VPS35 binding with multiple neurotransmitter receptors as well as to FAM21, a regulatory component of the WASH complex. Fluorescence recovery after photobleaching was used to assay AMPAR surface recycling. Whole-cell patch clamp and immunocytochemistry were used to explore differences in synapse number and efficacy in div 21 cultured neurons. Mutant cortical neurons had altered surface recycling of AMPARs and glutamate transmission relative to wild-type controls. We conclude that the D620N mutation alters binding to several neurotransmitter receptors, and alters glutamatergic synapse maintenance in cultured cortical cells. Many genes linked to PD appear involved in synaptic transmission; thus, understanding the neurophysiological role of VPS35 and the effects of VPS35 mutations may uncover pathophysiological processes that lead to neurodegeneration in PD

Disclosures: C. Kadgien: None. **L. Munsie:** None. **I. Tatarnikov:** None. **D. Beccano-Kelly:** None. **J. Khinda:** None. **S. MacIsaaac:** None. **M. Farrer:** None. **A.J. Milnerwood:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.08

Topic: C.03. Parkinson's Disease

Support: CIHR

Parkinson's Society Canada

Title: Activity-dependent plasticity of glutamatergic synapses in cortico-striatal co-cultures from G2019S LRRK2 transgenic mice

Authors: *N. KUHLMANN[1], A. MILNERWOOD[2], M. FARRER[3];
[1]Neurosci., [2]Neurol., [3]Med. Genet., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Striatal synaptic plasticity and dendritic spine morphology are implicated in numerous psychiatric and neurodegenerative disorders, including Parkinson's Disease (PD). However, few studies have explored the molecular mechanisms underlying this plasticity, particularly within the context of PD-linked gene mutations. We recently reported that mutations in the protein leucine rich repeat kinase 2 (LRRK2; the most common genetic risk factor for PD) alter synaptic activity of cortical neurons in cultures from LRRK2 G2019S knock-in mice: glutamatergic transmission was increased, and the phosphorylation status of presynaptic proteins was reduced. Here, we first developed assays to examine NMDAR-dependent long-term potentiation (LTP) and mGluR1/5 dependent long-term depression (LTD) in cortico-striatal co-cultures from non-transgenic mice. We quantified striatal spiny projection neuron (SPN) spine morphology and density by confocal microscopy to examine the activity-dependence of structural plasticity, and measured changes in synaptic proteins, including surface expression of glutamate receptors. In neurons from non-transgenic mice, LTP increased spine density and AMPA-type glutamate receptor subunit density/intensity; the reverse was observed for LTD. We then extended these findings into cultures from G2019S knock-in mice to determine how LRRK2 may regulate cortico-striatal plasticity and morphology, and additionally examined electrophysiological changes. This study provides a launching point and the necessary assays to further investigate the role of LRRK2 in striatal plasticity, and how this may contribute to PD pathology.

Disclosures: N. Kuhlmann: None. **A. Milnerwood:** None. **M. Farrer:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.09

Topic: C.03. Parkinson's Disease

Title: Effects of tyrosine hydroxylase overexpression in transgenic mice

Authors: *L. M. VECCHIO[1], M. K. BERMEJO[1], A. J. RAMSEY[1], G. W. MILLER[2], A. SALAHPOUR[1];
[1]Dept. of Pharmacol. and Toxicology, Univ. of Toronto, Toronto, ON, Canada; [2]Div. of Biol. and Biomed. Sciences, and Dept. of Envrn. Hlth., Emory Univ., Atlanta, GA

Abstract: The neuropathology of Parkinson's disease is characterized by profound degeneration of dopamine (DA) and noradrenaline cells. While oxidative stress is believed to contribute to the pathology of the disease, why dopaminergic and noradrenergic neurons are particularly susceptible remains unclear. Tyrosine hydroxylase (TH) is an enzyme specifically expressed in catecholamine neurons, and is the rate-limiting enzyme in the production of both DA and noradrenaline. A pathological role of TH has been suggested, as H2O2 and other reactive oxygen species are known by-products of its reaction. Dysregulation of TH activity can also lead to the accumulation of free cytosolic dopamine, known to be neurotoxic. Here, we have created and characterized a mouse over-expressing TH with the aim of assessing the potential contribution of increased levels to oxidative stress and the specific loss of catecholamine neurons. Using bacterial artificial chromosomal transgenesis, we developed a transgenic mouse with six total copies of the TH gene (TH-HI), resulting in both a three-fold increase in mRNA ($p<0.0001$) and in TH protein levels (midbrain and striatum, all $p\leq0.01$). To confirm that the produced TH was functional, we showed that there was a significant increase in the accumulation of L-DOPA in TH-HI mice following administration of NSD-1015, a dopa-decarboxylase inhibitor ($p<0.00001$). The mice also demonstrate behavioural changes consistent with increased DA production, including a potentiated locomotor and stereotypic response to amphetamine (2.0 and 3.0 mg/kg, $p<0.001$ for all). Striatal tissue content of DA and its metabolites, homovanillic acid and 3,4-dihydroxyphenylacetic acid, were also measured by high-performance liquid chromatography. Importantly, at 4 weeks of age, DA content was significantly higher in transgenic mice than wildtype counterparts ($p=0.018$); however, there was no significant change in DA tissue content beyond 10 weeks ($p=0.99$). A loss in tissue content of DA may be suggestive of dopaminergic cell loss. Striatal tissue content of metabolites remained significantly higher at both time points, as did the ratio of metabolite to DA, which could indicate an increased DA turnover and may be predictive oxidative stress ($p\leq0.001$ for all). To our knowledge, the mice described here are the first to successfully over-express TH *in vivo*. We aim to use this model to further evaluate if increased levels of TH can lead to oxidative stress and cell loss. In doing this, we therefore hope to establish, proof-of-principle, if TH could represent a target for therapeutic intervention.

Disclosures: L.M. Vecchio: None. **M.K. Bermejo:** None. **A.J. Ramsey:** None. **G.W. Miller:** None. **A. Salahpour:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.10

Topic: C.03. Parkinson's Disease

Support: The Lundbeck Foundation

The Michael J. Fox Foundation

Title: A novel transgenic mouse line co-expressing alpha-synuclein and p25alpha displays increased oligomer formation

Authors: L. BERKHOUDT LASSEN[1], *P. H. JENSEN[1], C. BETZER[2], T. MOOS[3];
[1]Univ. Aarhus, Aarhus-C, Denmark; [2]Aarhus Univ., Aarhus, Denmark; [3]Aalborg Univ., Aalborg, Denmark

Abstract: The molecular state of alpha-synuclein (AS) changes in the course of neurodegenerative synucleinopathies, where it ultimately deposits in intracellular Lewy-like inclusions as filamentous aggregates. Soluble oligomeric aggregates are formed in the process of aggregation and are considered toxic species that cause a range of cell-autonomous effects and tissue responses including prion-like spreading. We have previously demonstrated that p25alpha stimulates aggregation of AS, so we generated a mouse model of enhanced oligomer formation by expressing low level human p25alpha in forebrain neurons together with human AS from the Thy1 promoter (Rosa26-p25α/Nex-Cre/Thy1-AS) (AS-p25alpha mice). As control mice, we use mice 1) without p25alpha but with the same level of AS overexpression (Thy1-AS mice) and 2) with p25alpha but without human AS (Rosa26-p25alpha mice). Preliminary data shows that p25alpha augments the phenotype of Thy1-AS mice as AS-p25alpha mice have severe difficulties turning and initiating movement in the pole test. Increased ser129 phosphorylated AS is associated with aggregated AS in disease, and immunohistochemical analysis reveals that S129 phosphorylated AS is increased in brain regions where p25alpha and human AS is co-expressed of AS-p25alpha mice. Immunoblotting confirms increased S129 phosphorylated AS in total brain extracts of AS-p25alpha mice. Biochemically, we can demonstrate a significant AS oligomer formation in the AS-p25alpha mice compared to the Thy1-AS mice as determined by a sucrose density sedimentation assay. Differential extraction analysis of brain tissues supports this finding, as we find increased SDS extractable AS in AS-p25alpha mice We first want to determine if the enhanced p25alpha induced AS aggregation is taking place in the presynaptic compartment and use the mice to study effects induced by AS aggregates initiating from this site.

Their down-stream toxic signalling may uncover neuroprotective strategies to be exploited to identify future drug targets.

Disclosures: L. Berkhoudt Lassen: None. **P.H. Jensen:** None. **C. Betzer:** None. **T. Moos:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.11

Topic: C.03. Parkinson's Disease

Support: Italian Ministry of Health (Giovani Ricercatori 2009), Italian Ministry of Instruction, University, and Research (MIUR) (PRIN 2010, 2011), and Istituto Nazionale Assicurazione contro Infortuni sul Lavoro (INAIL, project 2/2009) to A.P.

Italian Ministry of Health (Ricerca Corrente 2013, Ricerca Finalizzata Malattie Rare 2008, and Giovani Ricercatori 2009), the Italian Telethon Foundation (GGP10140), and MIUR (FIRB Accordi di Programma 2010) to E.M.V.

NS 041779 from the National Institutes of Health to J.S.

(NIH/ORIP) OD P51OD011132 to YS

Title: PINK1 gene mutations differentially impair striatal dopamine-dependent synaptic plasticity

Authors: *G. MADEO[1,2], M. MALTESE[1], G. MARTELLA[1,2], E. VALENTE[3,4], J. SHEN[5], M. FEDERICI[2], N. MERCURI[1,2], A. SHIBATA[6], Y. SMITH[6], P. BONSI[2], A. PISANI[1,2]; [1]Univ. of Rome Tor Vergata, Rome, Italy; [2]Neurophysiol. and Plasticity Lab., Fondazione Santa Lucia IRCCS, Rome, Italy; [3]Mendel Lab., Inst. di Ricovero e Cura a Carattere Scientifico, Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; [4]Dept. of medicine and Surgery, Univ. of Salerno, Salerno, Italy; [5]Ctr. for Neurologic Diseases, Brigham and Women's Hospital, Program in Neurosci., Harvard Med. Sch., Boston, MA; [6]Yerkes Natl. Primate Res. Center, Dept Neurol. and Udall Ctr. of Excellence for Parkinson's Disease, Emory Univ., Atlanta, GA

Abstract: Homozygous and compound heterozygous mutations in PTEN-induced kinase (PINK1) gene are responsible for an autosomal recessive early-onset Parkinson's disease (PD) and represent a well defined susceptibility risk factor for sporadic PD. PINK1 gene encodes for a

mitochondrial protein kinase with established neuroprotective functions that is known to counteract stress-induced apoptotic neuronal death and sustain synaptic transmission by regulating mitochondrial homeostasis and wellness. Compelling evidence from both human and animal studies points out to defects of synaptic vesicular functions and mitochondria dynamics as early determinants influencing the susceptibility of dopaminergic neurons to neurodegeneration in PD. We provide a multidisciplinary characterization of PINK1 mouse model carrying either heterozygous or homozygous PINK1 gene mutations, $PINK1^{+/-}$ and $PINK1^{-/-}$ mice respectively. By means of intracellular and whole-cell patch clamp recordings we characterized both short- and long-term changes in synaptic transmission at corticostriatal synapses. We demonstrated a specific pattern of changes in synaptic plasticity related to the PINK1 mutation state. Indeed, while striatal medium spiny neurons (MSNs) from $PINK1^{-/-}$ mice were not capable of expressing corticostriatal long-term depression (LTD) and potentiation (LTP), MSNs from $PINK1^{+/-}$ mice showed only a selective and partial reduction of the LTP magnitude. The dopamine release from nigrostriatal terminals is the main regulator of corticostriatal synaptic plasticity. We found a lower striatal dopamine content upon stimulation in both mutated groups of animals, suggesting that the reduced dopamine release might be the common factor underlying abnormalities of corticostriatal synaptic plasticity in these animals. We further characterized the possible source of changes in neurotransmitter release by an electron microscopy analysis. A slight reduction of the average surface area of individual synaptic vesicles in tyrosine hydroxylase (TH)-positive terminals was found in the striatum of mutated mice, suggesting that the vesicular content of dopamine may be reduced in nigrostriatal terminals of mutants. Our data clearly support the role of loss-of-function PINK1 mutations in regulating synaptic transmission at corticostriatal synapses through the impairment of nigrostriatal dopamine release. We suggest that PINK1 might disrupt synaptic neurotransmitter release by altering the synaptic vesicle dynamics. Further investigations of this pathway will provide insights in PD pathogenesis and will offer new molecular targets for preventive therapeutic approaches.

Disclosures: **G. Madeo:** None. **M. Maltese:** None. **G. Martella:** None. **E. Valente:** None. **J. Shen:** None. **M. Federici:** None. **N. Mercuri:** None. **A. Shibata:** None. **Y. Smith:** None. **P. Bonsi:** None. **A. Pisani:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.12

Topic: C.03. Parkinson's Disease

Support: The Michael J. Fox Foundation

Title: Longitudinal behavioral characterization of genetic mouse models of Parkinson's disease

Authors: *S. CATALDI[1], M. VOLTA[1], S. PASCHALL[1], S. BERGERON[1], M. J. FARRER[2], A. J. MILNERWOOD[1];
[1]Grad. program in Neurosci., [2]Med. Genet., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Parkinson Disease (PD) affects approximately 1% of the population by 65 years, increasing to 4-5% in 85-years-olds. PD is generally considered a multifactorial disorder that arises owing to a combination of genes and environmental factors. Many genes have been implicated in PD. SNCA encodes α-synuclein, the key component of Lewy body inclusions, which are the hallmark of PD. Linkage analysis identified PD-associated mutations and genomic multiplication of SNCA in familial, late-onset Lewy body PD where additional SNCA copies lead to earlier-onset and more pronounced Lewy body disease in which dementia is a prominent feature. Mutations in Leucine-rich repeat kinase 2 (LRRK2) are the most common genetic risk factor for PD, including substitutions R1441C and G2019S. LRRK2 has GTPase and kinase activity and has been implicated in striatal neurotransmission, neurite arborization, endocytosis and autophagy. The vacuolar protein sorting 35 (VPS35) D620N mutation has been shown to cause late-onset autosomal dominant parkinsonism, VPS35 is a critical component of the retromer system that mediates endosomal traffic of proteins to the trans-Golgi network, lysosome and plasma membrane. To evaluate the behavioral consequences of these PD protein mutations we performed comparative testing (at the same facility) of multiple transgenic mouse models; 1) LRRK2 G2019S knock-in mice (GKI) 2) LRRK2 R1441C knock-in mice (RKI), 3) VPS35 D620N knock-in mice (VKI) and 4) human SNCA (SNCA OE) overexpressing mice. Mice were examined at consistent, linear time points ranging from 1 to 12 months, in a constant in-house setting, by standardized testing to reduce variability in phenotype characterization. Behavioral assessments of motor activity (open-field, cylinder tests), learning and memory (novel object location and novel object recognition), and anxiety (open-field) were performed. *In vivo* microdialysis was also conducted to correlate behavioral deficits with neurotransmitter levels. Our behavior models represent a clear useful tool for the study of PD and may play a role in future studies for the discovery of new therapies. Data in RKI and GKI mice suggest the involvement of LRRK2 in the modulation of cognitive function and dopamine release. SNCA over-expression led to hyperactive behavior and increased dopamine release. These studies provide clearly defined, clinically relevant phenotypes that enable screening of small molecules targeted at symptoms control and slowing (or halting) disease progression.

Disclosures: S. Cataldi: None. **M. Volta:** None. **S. Paschall:** None. **S. Bergeron:** None. **M.J. Farrer:** None. **A.J. Milnerwood:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.13

Topic: C.03. Parkinson's Disease

Support: Cure Parkinson Trust UK

Title: Neuroprotective effects of lixisenatide and liraglutide in the MPTP mouse model of Parkinson's disease

Authors: *C. HOLSCHER[1], M. SHARMA[2], J. JALEWA[2], W. LIU[3], L. LI[3], G. LI[4]; [2]Biomed. and Life Sci., [1]Lancaster Univ., Lancaster, United Kingdom; [3]Key Lab. of Cell. Physiol., [4]Neurolog. Hosp., Shanxi Med. Univ., Taiyuan, China

Abstract: Glucagon-like peptide 1 (GLP-1) is a growth factor. GLP-1 mimetics are on the market as treatments for type 2 diabetes and are well tolerated. These drugs have shown neuroprotective properties in animal models of neurodegenerative disorders. In addition, the GLP-1 mimetic exendin-4 has shown protective effects in animal models of Parkinson's disease (PD), and a clinical pilot study in PD patients showed promising first results. Liraglutide and lixisenatide are two newer GLP-1 mimetics which have a longer biological half-life than exendin-4. We previously showed that these drugs have neuroprotective properties in an animal model of Alzheimer's disease. Here we demonstrate the neuroprotective effects in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD. MPTP was injected once-daily (20mg/kg i.p.) for 7 days, and drugs were injected once-daily for 14 days i.p.. Results: When comparing exendin-4 (10nmol/kg), liraglutide (25nmol/kg) and lixisenatide (10nmol/kg), it was found that exendin-4 showed no protective effects at the dose chosen. Both liraglutide and lixisenatide showed effects in preventing the MPTP- induced motor impairment (Rotarod, open field locomotion, catalepsy test), reduction in Tyrosine Hydroxylase (TH) levels (dopamine synthesis) in the substantia nigra and basal ganglia, a reduction of the pro-apoptotic signaling molecule BAX and an increase in the anti-apoptotic signaling molecule Bcl-2. The results demonstrate that both liraglutide and lixisenatide are superior to exendin-4, and both drugs show promise as a novel treatment of PD. The work has been supported by a project grant of the Cure Parkinson's Trust UK.

Disclosures: **C. Holscher:** None. **M. Sharma:** None. **J. Jalewa:** None. **W. Liu:** None. **L. Li:** None. **G. Li:** None.

Nanosymposium

647. Parkinson's Disease: Rodent Models I

Location: S405

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 647.14

Topic: C.03. Parkinson's Disease

Support: NYITCOM Intramural Grant

Title: Point of entry: a first step towards bacterial Parkinsonism

Authors: *J. R. LEHESTE, K. E. RUVOLO, M. CAUGHEY, M. GOLDFINGER, G. TORRES;
Biomed. Sci., NYIT Col. of Osteo. Med., Old Westbury, NY

Abstract: The circumstances of disease onset and progression of Parkinson's disease (PD) are largely obscure (> 90%). A common denominator among many neurodegenerative diseases is the occurrence of some level of chronic inflammation affecting the central nervous system (CNS). Dopamine (DA) producing neurons in the *substantia nigra pars compacta* of the midbrain are particularly vulnerable to inflammatory insults, likely because of the high degree of oxidative reactions involved in the synthesis of DA as well as the unusual density of immune-competent microglia. In a previous screen of *post mortem* brain sections of advanced-stage PD and matching control individuals (n=12 per group; Banner Sun Health Research Institute, Mayo Clinic, AZ), we established the intra-neuronal presence of the Gram positive anaerobe, *Propionibacterium acnes* (*P. acnes*), in the majority of PD samples (>83%) at more than twice the rate of controls. Furthermore, we were able to replicate this finding in cultured DA neuronal cells (SH-SY5Y) scored with transmission electron microscopy (TEM). Work by others on the initial cellular signs and progression of alpha-synuclein deposits in PD brains in combination with studies on natural weak spots in the blood brain barrier are suggestive of circumventricular organs (CMO), the olfactory system (OF) and the choroid plexus (CP) as potential points of entry for an opportunistic pathogen. To test this hypothesis, we administered intra-nasal and intra-venous injections of *P. acnes* and a control organism, *Staphylococcus epidermidis* (*S. epidermidis*), into wild type mice of various ages followed by immunohistochemical analyses of brain, blood and cerebrospinal fluid. Our results indicate that whereas both, *P. acnes* and *S. epidermidis*, appear to be capable of invading OF, CP and ventricular spaces, microglial activation and handling differed markedly between the two pathogens with *P. acnes* adopting a much more evasive strategy. Further tests in cultured microglial cell lines confirmed our *in vivo* observations and continue for the dissection of underlying mechanisms. These results confirm the OF and CP as entry points for opportunistic pathogens into the CNS and demonstrate

opportunistic success of *P. acnes* through immune-evasive mechanisms. The scope of this work is currently being expanded to explore a cause and effect relationship between intracranial *P. acnes* and PD. If consistent with our findings in *post mortem* human brain sections, intra-nigral *P. acnes* injections into mouse brains are projected to recapitulate much of the cellular signs and symptoms of PD.

Disclosures: J.R. Leheste: None. **K.E. Ruvolo:** None. **M. Caughey:** None. **M. Goldfinger:** None. **G. Torres:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.01

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH/NINDS Contract HHSN271200800033C

Title: The NINDS repository collection of patient-derived biomaterials available for neurodegenerative disease research

Authors: *C. A. PEREZ, K. REEVES, J. SANTANA, S. HEIL, A. GREEN, A. AMBERSON, D. HUBER, G. BALABURSKI;
NINDS Repository, Coriell Inst., Camden, NJ

Abstract: Neurological disorders are a major public healthcare concern. The pathophysiology of neurodegenerative disorders remains largely unknown while the limited availability of reliable disease models hinders progress leading to the identification of reliable genetic and molecular biomarkers for disease onset, diagnosis, progression and therapeutic response. The National Institute of Neurological Disorders and Stroke (NINDS) Repository was established in 2002 with the mission of providing high quality biospecimens as a strategy to facilitate and accelerate research in neurological diseases. The NINDS Repository collects biospecimens and de-identified clinical data from patients with neurological disorders as well as neurologically normal controls. In addition, the NINDS Repository features collections of patient-derived fibroblasts and induced pluripotent stem cells (iPSCs) with well-defined mutations as essential research tools for the establishment of cellular models. To further enhance the investigation and discovery of novel biomarkers the NINDS Repository also maintains extensive, long term longitudinal collections of biological samples such as plasma, serum, cerebrospinal fluid, and urine obtained from affected and neurologically healthy individuals. Since its establishment, biomaterials from

more than 46,000 individuals with cerebrovascular diseases, Parkinsonism, motor neuron diseases, epilepsy, Tourette syndrome, dystonia, Huntington's disease, frontotemporal degeneration and neurologically-normal controls have been banked in the NINDS Repository and are available at http://catalog.coriell.org/1/NINDS The NINDS Repository has established validated standard operating procedures and rigorous quality control assessments that span the life cycle of all biospecimens collected to provide premium samples. The NINDS Repository aims to ensure and implement standardization for collecting and processing across all samples without compromising patient safety and privacy. In addition, the NINDS Repository utilizes secure and integrated laboratory information management systems to monitor inventory, sample processing, storage, and distribution of biospecimens, and facilitates sample-data association by cross-referring with other resources such as dbGaP, etc. The development of such a centralized collection of human biospecimens and their associated de-identified clinical data allows the NINDS Repository to provide a vital resource for research designed to discover and validate genetic and molecular biomarkers relevant for the study and treatment of neurological disorders.

Disclosures: **C.A. Perez:** None. **K. Reeves:** None. **J. Santana:** None. **S. Heil:** None. **A. Green:** None. **A. Amberson:** None. **D. Huber:** None. **G. Balaburski:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.02

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIMH (MH090115)

Whitehall foundation

Mayo Clinic Center for Regenerative Medicine

Mayo foundation

Title: BubR1 mutant mice exhibit motor function deficits and Purkinje cell dysfunction

Authors: ***C. CHOI**[1], C. CHO[1], J. WELBY[1], B. JEON[1], M.-H. JANG[1,2];
[1]Dept. of Neurolog. Surgery, Mayo Clin., Rochester, MN; [2]Dept. of Biochem. and Mol. Biol., Mayo Clin. Col. of Med., Rochester, MN

Abstract: Aging is strongly associated with deficits in balance and motor coordination, leaving older adults prone to serious injury and a reduced quality of life. Despite extensive research, the underlying molecular mechanisms contributing to age-related motor function deficits remain poorly understood. Previously, the spindle assembly checkpoint protein BubR1 emerged as a novel genetic component contributing to aging-related pathology. Mutant mice expressing low levels of BubR1 (BubR1 hypomorphic or BubR1H/H mice) show an accelerated onset of aging-related features including reduced lifespan, cachectic dwarfism, sarcopenia, cataracts, craniofacial dysmorphisms, and heart arrhythmias. In addition, mutations in the human BUBR1 gene are linked to mosaic variegated aneuploidy (MVA) syndrome, a rare autosomal recessive disorder. Children with MVA syndrome exhibit low levels of BubR1 protein and display similar progeroid traits. Moreover, BubR1 expression in wild-type (WT) mice undergoes a marked reduction in multiple tissues throughout the natural aging process. Together, these observations suggest a key role for BubR1 in age-related pathologies. Although motor function deficits are frequently observed in aged populations, whether reductions in BubR1 contribute to such deficits is not known. Here we found that BubR1 is expressed within the adult mouse cerebellum and is significantly reduced with chronological aging. We further demonstrate that BubR1H/H mice show several features of motor function impairment such as severe coordination deficits, reduced locomotor activity, abnormal gait, hindlimb clasping, and reduced neuromuscular strength. At the cellular level, we found BubR1H/H mice exhibit cerebellar abnormalities including decreased Purkinje cell number and spine density. Given strong evidence that motor deficits commonly arise from cerebellar circuit dysfunction, we suggest that such cerebellar defects in BubR1 mutants contribute to motor function impairment. Collectively, our study identifies a novel role for BubR1 as a key component required for normal motor function and provides new insight into age-related neuropathology.

Disclosures: **C. Choi:** None. **C. Cho:** None. **J. Welby:** None. **B. Jeon:** None. **M. Jang:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.03

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH Grant 5R01NS083846-02

Title: A *Drosophila* model of CLN4B, a neurodegenerative adult-onset Neuronal Ceroid Lipofuscinosis, links CSPα's chaperone activity to toxicity

Authors: *E. IMLER[1], J. S. PYON[1], Y.-Q. ZHANG[3], S. S. CHANDRA[3,4], K. E. ZINSMAIER[1,2];
[1]Dept. of Neurosci., [2]Dept. of Mol. and Cell. Biol., Univ. of Arizona, Tucson, AZ; [3]Dept. of Neurol., [4]Dept. of Molecular, Cell. and Developmental Biol., Yale Univ., New Haven, CT

Abstract: Synaptic vesicle (SV)-associated cysteine-string protein α (CSPα)maintains synaptic function and is neuroprotective. CSPα recruits Hsc70 and activates its ATPase activity ensuring proper activity of SNARE proteins, dynamin and a limited number of other synaptic client proteins. Deletion of CSP in flies and mice causes progressive synaptic failure, paralysis, neuronal loss and premature death. Mutations in human CSPα (hCSPα, L115R and L116Δ) cause a dominant adult-onset form of Neuronal Ceroid Lipofuscinoses (ANCL, CLN4B), a progressive neurodegenerative disease with lysosomal pathology causing seizures, dementia, and early death. We have generated a *Drosophila* model of ANCL by transgenically expressing normal hCSPα and the CLN4B-causing mutations L115R and L116Δ in fly neurons. Normal hCSPα is functional in flies and can significantly restore defects of *Drosophila* CSP (dCSP) null mutants. Neuronal expression of hCSPα in wild type flies has no significant detrimental effects while CLN4B-mutant hCSPα induces neurodegeneration and reduces lifespan is a dose-dependent manner. Expression of hCSP-L115R and L116Δ induces the formation of abnormal SDS-resistant protein aggregates (>250 kD) containing both hCSPα and endogenous dCSP. CSP aggregates accumulate on late endosomes found at axon terminals, axons and neuronal somata in a dose-dependent manner and arrest the formation of functional lysosomes and/or autophagosomes. Electron microscopy images show numerous pathological structures including abnormally large autophagosome-like structures, multi-laminar membrane “whirls”, large osmophillic bodies and widespread degeneration. To define mechanisms that contribute to CLN4B-induced neurodegeneration, we are conducting F1 dominant gain- and loss-of-function genetic modifier screens. So far, we have identified a number of candidate genes that enhance or suppress the phenotypic effects of hCSP-L116Δ expression. Interestingly, some of these are associated with CSP’s synaptic function, indicating a tight link between ANCL/CLN4B disease pathology and CSP function.

Disclosures: E. Imler: None. **J.S. Pyon:** None. **Y. Zhang:** None. **S.S. Chandra:** None. **K.E. Zinsmaier:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.04

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: RC4NS073009

R21NS081182

R01NS033123

R37NS033123

R56NS033123

Title: Antisense oligonucleotides lowering ATXN2 expression for the treatment of spinocerebellar ataxia type 2 (SCA2)

Authors: *D. R. SCOLES[1], M. SCHNEIDER[1], P. MEERA[2], K. FIGUEROA[1], M. H. T. HO[1], G. HUNG[3], F. RIGO[3], C. BENNETT[3], T. OTIS[2], S. PULST[1];
[1]Dept. of Neurol., Univ. of Utah, Salt Lake City, UT; [2]Univ. of California Los Angeles, Los Angeles, CA; [3]Isis Pharmaceuticals, Inc., Carlsbad, CA

Abstract: SCA2 is an inherited disorder caused by CAG repeat expansion in an encoded region of the ATXN2 gene resulting in polyglutamine expansion and gain of toxic function. We hypothesize that lowering overall ATXN2 expression using antisense oligonucleotides (ASOs) would be therapeutic for SCA2. Objective: To demonstrate that lowering ATXN2 expression modifies molecular, motor, and neurophysiological phenotypes of SCA2 mice. Methods: We screened >100 ASOs designed to lower ATXN2 expression *in vitro* in HepG2 cells. ATXN2-Q127 transgenic mice were treated by intracerebroventricular (ICV) injection of ASOs. ASO effects on established ATXN2-Q127 mouse phenotypes were determined: Motor phenotypes were studied by rotarod testing, cerebellar molecular phenotypes were determined by qPCR, and Purkinje cell firing frequencies were determined by extracellular recordings in acute cerebellar slices. Results: Three ASOs lowered ATXN2 expression in ATXN2-Q172 transgenic mice, the best by >80% after 7 d, without evidence of toxicity (Iba1 activation). ATXN2 remained significantly reduced after 21 wks. Immunohistochemical staining of ASOs using anti-ASO antibody demonstrated ASO localization in Purkinje cells. ASOs also localized in motor neurons throughout the spinal cord and spinal cord ATXN2 expression was significantly reduced. ATXN2-Q172 mice treated 13 weeks with ATXN2 ASO had delayed motor phenotype onset (rotarod), and normal pacemaking Purkinje cell firing frequencies, unlike saline treated control mice. Conclusions: We identified ASOs that potently lower ATXN2 expression resulting in delayed progression of SCA2 phenotypes in ATXN2 transgenic mice. Ongoing studies include screens for more efficacious ASOs and determination of ASO effects on the SCA2 phenotypes in SCA2 BAC transgenic mice.

Disclosures: **D.R. Scoles:** None. **M. Schneider:** None. **P. Meera:** None. **K. Figueroa:** None. **M.H.T. Ho:** None. **G. Hung:** None. **F. Rigo:** None. **C. Bennett:** None. **T. Otis:** None. **S. Pulst:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.05

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH Grant T32HD007470

NIH Grant T32GM007618

CIRM Grant TG2-01153

Consortium for Frontotemporal Dementia Research

Taube-Koret Center

Hellman Family Foundation Alzheimer's Disease Research Program

Roddenberry Stem Cell Program

Title: The kinase RIPK1 regulates progranulin levels

Authors: *A. R. MASON[1,2,3,4], L. ELIA[1,2], S. FINKBEINER[1,2,5];
[1]Gladstone Inst. of Neurolog. Dis., San Francisco, CA; [2]Taube-Koret Ctr., San Francisco, CA; [3]UCSF DSCB Grad. Program, San Francisco, CA; [4]UCSF Med. Scientist Training Program, San Francisco, CA; [5]UCSF Departments of Physiol. and Neurol., San Francisco, CA

Abstract: Among the known genetic causes of frontotemporal dementia (FTD), progranulin (PGRN) haploinsufficiency is one of the most common. One potential approach to treating PGRN-deficient FTD is increasing PGRN levels. We performed a siRNA-based screen of the mouse kinome to identify genes that, when knocked down, lead to increased levels of extracellular progranulin. We identified receptor-interacting serine-threonine kinase 1 (RIPK1) as a regulator of PGRN levels. Eight distinct siRNAs against RIPK1 each increase extracellular PGRN levels in Neuro-2a cells, confirming RIPK as a genetic modifier of PGRN levels. This effect is not due to changes in cell number or changes in global secretion. Knockdown of RIPK1 with shRNA increases extracellular PGRN in primary mouse cortical neurons. RIPK1

knockdown does not change PGRN mRNA levels, indicating that RIPK1 regulates PGRN through a non-transcriptional mechanism. Additionally, RIPK1 knockdown leads to an increase in both intra- and extra-cellular PGRN, indicating that RIPK1 does not change the rate of PGRN secretion. Preliminary data indicates that kinase function may not be required for the effects of RIPK on PGRN. Future studies will determine which domains of RIPK1 and which downstream signaling pathways are involved in PGRN regulation. Primary support for this work was from the California Institute of Regenerative Medicine (A.R.M.), and the Consortium for Frontotemporal Dementia (S.F.). Additional support was provided by the Taube-Koret Center (S.F.), the Hellman Family Foundation Alzheimer's Disease Research Program (S.F.) and the Roddenberry Stem Cell Program (S.F.).

Disclosures: **A.R. Mason:** None. **L. Elia:** None. **S. Finkbeiner:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.06

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Academy of Finland

Sigrid Juselius Foundation

VTR funding of Kuopio University Hospital

Strategic Funding of the University of Eastern Finland (UEF-Brain)

Title: Characterization of the expression and interactions of C9orf72 protein isoforms in neuronal cells and human brain

Authors: ***A. HAAPASALO**[1], M. TAKALO[1], S. LESKELÄ[1], M. MARTTINEN[1], H. SOININEN[1,2], M. HILTUNEN[1], A. M. REMES[1,2];
[1]Univ. of Eastern Finland, Kuopio, Finland; [2]Kuopio Univ. Hosp., Kuopio, Finland

Abstract: Frontotemporal lobar degeneration (FTLD) is a heterogeneous group of neurodegenerative syndromes affecting frontal and temporal lobes and leading to dementia. At molecular level, FTLD pathogenesis is suggested to involve impairment of protein degradation pathways, including the proteasome, leading to formation of intracellular inclusions containing e.g. TDP-43, FUS and ubiquilin proteins. Recently, hexanucleotide repeat expansion in

C9ORF72 gene was identified as a major cause of FTLD and amyotrophic lateral sclerosis. The expansion is suggested to contribute to disease pathogenesis via mechanisms involving haploinsufficiency and aberrant RNA metabolism and protein translation. Physiological functions of C9orf72 protein are not well known, but it may control endosomal trafficking. Here, we have used overexpression of the two C9orf72 protein isoforms A and B to investigate their expression, subcellular localization, and relationship with other FTLD-associated proteins in neuronal SH-SY5Y cells under normal conditions or proteasome inhibitor-induced proteasomal impairment. Human frontal cortex samples were used to examine levels of C9orf72 isoforms and other FTLD-associated proteins in relation to presence or absence of C9ORF72 repeat expansion. Levels of both C9orf72 isoforms significantly increased after proteasomal inhibition, implying that their cellular levels are regulated by proteasomal degradation. There were no signs of C9orf72 aggregation in the cells. We found no differences in the protein levels of TDP-43 or FUS in isoform A or B overexpressing cells in either conditions compared to control cells. However, overexpression of isoform A, but not B, led to significantly decreased ubiquilin-1 levels under both conditions. Microscopy revealed that isoform B was evenly distributed in the cytoplasm, while A was clearly localized in intracellular vesicles. These results suggest that subcellular localization and protein interactions of isoform A and B may differ. Protein levels of TDP-43 or FUS were not altered in correlation with the repeat expansion in human brain, but ubiquilin-1 levels were lower in expansion carriers. Using a commercially available antibody, we observed no significant differences in C9orf72 isoform levels in expansion carriers and non-carriers. Interestingly, C9ORF72 mRNA levels were decreased in human temporal cortex in relation to the progression of neurofibrillary pathology. Taken together, our studies provide novel data on the expression and biology of the two C9orf72 protein isoforms in neuronal cells and human brain.

Disclosures: **A. Haapasalo:** None. **M. Takalo:** None. **S. Leskelä:** None. **M. Marttinen:** None. **H. Soininen:** None. **M. Hiltunen:** None. **A.M. Remes:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.07

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Tornspiran Foundation

Title: Altered Na+ homeostasis lead to neuronal hyperexcitability in a cellular model of Rapid onset Dystonia Parkinsonism

Authors: E. AKKURATOV[1], M. ANDERSSON[2], T. LIEBMANN[1], M. LINDSKOG[1], H. BRISMAR[2], A. APERIA[1], *N. P. FRITZ[2];
[1]Karolinska Institutet, Solna, Sweden; [2]KTH the Royal Inst. of Technol., Solna, Sweden

Abstract: Mutations in ATP1A3, the gene encoding the neuron-specific sodium-potassium pump Na^+, K^+, ATPase alpha 3 subunit (Na,K-ATPase alpha3), lead to the debilitating brain disorder, Rapid-onset Dystonia-Parkinsonism (RDP). Symptoms, including dystonia and cognitive disorders, are triggered by intense stress. The Na,K-ATPase exports three Na^+ ions and imports two K^+ ions for each ATP hydrolyzed. In neurons, the energetic costs of action potentials mainly arise from the ATP required for the Na,K-ATPase to restore the resulting electrochemical gradients and approximately 50% of brain energy consumption is used for the turn-over of Na,K-ATPase. Notably, the most common mutation observed in RDP patients, T613M, is located close to the nucleotide-binding domain. Complementary approaches were used here to investigate the molecular mechanisms of RDP and create a relevant cellular model of the disease. We performed molecular dynamics simulations of the wild-type or T613M mutant Na,K-ATPase alpha3 and predict that the T613M mutant is structurally unstable around the ATP binding site, which can affect forward cycling of the protein and ion transport. Live imaging experiments using the Na^+-sensitive dye ANG2 were then performed to analyze intracellular Na^+ (Na_i) homeostasis in primary cultures of hippocampal neurons expressing fluorescently tagged wild-type or T613M mutant Na,K-ATPase alpha3. Expression of T613M leads to robust changes in both baseline Na_i and rate of Na_i recovery after challenges that specifically activate the Na,K-ATPase or provoke and mimic intense neuronal activity. Finally, analysis of both resting membrane potential and spontaneous spiking activity during current clamp recordings supports the conclusion that T613M-expressing neurons that have a higher resting membrane potential are prone to respond to depolarization with higher frequency action potential firing. Thus, our study shows that the pathophysiology of RDP can involve altered nucleotide binding, increased intracellular Na_i, decreased maximum rate of restoration of Na_i leading to increased neuronal excitability which during severe stress that triggers RDP can result in neuronal malfunction.

Disclosures: E. Akkuratov: None. **M. Andersson:** None. **T. Liebmann:** None. **M. Lindskog:** None. **H. Brismar:** None. **A. Aperia:** None. **N.P. Fritz:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.08

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH R01 NS082265

Burroughs Wellcome Fund

NIH F31-NS086428

Title: Increased expression of the frontotemporal dementia risk factor TMEM106B causes C9orf72-dependent alterations in lysosomes and autophagosomes

Authors: ***A. S. CHEN-PLOTKIN**, J. BUSCH, T. UNGER, N. JAIN, T. SKRINAK, R. CHARAN;
Neurol., Univ. of Pennsylvania Dept of Neurol., Philadelphia, PA

Abstract: Frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP) is an important cause of dementia in individuals under age 65. Common variants in the minimally characterized TMEM106B gene were previously discovered by genome-wide association to confer genetic risk for FTLD-TDP (p=1x10-11, OR=1.6). In addition, evidence suggests that TMEM106B variants increase risk for developing FTLD-TDP by increasing TMEM106B expression levels. To further understand the role of TMEM106B in disease pathogenesis, we therefore investigated the cell biological effects of increased TMEM106B expression. Here, we report that increased TMEM106B expression results in a decrease in the average number of late endosomes/lysosomes per cell, loss of lysosomal acidification, and impaired lysosomal degradation. Taken together, these results indicate a decrease in the functional lysosomal pool, with cytotoxic consequences for cells with increased TMEM106B expression. In addition, lysosomal deficits are accompanied by the appearance of enlarged organelles (>2-3μm) demonstrating ultrastructural characteristics of late autophagic vacuoles (autolysosomes/amphisomes), with a concomitant increase in the number of autophagosomes and autolysosomes. We observed these effects in both immortalized cell lines and in primary neurons over-expressing TMEM106B. Furthermore, we show that the effects of increased TMEM106B expression can be abrogated by (1) point mutations to a lysosomal sorting motif in TMEM106B newly identified here, or (2) knockdown of C9orf72 protein. In sum, our results suggest that TMEM106B exerts its effects on FTLD-TDP disease risk through alterations of lysosomal and autophagic pathways and that TMEM106B and C9orf72 may interact in disease pathophysiology.

Disclosures: **A.S. Chen-Plotkin:** None. **J. Busch:** None. **T. Unger:** None. **N. Jain:** None. **T. Skrinak:** None. **R. Charan:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.09

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH Grant R01 NS085770

Louis Family Foundation

Title: MRI of mouse model of TDP-43 shows widespread volume loss at 10 weeks of age

Authors: *L. WANG[1], T. RUSSELL[1], A. WATERS[1], D. PROCISSI[2], H. DONG[1], K. R. SADLEIR[3], L. KUKREJA[4], J. G. CSERNANSKY[1], M. MESULAM[4], R. J. VASSAR[3], C. GEULA[4];
[1]Psychiatry, [2]Radiology, [3]Cell and Mol. Biol., [4]Cognitive Neurol. and Alzheimer's Dis. Ctr., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Frontotemporal lobar degeneration (FTLD) is a heterogeneous group of disorders whose clinical manifestations include behavioral variant FTD, primary progressive aphasia, corticobasal degeneration and progressive supranuclear palsy. Neuropathologically, FTLD is associated with accumulations of tau, TDP-43 or FUS proteins. Further, brains of patients with FTLD exhibit pronounced atrophy in the frontal and anterior temporal lobes. The ability to understand the specific relationships between brain atrophy patterns (i.e., neuroimaging biomarker), protein inclusions (i.e., neuropathological markers), and clinical diagnoses would be important when we have the ability to treat and manage individual patient's specific disease. As part of a series of studies aimed at understanding these relationships and disease mechanisms, we utilized a conditional transgenic mouse model of human TDP-43 (hTDP-43) overexpression. We performed a preliminary analysis of brain regional volumes using magnetic resonance imaging (MRI), focusing on the hippocampus and insular cortex due to their involvement in human FTLD (McKhann et al., 2001; Hatanpaa et al., 2004). Five inducible hTDP-43-overexpressing transgenic mice (Cannon et al., 2012) in which hTDP-43 expression was induced after weaning (21 days of age) and seven controls, all at 10 weeks of age, were anesthetized and imaged on a 9.4T Bruker MRI small-animal scanner, using a respiratory gated 3D gradient echo sequence (FLASH) at an isotropic resolution of 120 um^3. Three repetitions of this sequence were acquired and averaged. Bilateral hippocampus and insular cortex were manually segmented using DTI Studio software suite according to a stereotaxic atlas. Areas of single slices through the midsagittal plane were used as proxies for total brain volume. Statistical analyses were performed using SPSS software. No significant difference was seen in the midsagittal slice area between the control (63.9 ± 0.5 mm^2) and the TDP-43 overexpressing mice (64.0 ± 0.7 mm^2).

The TDP-43 overexpressing mice showed significantly reduced hippocampal (controls: 18.0 ± 0.2 mm^3, TDP-43: 17.3 ± 0.3 mm^3; $p = 0.043$), and insular cortex (controls: 5.54 ± 0.11 mm^3, TDP-43: 4.82 ± 0.08 mm^3; $p = 0.001$) volumes as compared to controls. Reliability was demonstrated through repeat segmentations (Cronbach's alpha = 0.81 for hippocampal volume, and 0.94 for insular cortex slices). This study demonstrates that TDP-43 overexpression is associated with volume reductions in specific mouse cortical areas. The relationship between cortical volume loss and level of TDP-43 expression and density of inclusions requires future experimental attention.

Disclosures: L. Wang: None. **T. Russell:** None. **A. Waters:** None. **D. Procissi:** None. **H. Dong:** None. **K.R. Sadleir:** None. **L. Kukreja:** None. **J.G. Csernansky:** None. **M. Mesulam:** None. **R.J. Vassar:** None. **C. Geula:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.10

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Title: Nuclear family sequencing in Multiple System Atrophy identifies novel genes associated with disease

Authors: M. J. HUENTELMAN, I. SCHRAUWEN, J. J. CORNEVEAUX, K. M. RAMSEY, *A. L. SINIARD;
Tgen, Phoenix, AZ

Abstract: Multiple System Atrophy (MSA) is a rare aggressive neurodegenerative disorder with adult onset. It can be characterized by a mixture of autonomic failure, ataxia, and parkinsonism. The two main disease subtypes can be distinguished clinically as "MSA-P" (predominant parkinsonism) or "MSA-C" (dominant cerebellar features). Both are associated with significant decline in dopamine transporter levels during disease progression. The cardinal pathology of MSA is glial cytoplasmic inclusions enriched for alpha-synuclein protein. The cause of MSA is unknown but is likely due to the combination of heritable and environmental factors. To investigate the heritable risk factors associated with MSA we decided to study nuclear families with one affected individual. Due to the midlife onset of the disorder a significant number of cases are diagnosed when the affected individual's parents are still living. Three nuclear families were analyzed by exome sequencing. By using a selective filtering and variant prioritization approach, we attempted to identify variants that met one or more of the following criteria: (1)

family specific variants or ones present at a very low frequency in the population (ExAc MAF <0.05), (2) variants predicted to have a damaging effect on the protein (CADD >11), and (3) familial segregation consistent with a digenic heterozygous inheritance model. In two families, variants were found in LRRK2 and SLC6A3 (aka DAT, dopamine transporter) or LRRK2 and SLC6A2 (aka NET, norepinephrine transporter). Mutations in LRRK2 have previously been associated with Parkinson's disease (PD) risk. Additionally, LRRK2 is known to regulate synaptogenesis and dopamine receptor activation. In the third family, we identified two variants in different voltage-gated calcium channel subunits, CAV1.3 and CAV2.1. CACNA1D, encoding CAV1.3, has been reported to be involved in neurodegenerative mechanisms associated with the development of PD. CACNA1A, encoding CAV2.1, was previously associated with spinocerebellar ataxia type 6, which shares several clinical manifestations with MSA-C. This study is the first report of a nuclear family analysis of MSA in a Caucasian cohort. While small, our findings suggest the presence of rare variants with significant heterogeneity as a possible mechanism of disease. Interestingly, although each family studied had a different combination of variants they coalesce on a common biological theme related to dopamine processing in the brain, a previously hypothesized disease mechanism. Future work is necessary to further generalize these findings but also to investigate the functional ramification of these newly identified variants.

Disclosures: M.J. Huentelman: None. **I. Schrauwen:** None. **J.J. Corneveaux:** None. **K.M. Ramsey:** None. **A.L. Siniard:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.11

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Associazione Amici del Centro Dino Ferrari – University of Milan

We are very grateful to Dr. Massimo Pandolfo from Université Libre de Bruxelles (Belgium), for kindly supplying SCA1 mice

Title: Purkinje cell mitochondrial oxidative defect and mtDNA depletion in an animal model of spinocerebellar ataxia type 1

Authors: M. RIPOLONE[1], V. LUCCHINI[1], G. FAGIOLARI[1], D. RONCHI[2], A. BORDONI[2], F. FORTUNATO[2], S. MESSINA[3], S. BONATO[2], M. MEREGALLI[4], S. CORTI[2], G. COMI[2], M.

MOGGIO[1], *M. SCIACCO[5,1];
[1]Neuromuscular and Rare Dis. Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Ctr. Dino Ferrari,, Università degli Studi di Milano, Italy, Italy; [2]Neurol. Unit, Neurosci. Section, Dept. of Pathophysiology and Transplantation (DEPT), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Univ. degli Studi di Milano Milano, Italy, Università degli Studi di Milano Milano, Italy, Italy; [3]Dept. of Neurol. - Stroke Unit and Lab. of Neurosci., IRCCS Inst. Auxologico Italiano, Milan, Italy, Italy; [4]Stem Cell Laboratory, Dept. di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Ctr. Dino Ferrari, Università degli Studi di Milano, Milan, Italy, Italy; [5]Neuromuscular and Rare Dis. Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Poli, Milano, Italy

Abstract: Spinocerebellar ataxia type 1 (SCA1) is an autosomal dominant inherited disorder characterized by degeneration of cerebellar Purkinje Cells (PC), spinocerebellar tracts, and selective brainstem neurons. The genetic cause of SCA1 consists in the expansion of a CAG trinucleotide repeat in the SCA1 gene that results in the atypical extension of a polyglutamine (polyQ) tract within the ataxin-1 protein and in the accumulation of ataxin-1 aggregates in nuclear neuronal processes. The length of the expansion is directly proportional to the severity of the disease. Main objective of our study was to investigate the mitochondrial oxidative metabolism *in vivo* in the cerebellum of transgenic SCA1 mice. Our experiments were performed on mice aged two and six months expressing the full length human SCA1 cDNA with 82 CAG repeats controlled by a specific PC protein-2 (Pcp2) promoter. These SCA1 transgenic mice develop clinical features in the early stages of life (around 5 weeks of age) presenting pathological cerebellar signs with concomitant progressive Purkinje neuron atrophy, but relatively little cell loss, at least at this age; this evidence suggests that the SCA1 phenotype is not the result of cell death per se, but a possible effect of cellular dysfunction that occurs before neuronal demise. In both heterozygous and homozygous two-months old mice we observed a mild loss of the PC population in the cerebellar cortex, and the loss became more evident in six-months old mice, in which we also observed numerous PC in heterotopic positions within the molecular and, occasionally, the granular layer. Histochemical examination showed a progressive, age-related cytochrome-c-oxidase (COX) deficiency in the PC of both heterozygous and homozygous mice, the percentage of COX-deficiency being up to 30% in six-months old mice. Using a laser-microdissector we selectively isolated COX-competent/deficient PC and granular cells to search for mtDNA defects. We found no mtDNA mutations, but Real-Time PCR allowed us to detect mtDNA depletion in COX-deficient PC, COX-competent PC and GC being spared. We thus conclude that the selective oxidative metabolism defect observed in neuronal PC expressing mutant ataxin could represent one of the earliest pathogenetic steps of PC degeneration in SCA1 disease.

Disclosures: **M. Ripolone:** None. **V. Lucchini:** None. **G. Fagiolari:** None. **D. Ronchi:** None. **A. Bordoni:** None. **F. Fortunato:** None. **S. Messina:** None. **S. Bonato:** None. **M. Meregalli:** None. **S. Corti:** None. **G. Comi:** None. **M. Moggio:** None. **M. Sciacco:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.12

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH SIBR R44NS076075

NIH COBRE P20 GM103620

NIH COBRE P20 GM103548

Title: A novel porcine model of ataxia telangiectasia reproduces neurological features and motor deficits of human disease

Authors: R. BERALDI[1], *M. C. KRUER[2], C. CHUN-HUNG[3], C. ROGERS[4], J. WEIMER[3], A. KOVÁCS[3], D. MEYERHOLZ[5], B. DARBRO[6], B. DACKEN[7], K. WEBER[3], D. PEARCE[8]; [1]Sanford Children's Hlth. Res. Ctr., Sioux Falls, SD; [2]Researcj/Neurology, [3]Sanford Children's Hlth. Res. Ctr., Sioux Falls, SD; [4]Exemplar Genet., Iowa, IA; [5]Dept. of Pathology, Univ. of Iowa, Iowa, IA; [6]Dept. of Cytogenetics/Pediatrics, Univ. of Iowa Carver Col. of Med., Iowa, IA; [7]Exemplar genetics, Iowa, IA; [8]Sanford Children's Hlth. Res. Center, Sioux Falls, SD, United States, SIoux falls, SD

Abstract: Ataxia telangiectasia (AT) is a progressive multisystem disorder caused by mutations in the AT-mutated (*ATM*) gene. AT is a neurodegenerative disease primarily characterized by cerebellar degeneration with loss of Purkinje cells in children leading to motor impairment. The disease progresses with other clinical manifestations including oculocutaneous telangiectasia, immune disorders, increased susceptibly to cancer and respiratory infections. Although genetic investigations and physiological models have established the linkage of ATM with AT onset, the mechanisms linking ATM to neurodegeneration remain undetermined, hindering therapeutic development. The current murine models carrying mutated *ATM* have shown high fidelity in mimicking the ancillary symptoms of AT. However, the hallmark neuropathological phenotypes of Purkinje cell loss have not been fully recreated to date, thus highlighting the need for a more suitable animal model. Utilizing gene targeting and somatic cell nuclear transfer strategies, we

engineered an unprecedented porcine model of AT in order to bridges the gap between patients and mouse models and ultimately, unmask basic mechanisms underlying the neuropathology of the disease. The initial characterization of AT pigs revealed congenital cerebellar lesions including loss of Purkinje cells and altered cytoarchitecture. These findings suggest a fetal origin for AT lesions and could advocate for early therapies for AT patients. Similar to patients, AT pigs develops several motor deficit phenotypes. The measurable PC loss and motor deficits can be used as metrics to evaluate disease progression. The porcine model of AT is the first animal model that faithfully mimics the neurological human and may become a useful tool to enable pharmacological screening and to pinpoint regulatory mechanisms that are able to halt or reverse the neurological dysfunction and potentially, in the future, provide quantifiable endpoints for preclinical therapeutics in translational medicine

Disclosures: **R. Beraldi:** None. **M.C. Kruer:** None. **C. Chun-Hung:** None. **C. Rogers:** None. **J. Weimer:** None. **A. Kovács:** None. **D. Meyerholz:** None. **B. Darbro:** None. **B. Dacken:** None. **K. Weber:** None. **D. Pearce:** None.

Nanosymposium

648. Ataxias and Non-Huntington's Disease Neurodegenerative Diseases

Location: N426A

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 648.13

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: CSRS, 21st Century Grant

Title: Surgical decompression attenuates neurobehavioral deficits in an experimental model of cervical spondylotic myelopathy in mice

Authors: ***P. VIDAL VERA**[1,2], S. K. KARADIMAS[3,5], S. FORNER[6], W. D. FOLTZ[7,8], M. G. FEHLINGS[4,9,10];
[1]Genet. and Develop., UHN, Toronto, ON, Canada; [2]Genet. & Develop., Toronto Western Res. Inst. and spinal program, Krembil Neurosci. Centre, Univ. Hlth. Network, Toronto, ON, Canada, Toronto, ON, Canada; [3]Gentics & Develop., [4]Toronto Western Res. Inst. and spinal program, Krembil Neurosci. Centre, Univ. Hlth. Network, Toronto, ON, Canada; [5]Inst. of medical Sciences, Univ. of Toronto, Toronto, ON, Canada; [6]Pharmacol., Univ. Federal de Santa Catarina, currently Univ. of California Irvine, Florianópolis, Brazil; [7]Radiation Med. Program, Princess Margaret Hosp., Toronto, ON, Canada; [8]STTARR Innovation Ctr. Toronto, Toronto, ON, Canada; [9]. Inst. of Med. Sciences, Univ. of Toronto, Toronto, ON, Canada; [10]Dept. of Surgery, Div. of Neurosurgery, Univ. of Toronto, Toronto, ON, Canada

Abstract: Cervical spondylotic myelopathy (CSM) is the most common cause of adult spinal cord impairment in the world. It is caused by prolonged compression of the spinal cord from degenerative conditions, and is mainly characterized by hand impairment, gait instability, bladder dysfunction, pain and weakness. Although there is increasing evidence to support the role of surgical decompression for CSM in patients, neurological complications occur in at least 5% of cases with surgical management. The primary objective of this study was to characterise the neurobehavioral and biochemical changes in a decompression model using C57B/L mice to replicate the surgical outcomes in the clinics, and to test potential therapies. Briefly, we induced a progressive cord compression at C5-6 by inserting a biomaterial strip under the laminae at these levels followed by a surgical decompression at 6 weeks after material implantation. Neurobehavioral recovery was periodically followed before and after surgical decompression. Immunohistochemistry, western blot and ELISA were used to characterise the decompressive environment. We use T1 weighted MRI to characterise the compression ratio before and after surgical decompression. Surgical decompression for CSM caused a local increase of pro-inflammatory cytokines and chemokines (*<p0.05; **p<0.01) around the level of compression at 24 hours after surgery, as well as a two-fold decrease in iba-1 expression over time. Capellini handling and wire hang test for forelimb function. Deterioration in hand dexterity was significantly decline at 3-4 days and 5 weeks after surgical decompression (*p<0.05). In addition grip/muscle strength, measure with wire hang tests was significantly improved at 2 weeks after surgery (*p<0.05). Pain response was significantly reduced in forelimbs after surgery, without significant changes in the hindlimbs. We also performed a detailed analysis of gait deficits. This study shows a transient increase in inflammation response after surgical decompression, followed by attenuation of neurobehavioral deficits after surgical decompression in mice.

Disclosures: P. Vidal Vera: None. **S.K. Karadimas:** None. **S. Forner:** None. **W.D. Foltz:** None. **M.G. Fehlings:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.01

Topic: C.08. Ischemia

Support: AHA Grant 14PRE20350007

NIEHS Grant 1R01ES022936-01A1

Suzanne & Walter Scott Foundation

Society for Neuroscience NSP Scholarship

Title: When E3-ligases don't play tag: unfolding the protective roles of CHIP in hypoxia

Authors: *B. N. LIZAMA-MANIBUSAN[1], A. M. PALUBINSKY[1], A. J. WINLAND[1], A. GUPTA[1], R. SINGER[2], B. MCLAUGHLIN[1];
[1]Vanderbilt Univ. Med. Ctr., Nashville, TN; [2]Dartmouth-Hitchcock Med. Ctr., Lebanon, NH

Abstract: Protein ubiquitination and proteasomal degradation are integral determinants of cell survival under conditions of acute and chronic neural stress. Neurons have a complex relationship with damaged proteins. While short term proteasomal inhibition is often neuroprotective in the context of acute hypoxic stress, chronic proteasomal inhibition promotes protein aggregation and dysfunction. Understanding the complexities of protein triage is essential for developing well-tolerated therapies for conditions associated with protein oxidation, denaturation and abnormal trafficking. Oxidized or denatured proteins associate with the Heat Shock Protein 70 (HSP70) chaperone complex where C-Terminus of HSP70-Interacting Protein (CHIP) tags proteins for degradation. Previous studies suggest that driving expression and activity of E3 ligases such as Parkin and CHIP, each tagging a specific subset of client proteins with ubiquitin chains, may offer more discreet and longer lasting benefits than were observed with blunt proteasome inhibition. We have found that long term CHIP overexpression fails to protect neurons from acute stress and is, in fact, detrimental to survival. In response to oxygen and glucose deprivation (OGD), CHIP translocates to mitochondria and promotes calcium buffering suggesting it may have a role beyond standard polyubiquitination of clients. Indeed, CHIP deficient mice have shortened life-spans, high levels of protein and lipid oxidation, and profound motor impairments. As CHIP knockout mice are the only E3 ligase deficient animals that have overt behavioral and molecular dysfunction we hypothesize that CHIP is uniquely poised to impact cell stress signaling. We found that CHIP is acutely overexpressed in response to OGD, and hypothesize that it may play a neuroprotective role in the context of ischemic preconditioning (PC). PC is a phenomena where mild stress (15-min OGD) confers protection from subsequent stroke-like insults. Both CHIP and HSP70 expression peak 6-hrs after mild OGD and remain elevated for 24-hrs. While PC is non-toxic, proteins are damaged as evidenced by high levels of ubiquitin aggregation 24-hrs after stress. Using subcellular fractionation, we observe that the majority of CHIP is present in mitochondrial fractions at 6-hrs. In order to determine if the E3-ligase activity of mitochondrial CHIP promotes survival, mouse embryonic fibroblasts (MEFs) from CHIP KO animals were transfected with full-length CHIP or a truncated mutant lacking E3-ligase function. Ongoing experiments seek to determine the contribution of the E3 ligase domain to survival and mitochondrial relocalization in acute stress.

Disclosures: B.N. Lizama-Manibusan: None. **A.M. Palubinsky:** None. **A.J. Winland:** None. **A. Gupta:** None. **R. Singer:** None. **B. McLaughlin:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.02

Topic: C.08. Ischemia

Support: NIH grant P20GM109098

NIH grant P01AG027956

NIH grant U54GM104942

Title: Mitochondria dysfunction opens blood-brain barrier and exacerbates murine experimental stroke

Authors: X. REN[1], *H. HU[2], J. W. SIMPKINS[1];
[1]Physiolgoy & Pharmacol., West Virginia University, Exptl. Stroke Core, Ctr. For Basic and Translational Stroke Res., Morgantown, WV; [2]Physiolgoy & Pharmacol., West Virginia University, Ctr. For Basic and Translational Stroke Res., Morgantown, WV

Abstract: Stroke is the second leading cause of death and the leading cause of disability worldwide with limited treatments. Ischemic stroke disrupts the blood-brain barrier (BBB) that increases vasogenic and cytotoxic brain edema. To investigate the mechanisms of the BBB disruption is important to develop effective treatments to control brain edema for human stroke. The BBB is primarily formed by brain vascular endothelial cells (BVECs) interconnected with well-developed tight junctions. It is documented that a large volume of mitochondria exists in BVECs. To investigate the role of mitochondria in maintenance of BBB integrity, we used a pharmacological strategy to manipulate mitochondrial respiration. We demonstrated that inhibition of mitochondrial Complex I with rotenone, uncoupling of electron flow from ATP production with FCCP, or inhibition of mitochondrial Complex V with oligomycin rapidly increased FITC-dextran 70 permeability in a transwell system of cultured BVEC monolayers *in vitro*. Immunocytochemical analysis revealed that the normally well-defined, linear cell-cell junctions in BVECs were disrupted when oxidative phosphorylation was inhibited by mitochondrial inhibitors. Using an epidural application model for CNS drug delivery *in vivo*, we found that inhibition of Complex I with rotenone significantly increased Evan's blue extravasation in the mouse brain. Using transient middle cerebral artery occlusion model, rotenone caused significant BBB damage and exacerbated infarct volumes, and worsened neurological deficits in stroke. These data suggest that mitochondria are critical for the regulation of cerebrovascular permeability. They also suggest a potential new therapeutic strategy for ischemic stroke by regulating endothelial cell mitochondrial energy production.

Disclosures: **X. Ren:** None. **H. Hu:** None. **J.W. Simpkins:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.03

Topic: C.08. Ischemia

Support: AHA Grant-In-Aid 11GNT7990120

AHA PreDocFellow 14PRE19570010

Title: Amyloid-β25-35 potentiates ischemia-induced neuronal injury

Authors: ***A. A. BEHENSKY**, J. CUEVAS;
Mol. Pharmacol. & Physiol., Univ. of South Florida, Tampa, FL

Abstract: Stroke is the second leading cause of death world-wide and a major cause of serious long-term disability. Two comorbidities have been shown to accompany ischemic stroke: tissue acidosis and increase deposition of amyloid-β peptide (Aβ). We have previously shown that either of these comorbidities can enhance the dysregulation of intracellular calcium ($[Ca^{2+}]_i$) homeostasis caused by neuronal ischemia, which ultimately results in increased neuronal death. To date, the molecular mechanism(s) mediating Aβ-induced potentiation of ischemia remains unknown. Furthermore, the effects of Aβ on concurrent ischemia + acidosis have not been investigated. Fluorometric calcium imaging was used to determine if application of Aβ affects the $[Ca^{2+}]_i$ overload produced by concurrent ischemia + acidosis in isolated cortical neurons. Incubation of neurons in 25 μM $A\beta_{25-35}$ for 24 hr results in a 59 ± 9% increase in peak elevations in $[Ca^{2+}]_i$ evoked by ischemia + acidosis. The kinetics of the $[Ca^{2+}]_i$ overload produced by ischemia + acidosis following pre-incubation in Aβ suggest that the acid-sensing ion channels 1a (ASIC1a) is involved in the effects of the amyloid peptide. Whole-cell patch-clamp electrophysiology was used to determine if a change in ASIC1a activity is responsible for Aβ-evoked potentiation of ischemia + acidosis induced $[Ca^{2+}]_i$ overload in isolated cortical neurons. Following a 24 hr incubation in Aβ there was a 68 ± 17% increase in the inward currents (holding potential, -70 mV) produced by focal application of physiological saline solution at pH 6.0. Given that activation of sigma-1 receptors can modulate both ischemia + acidosis- and Aβ-evoked $[Ca^{2+}]_i$ overload, experiments were carried out to see how sigma-1 receptor activation affects Aβ modulation of responses to ischemia + acidosis. Fluorometric $[Ca^{2+}]_i$ imaging experiments showed that the sigma receptor agonist, afobazole (100 μM), abolished Aβ

potentiation of ischemia + acidosis evoked $[Ca^{2+}]_i$ overload. In conclusion, our data show a mechanism by which Aβ may enhance neuronal injury during ischemia, increased $[Ca^{2+}]_i$ overload, and identify ASIC1a as the channel mediating this phenomenon. Finally, our data suggest that activation of sigma receptors may represent a therapeutic strategy for mitigating injury produced by Aβ and stroke.

Disclosures: A.A. Behensky: None. **J. Cuevas:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.04

Topic: C.08. Ischemia

Support: NIH 1R01NS064136

Title: Ischemic postconditioning inhibits the accumulation of macrophages derived from monocytes and their M1 polarization in the ischemic mouse brain after stroke

Authors: *H. ZHAO, Y. ZHANG, X. XIONG, D. YAN, Z. JIAN, Q. JI, Y. JI;
Dept Neurosurg, Stanford Univ., Stanford, CA

Abstract: Ischemic postconditioning (IPostC) protects against brain injury induced by stroke, but the underlying protective mechanisms remain unknown. We hypothesize that IPostC reduces brain injury by inhibiting the infiltration of macrophages in the ischemic brain. Macrophages in the ischemic brain are composed of two subsets, microglia-derived macrophages (MiDMs) and monocyte-derived macrophages (MoDMs). Upon activation, both MiDMs and MoDMs are polarized into two functional subsets, pro-inflammatory M1 and anti-inflammatory M2 macrophages. Thus, we investigated the potential different roles of MoDMs vs MiDMs, and their associated M1 and M2 functional subsets, in the protective effect of IPostC against ischemic brain injury. Stroke was induced by transient middle cerebral artery occlusion (MCAo) in C57/BL mice. We first confirmed that IPostC significantly reduced infarct sizes measured on day 3 post-stroke, and that IPostC inhibited accumulation of MoDMs (CD45hiCD11b+), but not MiDMs (CD45intCD11b+) in the ischemic brain, as measured by FACS based on macrophage specific cell surface markers, CD45 and CD11b. LPS injection in non-stroke mice resulted in robust increases in pro-inflammatory monocytes (Ly6chiCD11b+) in the peripheral blood. In addition, LPS injection resulted in significant increases in brain infarction. Nevertheless, IPostC robustly inhibited brain infarction induced by LPS, and inhibited LPS-induced accumulation of

MoDMs in the ischemic brain. The results of confocal immunostaining further suggest that IPostC reduced LPS-induced CD68 positive macrophages in the ischemic brain. We found that stroke resulted in increases in both M1 and M2 macrophages in the ischemic brain, and IPostC robustly inhibited M1 but not M2 macrophages in the ischemic brain with and without LPS treatment. Taken together, we conclude that IPostC attenuates brain injury by inhibiting infiltration of MoDMs and their M1 polarization.

Disclosures: H. Zhao: None. **Y. Zhang:** None. **X. Xiong:** None. **D. Yan:** None. **Z. Jian:** None. **Q. Ji:** None. **Y. Ji:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.05

Topic: C.08. Ischemia

Support: NIH Grant NS45676

NIH Grant NS054147

NIH Grant NS34773

NIH Grant 1F31NS089356-01

NIH Grant 5R01NS073779-04

Title: Resveratrol preconditioning induces a novel extended window of ischemic tolerance in the mouse brain

Authors: *K. B. KORONOWSKI[1], K. R. DAVE[1], I. SAUL[1], V. CAMARENA[2], J. W. THOMPSON[1], J. T. NEUMANN[1], J. I. YOUNG[2], M. A. PEREZ-PINZON[1];
[1]Neurol., [2]Human Genet., Univ. of Miami, Miami, FL

Abstract: Objectives: Resveratrol preconditioning (RPC) mimics ischemic preconditioning and reduces ischemic injury when administered two days prior to cardiac arrest in rats as well as stroke in mice. This protection is postulated to occur at least in part through signaling pathways involving Sirt1. The goal of this study is to identify the conditions of RPC that most robustly induce neuroprotection from focal ischemia and further investigate the contribution of Sirt1 to this end. Methods: We tested four different RPC (10 mg/kg resveratrol i.p.) treatment paradigms

against middle cerebral artery occlusion (MCAo). Functional outcome was assessed by neurological scoring and infarct volume was quantified via tetrazolium chloride staining 24 hours post-stroke. Sirt1-chromatin binding was evaluated by ChIP-qPCR. Percoll gradient fractionation was used to obtain synaptic fractions for western blot analysis. BDNF concentration was measured using an ELISA. Inducible, neuron-specific Sirt1 knockout mice were generated by crossing SLICK-H CreERT2 and Sirt1flox/flox mice. Data are represented as mean ± SEM. Results: Strikingly, a single application of RPC 14 days prior to stroke afforded the most robust protection, reducing infarct volume by 33% ($p<0.01$, veh n=9, RPC n=10) and improving neurological score by 28% ($p<0.05$) compared to vehicle. 14 days following RPC, cortical Sirt1 protein levels were increased 1.5 fold of vehicle ($p<0.01$, n=10) and Sirt1 binding to both the BDNF and UCP2 promoters was significantly enhanced, 2.66-fold and 1.14-fold, respectively (BDNF $p<0.01$, UCP2 $p<0.05$, n=3). At the same time point, synaptic UCP2 protein decreased by 23% (student's T-test, $p<0.05$, n=6) and cortical BDNF concentration increased 27% of vehicle ($p<0.05$, n=7). To determine whether the Sirt1 signaling axis is key for this extended window of protection, we have generated inducible, neuron-specific Sirt1 knockout mice (Sirt1neu-/-). In these mice, the thy1 promoter drives inducible Cre expression (and YFP reporter) exclusively in neurons. Tamoxifen treatment induces deletion of exon 4 (catalytic domain) from the Sirt1 gene, resulting in production of a mutant, non-functional Sirt1 protein. Conclusions: RPC induces a novel extended window of chronic ischemic tolerance in the brain that lasts for at least 14 days. This tolerance is concordant with enhanced Sirt1 and two of its potential targets that are involved in modification of mitochondrial function and the synapse. Induction of adult Sirt1neu-/- mice results in loss of Sirt1 function specifically in neurons; these mice will be utilized to further test the role of Sirt1 in this extended window of protection.

Disclosures: **K.B. Koronowski:** None. **K.R. Dave:** None. **I. Saul:** None. **V. Camarena:** None. **J.W. Thompson:** None. **J.T. Neumann:** None. **J.I. Young:** None. **M.A. Perez-Pinzon:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.06

Topic: C.08. Ischemia

Support: AHA Fellowship 14PRE20460380

R01AG033570

5T32 HL 07692-24

Title: Endothelial Caveolin-1 regulates the neurogenic vascular niche

Authors: *J. A. BONDS[1], M. K. TOBIN[2], R. MINSHALL[3], D. PELLIGRINO[4], O. LAZAROV[2];
[1]Anat. and Cell Biol., Univ. of Illinois, Chicago, Chicago, IL; [2]Anat. and Cell Biol., [3]Anesthesiol. and Pharmacol., [4]Anesthesiol., Univ. of Illinois at Chicago, Chicago, IL

Abstract: The vascular niche is critical for the maintenance of neural stem cells (NSCs) in the adult brain. However, little is known about the structure and function of the vascular niches. Vascular endothelial cells support and regulate NSC proliferation and differentiation. Endothelial Caveolin-1 (Cav-1) is a cholesterol binding protein that resides in cell membrane lipid rafts and is critical for endothelial cell function. Thus, we hypothesized that Cav-1 regulates NSC maintenance. Here we show that loss of Cav-1 in the adult brain results in compromised vascular networks, a reduction in neurogenic markers, and altered neurogenesis. Furthermore, loss of Cav-1 induces alterations in the protein distribution in the lipid raft. Importantly, we observe an age-linked decline in Cav-1 expression within neurogenic environments. Recent evidence suggests hypoxic conditions in the neurogenic vascular niche influence proliferation, differentiation and migration of NSCs. Interestingly, we observed that hypoxic conditions induce endothelial Cav-1 degradation. Taken together, our data suggests that endothelial Cav-1 may play an important role in the regulation and homeostasis of the neurogenic vascular niche and that reduction in Cav-1 may underlie the age-dependent decline in neurogenesis.

Disclosures: J.A. Bonds: None. **M.K. Tobin:** None. **R. Minshall:** None. **D. Pelligrino:** None. **O. Lazarov:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.07

Topic: C.08. Ischemia

Support: Wellcome Trust Programme Grant (WT094823)

Title: Inhibiting Caspase-2: A novel neuroprotective strategy to combat neonatal hypoxic-ischaemic brain injury

Authors: *C. THORNTON[1], C. ALVIANI[1], A. A. BABURAMANI[1], E. JACOTOT[2], P. GRESSENS[1,3], H. HAGBERG[1,4];
[1]Ctr. For the Developing Brain, KCL, London, United Kingdom; [2]Inst. de Biologie Paris Seine (IBPS), Univ. Pierre & Marie Curie, Paris, France; [3]Inserm U1141, Paris, France; [4]Sahlgrenska Acad., Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Babies who develop perinatal hypoxic-ischaemic encephalopathy (HIE) after severe asphyxia during birth go on to suffer lifelong neurological impairment. Hypoxia-ischaemia (HI) results in an initial cellular energy depletion, followed by a recovery phase and a secondary energy failure characterised by delayed cell death. Therapeutic hypothermia is the only treatment option available; it improves outcome for around 1 in 7 infants. However, it does establish a proof-of-concept that post-injury treatment can be effective. Activation of caspase-2 (an initiator caspase) is implicated in inducing Bax-mediated mitochondrial outer membrane permeabilisation (MOMP), the predicted convergence point for mechanisms underlying the pathological damage in neonatal brain. Previously we found that in neonatal mice lacking caspase-2, there was reduced Bax-mediated mitochondrial permeabilisation, increased protection in HI and excitotoxic models of neuronal damage, and significantly, synergistic protection when combined with hypothermia. TRP601, a pharmacological caspase-2/3 inhibitor developed by collaborators, also reduced brain injury in both models. This study investigates the molecular underpinnings of caspase-2 activation and its downstream consequences. We find that after initiating HI in P9 mouse pups and oxygen glucose deprivation (OGD) in primary neuronal cultures, caspase-2 activity increases very rapidly, from as early as 8h post insult. Furthermore, preliminary proteomics analysis has identified novel caspase-2 interactants in which binding is induced after HI. We are currently investigating how these binding partners facilitate caspase-2 mediated mitochondrial permeabilisation. In addition we have generated a conditional (loxP) caspase-2 mouse in order to overcome compensation effects from other caspases observed in the traditional KO animal; OGD-induced cell death was substantially reduced in primary neurons lacking caspase-2 expression. Future work centres on mitochondrial health in the presence and absence of caspase-2, the functional implications offered by the binding partners and development of a specific caspase-2 inhibitor. Thus, caspase-2 inhibition offers exciting potential for generating protective “mitotherapeutics” to target the devastating effects of neonatal HIE.

Disclosures: C. Thornton: None. **C. Alviani:** None. **A.A. Baburamani:** None. **E. Jacotot:** None. **P. Gressens:** None. **H. Hagberg:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.08

Topic: C.08. Ischemia

Support: NIH/NCATS 5UH2TR000491

NIEHS 1R01ES022936

American Heart Association

Walter and Suzanne Scott Foundation

Dan Marino Foundation

Title: Promoting damaged protein refolding boosts neuroprotection afforded by ischemic preconditioning

Authors: *A. M. PALUBINSKY[1], B. N. LIZAMA-MANIBUSAN[1], I. S. KHAN[3], J. E. GESTWICKI[4], R. J. SINGER[3], B. MCLAUGHLIN[2];
[1]Neurosci. Grad. Program, [2]Neurol., Vanderbilt Univ. Med. Ctr., Nashville, TN; [3]Neurosurg., Dartmouth Hitchcock Hosp., Hanover, NH; [4]Pharmaceut. Chem., Univ. of California, San Francisco, San Francisco, CA

Abstract: Neurons can utilize powerful adaptive mechanisms to increase survival in response to a diverse set of insults including hypoxia. Ischemic preconditioning (PC) is a prime example of this phenomenon wherein neuronal cultures subject to non-toxic, oxygen and glucose deprivation (OGD), have a far greater likelihood of surviving a subsequent injury that would normally be lethal. We have shown that although no neurons die in response to the initial PC stimulus, far more protein oxidation and ubiquitination occurs during this priming stress than has been previously reported. Neurons rely heavily on upregulating expression of the Heat Shock Protein 70 (HSP70) molecular chaperone complex as part of the PC response. We have recently reported congruent changes in the expression of HSP70 and the HSP70 co-chaperone and E3 ubiquitin ligase, C-terminus of HSP70 Interacting Protein (CHIP) in response to ischemia. However, once oxidized or denatured proteins dock with the chaperone complex it is unknown whether it is more advantageous to degrade or refold these substrates. Using a new group of small molecule modulators of the HSP70 complex, we found that both pro-folding molecules and pro-degradation compounds are non-toxic and have minimal effect on the expression of chaperone complex proteins such as HSP70, HSP90, HSP40, HSC70, BAG1, HIP, and HOP at baseline and in response to PC. Additionally, we found that compounds that promote protein refolding offer significant advantages over those that promote degradation. Compounds that positively impact protein refolding augment neuronal survival an additional 20-30% over PC alone. We also observe that CHIP expression is further increased in the presence of pro-folding compounds, as are levels of mono- and poly-ubiquitinated proteins, while levels of free ubiquitin remain unchanged. These data suggest that in instances of ischemic stress, CHIP may function

independent of its typical E3 ligase activity protecting neurons without depleting the free ubiquitin pool. Future experiments include analysis of pro-folding compounds in an *in vivo* model of ischemia as well as further exploration of the mechanisms through which HSP70 modulators afford increased neuroprotection.

Disclosures: A.M. Palubinsky: None. **B.N. Lizama-Manibusan:** None. **I.S. Khan:** None. **J.E. Gestwicki:** None. **R.J. Singer:** None. **B. McLaughlin:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.09

Topic: C.08. Ischemia

Support: NRF-2014R1A2A1A11050246

Title: Spatiotemporal progression of microcalcification in the hippocampal CA1 region following transient forebrain ischemia in rats. An ultrastructural study

Authors: *T. RIEW[1,2,3], Y.-J. SHIN[1,2,3], J. CHO[1,2,3], H. KIM[4], J.-H. PARK[1,2,3], H.-J. PAK[1,2,3], M.-Y. LEE[1,2,3];
[1]Dept. of Anatomy, Col. of Medicine, The Catholic Univ. of Korea, Seoul/seocho-Gu, Korea, Republic of; [2]Catholic Neurosci. Institute, The Catholic Univ. of Korea, Seoul, Seocho-gu, Korea, Republic of; [3]Cell Death Dis. Res. Center, The Catholic Univ. of Korea, Seoul, Seocho-gu, Korea, Republic of; [4]Integrative Res. Support Center, Lab. of Electron Microscope, Col. of Medicine, The Catholic Univ. of Korea, Seoul/seocho-Gu, Korea, Republic of

Abstract: Calcification on areas of neuronal degeneration is a common finding in several neuropathological disorders including ischemic injury, and calcium precipitation in neurons could be regarded as a part of compensatory mechanism to reduce further brain damage. Although central to the understanding of ischemic brain injury, the onset and spatiotemporal progression of calcification in the ischemic hippocampus have not been characterized in detail. The present study examined spatiotemporal profile of the calcification induced in the CA1 hippocampal region, an area that undergoes delayed neuronal death after transient forebrain ischemia. No specific staining for alizarin red S was detected in the hippocampus of sham-operated and ischemic rats by 7 days after reperfusion. At 14 days, however, amorphous to granule-like alizarin red staining was evident in the CA1 dendritic subfields such as the strata oriens and radiatum, but not in the pyramidal cell layer, and there was a further increase

throughout the CA1 region at 28 days, although weaker in the pyramidal cell layer than its dendritic subfield. By the osmium/potassium-bichormate method and electron probe microanalysis, we found in the CA1 dendritic subfield that electron-dense precipitation was abundantly observed within the mitochondria in degenerating dendrites that were still contacted by uncalcifying neurites by 7 days after reperfusion. At 14 days, calcium deposits appeared to spread beyond mitochondria and extend over the whole neurite and these calcifying neurites were frequently aggregated and fused together. Most of these calcifying dendrites were surrounded by astrocytes showing dense bundles of intermediate filaments. In degenerated soma in the CA1 pyramidal cell layer, however, calcium deposition was noted within, but not beyond, mitochondria, although most of cell organelles disappeared and only amorphous substances remained. These calcification patterns were maintained by 28 days after reperfusion, but large folded, or multilobulated calcifying deposits of variable form and size were frequently observed throughout the CA1 hippocampus. Our data suggest that microcalcification occurring within mitochondria of degenerating dendrites may serve as a nidus for further calcium precipitation in the ischemic hippocampus. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and future Planning (NRF-2014R1A2A1A11050246).

Disclosures: **T. Riew:** None. **Y. Shin:** None. **J. Cho:** None. **H. Kim:** None. **J. Park:** None. **H. Pak:** None. **M. Lee:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.10

Topic: C.08. Ischemia

Support: NIH NINDS NS 38362

Title: Increased cerebral capillary density following severe transient neonatal hypoxia in mice

Authors: J. C. LAMANNA, C. P. TSIPIS, X. SUN, *K. XU;
Dept Physiology/Biophysics, Case Western Reserve Univ., Cleveland, OH

Abstract: Brief hypoxic exposure in early life may lead to persistent structural and functional changes in the brain. In this study, we investigated the effect of severe transient neonatal hypoxia or hypoxia/hypercapnia on adult cerebral capillary density and the angiogenic hypoxic response. Mice were exposed to either hypoxia (5% O2) or hypoxia/hypercapnia (5%O2 / 8% CO2) in a

normobaric chamber for 2 hours at postnatal day 2 (P2), and then returned to normoxia; littermates were maintained normoxic in the same room and used as controls. At 3 months of age, for each P2-conditioned group, mice were assigned to hypoxic or normoxic groups. Hypoxic mice were exposed to hypoxia (8% O2 in N2) in a normobaric chamber for 3 weeks and the normoxic mice of each type were kept normoxic in the same location. Cerebral capillary density was identified by GLUT-1 immunohistochemistry staining and was quantified from the number of the positive counts per unit area (number/mm2). Results showed that the adult normoxic baseline capillary density was similar in the P2-normoxia and the P2-hypoxia/hypercapnia groups (425 ± 60, n = 12 and 439 ± 52, n = 6, respectively, mean ± SD), however, the P2-hypoxia group had a significantly higher normoxic baseline capillary density (521 ± 83, n = 6) compared to that of the P2-normoxia group. Adult prolonged moderate hypoxic exposure resulted in increased cerebral capillary density (about 20%) in both P2-normoxia and P2-hypoxia groups (513 ± 58, n = 15 and 612 ± 70, n = 5, respectively), but not in the P2-hypoxia/hypercapnia group (451 ± 52, n = 8). These data suggest that early postnatal hypoxic stress or hypoxic/hypercapnic stress play different roles in fetal programming of the adult cerebral vasculature as shown by altered baseline cerebral capillary density and response to prolonged hypoxic exposure. Transient severe hypoxic exposure at P2 induces angiogenesis in brain; on the other hand, transient exposure to hypoxia/hypercapnia seems to blunt the adult angiogenic response to further hypoxia.

Disclosures: **J.C. LaManna:** None. **C.P. Tsipis:** None. **X. Sun:** None. **K. Xu:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.11

Topic: C.08. Ischemia

Support: NIH Grant R00 AG033050

Ellison Medical Foundation New Scholar in Aging

NIH Grant R01 ES024958

NIH Cellular and Molecular Biology Training Grant

NIH Genetic Approaches to Aging Training Grant

Title: Interactions between HIF-1 and SKN-1/Nrf in the response to hydrogen sulfide

Authors: *D. L. MILLER, J. HORSMAN, K. MANBECK;
Biochem., Univ. of Washington, Seattle, WA

Abstract: Hydrogen sulfide protects against the effects of ischemia-reperfusion injury in a variety of mammalian models. We have shown that in *C. elegans* the transcriptional response to H_2S absolutely requires the *hif-1* transcription factor. HIF-1 is a highly conserved, bHLH transcription factor that is well-known to coordinate the response to low oxygen (hypoxia) in metazoans. However, our data indicate that different genes are regulated by *hif-1* in H_2S and hypoxia. Whereas *hif-1(ia04)* mutant animals exposed to hypoxia survive and enter into a reproductive and developmental diapause, these mutants die within hours when exposed to low H_2S. To understand molecular and genetic pathways that mediate the effects of hif-1 in H_2S, we performed an unbiased forward genetic screen to identify suppressers of *hif-1* lethality in H_2S. We have recovered gain-of-function alleles in *skn-1*, the worm orthologue of mammalian Nrf, and alleles in *wdr-23*, a negative regulator of SKN-1. A subset of genes induced in H_2S require both HIF-1 and SKN-1, further supporting the hypothesis of an interaction between these transcription factors. These results reveal a new interaction between conserved transcription factors that may have an important role in the protective effects of H_2S in mammals, and provides unique insight into the mechanisms by which adaptation to hydrogen sulfide is integrated with the response to hypoxia at the cellular and organismal level.

Disclosures: D.L. Miller: None. **J. Horsman:** None. **K. Manbeck:** None.

Nanosymposium

649. Ischemia: Cellular Mechanisms

Location: S404

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 649.12

Topic: C.08. Ischemia

Support: CONACyT416882

Instituto Mexicano del Seguro Social

Title: CD95/CD95L Identification in acute ischemic stroke patient's serum

Authors: *O. HUET[1,2], S. RATKOVICH-GONZÁLEZ[2], D. ARANA-VALADEZ[2], S. LUQUÍN[3], L. JAVE-SUÁREZ[2];
[1]Univ. De Guadalajara, Zapopan, Mexico; [2]Inst. Mexicano del Seguro Social, Guadalajara, Mexico; [3]Univ. de Guadalajara, Guadalajara, Mexico

Abstract: Stroke is the second leading cause of death worldwide. Ischemic etiology accounts for ~85% of all events. Evidence suggests that necrotic, but also apoptotic cell death contributes to the final volume of the infarct. Necrotic mechanisms happen rapidly and are therefore extremely difficult to treat or prevent. The focus of investigation is to elucidate apoptotic processes to find new therapeutic targets. Death receptor CD95 has been implicated in neuronal and glial apoptosis after ischemia. Its ligand (CD95L), can be found bounded to cell membrane (on cells or microvesicles) or cleaved by metalloproteases. Membrane bound ligand activate apoptosis while its shredded version has an antagonistic activity that promote migration, proliferation and inflammation. Objective: The aim of the present study was to measure whether CD95/CD95L level, varies between control subjects and acute ischemic stroke (AIS) patients. Methods: Serum samples from 58 human subjects (28 volunteers, 30 with AIS) were collected to measure CD95/CD95L by ELISA assay. Since the mentioned method it's unable to discriminate between the pro-apoptotic from the non-apoptotic form of CD95L, we separately used a cell based assay consisting in the stimulation of a CD95 expressing cell line with control and patient's serum and the subsequent measure of the apoptotic rate by flow cytometry. Results: The ELISA assay showed that control subjects had higher CD95L concentration but not higher concentrations of the receptor. Additionally, apoptosis induction measured by the cell based assay was significantly higher in the sera of the AIS group. Conclusions: It has been established that CD95/CD95L expression is induced in some neural and glial cells following cerebral ischemia and that blood brain barrier (BBB) is disrupted in the early phase, which is compatible with the rate of apoptosis founded between groups, but why we didn't observe higher levels of CD95L molecule in AIS patients? We infer that both forms of the ligands are entering the brain through the permeable BBB and occupying the cell receptors that are over expressed in the site of the lesion causing inflammation and apoptosis, leading to stress and cell death, which leads to extended infarct volume.

Disclosures: **O. Huet:** None. **S. Ratkovich-González:** None. **D. Arana-Valadez:** None. **S. Luquín:** A. Employment/Salary (full or part-time); Universidad de Guadalajara. **L. Jave-Suárez:** A. Employment/Salary (full or part-time); Instituto Mexicano del Seguro Social.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.01

Topic: C.10. Trauma

Support: KAKENHI 22500340

KAKENHI 24300197

the Strategic Research Foundation Grant-aided Project for Private Schools at Heisei 23rd from the Ministry of Education, Culture, Sports, Science and Technology of Japan, 2011–2015

Title: Functional recovery from chronic spinal cord injury by the reactivation of endogenous microglia

Authors: *M. HAMANOUE[1,2], K. MORIOKA[3], K. HAYAKAWA[4], K. NAKAJIMA[5], T. OGATA[6], K. TAKAMATSU[1,2];
[1]Dept. of Physiol., Toho Univesity Sch. of Med., Tokyo, Japan; [2]Div. of Chronic Inflammatory Diseases, Advanced Med. Res. Ctr., Toho Univ. Grad. Sch. of Med., Tokyo, Japan; [3]Neurolog. Surgery, Brain and Spinal Injury Ctr. (BASIC), San Francisco, CA; [4]Orthopaedic Surgery, The Univ. of Tokyo, Grad. Sch. of Med., Tokyo, Japan; [5]Sci. and Engin. for Sustainable Innovation, Fac. of Sci. and Engin., Soka Univ., Tokyo, Japan; [6]Rehabil. for the Movement Functions, Natl. Rehabil. Ctr. for Persons with Disabilities, Saitama, Japan

Abstract: During the chronic phase of spinal cord injury (SCI), fibrotic scar tissue was formed as if it was a barrier for regeneration. We hypothesized that reactivation of resting microglia, which are the resident macrophage in spinal cord, might eliminate such a structural barrier to prevent functional recovery. First, we investigated whether p38 MAP kinase (p38) could be an activator of residential microglia obtained from mice spinal cord. The addition of dominant active type of recombinant p38 protein (DA) to the culture medium promoted the activation of cultured microglia; the increased expression of growth factors including Glial cell-line derived neurotrophic factor, the phagocytotic clearance of spinal cord debris, and rapid phosphorylation of membrane protein obtained from the cultured microglia. In addition, continuous infusion of DA protein into the mice spinal cord for 7 days increased the number of Iba1-positive microglia. These results suggested that DA protein is an activator for microglia in the spinal cord. To ascertain the effect of DA protein on the chronic phase of SCI, DA injection into spinal cord was started three months after the contusion injury, and DA was injected intrathecally once a week for 2.5 months. Immunohistochemical analysis with anti-collagen antibody showed a significant reduction of scar tissue formation by long-term DA injection. Furthermore, rota rod test and BMS score revealed that DA-injected mice showed the improvement in motor function compared to the mice injected with p38 protein which lost kinase activity. These results suggest that DA protein provides a reasonable approach for functional recovery from chronic SCI by activating endogenous microglia from outside cells.

Disclosures: M. Hamanoue: None. **K. Morioka:** None. **K. Hayakawa:** None. **K. Nakajima:** None. **T. Ogata:** None. **K. Takamatsu:** None.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.02

Topic: C.10. Trauma

Support: NIH Grant UL1TR000117 (to C.G. Yu)

Kentucky Spinal Cord and Head Injury Research Trust (KSCHIRT) grant #11-9A (to C.G.Yu)

Title: Flubendazole reduces pathogenic B cell activation and improves recovery after spinal cord injury in rats

Authors: *C.-G. YU[1], C. ROGERS[1], V. BONDADA[1], J. JONES[1], M. SANDS[1], A. SHREWSBURY[1], S. BONDADA[2], J. W. GEDDES[1];
[1]Anat. and Neurobio. Spinal Cord and Brain Injury Res. Ctr., [2]Microbiology, Immunol. & Mol. Genet., Univ. of Kentucky Col. of Med., Lexington, KY

Abstract: Traumatic SCI causes systemic and intraspinal B cell activation/proliferation, which leads to delayed myelin and axon damage that result in locomotor deficits. B cell-directed therapy represents a novel therapeutic intervention for SCI. However, no approved anti-B cell products are available for SCI indications. Flubendazole (FluBZ) has been widely used in the treatment of intestinal and neural parasites in human. Here, we show a novel neuroprotective effect of FluBZ on pathogenic and functional deficits through inhibition of B cell pathway/antibody response. Intraperitoneal (IP) injection with 10 mg/kg/day (n=10) of FluBZ to Sprague-Dawley rats for 2 weeks started at 3 hrs post-SCI (180 kdyn) at T10. This resulted in improved locomotor function (BBB scores) 7 weeks after contusion SCI and reduced pain behaviors 4 weeks after excitotoxic SCI compared to vehicle-treated controls (n=9). FluBZ IP treatment also improved total tissue sparing, white matter sparing, and gray matter sparing at 7 weeks after contusive SCI. Mechanistic studies revealed that FluBZ reduced splenic population of CD45RA-positive B cells at 4 weeks post-injury and suppressed production of antibody IgG at lesion site 8 weeks post-injury. Moreover, we found that FluBZ inhibited phosphorylation of Bruton tyrosine kinase (pBTK) at lesion site 4 weeks post-injury. BTK has been shown to mediate pERK1/2 and inflammatory/autoimmune pathways and play a central role in B cell receptor signaling. FluBZ reduced pERK1/2 activation, cyclin B1 expression, and GFAP expression at lesion site 4 weeks post-injury. In conclusion, our results suggest that FluBZ targets the pathogenic B cell pathway and improves functional recovery after SCI.
Acknowledgments The authors thank Daisy Ramos for her contributions to behavior test of this work. This work was funded by the following grants from the NIH Clinical and Translational

Science Award (CTSA) grant UL1TR000117 (to C.G. Yu) and Kentucky Spinal Cord and Head Injury Research Trust (KSCHIRT) grant #11-9A (to C.G.Yu).

Disclosures: **C. Yu:** None. **C. Rogers:** None. **V. Bondada:** None. **J. Jones:** None. **M. Sands:** None. **A. Shrewsbury:** None. **S. Bondada:** None. **J.W. Geddes:** None.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.03

Topic: C.10. Trauma

Title: ku0063794, a dual mtorc1 and mtorc2 inhibitor, reduces neural tissue damage and locomotor impairment after spinal cord injury in mice

Authors: ***I. PATERNITI**, D. IMPELLIZZERI, M. CORDARO, R. SIRACUSA, E. ESPOSITO, S. CUZZOCREA;
Univ. of Messina, Messina, Italy

Abstract: Autophagy is an intracellular catabolic mechanism for the degradation of cytoplasmic constituents in the autophagosomal-lysosomal pathway. This mechanism plays an important role in homeostasis and it is defective in certain diseases. However, whether enhanced autophagy will reveal a possible cause of cell death or whether it serves as part of the induction of an endogenous protective response are still controversial. The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that plays a key role in the regulation of cell metabolism, cell proliferation, cell death and is involved in physiological processes. Moreover, mTOR is involved in the regulation/inhibition of autophagy. Spinal cord injury (SCI) is a serious and debilitating health problem that usually causes lifelong disability and leads to neurological dysfunction at and/or below the level of the injury. Previous studies have shown that autophagy is emerging as an important mediator of pathological responses associated to SCI and plays a key role in secondary injury causing progressive degeneration of the spinal cord. Thus, based on this evidence in the present study we used different selective inhibitors of mTOR activity to better investigate the functional role of autophagy in an *in vivo* model of SCI and to better determine whether the autophagic process is involved in spinal cord tissue damage. We treated animals with a new synthetic inhibitor Temsirolums and with a dual mTORC1 and mTORC2 inhibitor KU0063794 compared all with the well know inhibitor of mTOR the Rapamycin. Our results demonstrated that the administration of Rapamycin and Temsirolums significantly decreased the phosphorylation of the p70S6K and pAKT protein and control the expression levels of LC3 and

Beclin 1 in the injured spinal cord but KU0063794 is able to modulate the autophagy process better than Rapamycin and Temsirolimus. Moreover, we investigated if the mTOR inhibitors could modulate the neuroinflammation associated to SCI and the results that we obtained clearly demonstrated that Rapamycin and Temsirolimus significantly decreased the expression of iNOS, COX2,GFAP and restored nNOS levels; but the administration of KU0063794 is able to blunt the neuroinflammation better than Rapamycin and Temsirolimus. In addition, neuronal loss and cell death in the injured spinal cord were significantly reduced in the KU0063794 treated mice. Thus, taken together our results indicate that the administration of KU0063794 produced a neuroprotective function at the lesion site following SCI, representing a novel therapeutic strategy after SCI.

Disclosures: I. Paterniti: None. **D. Impellizzeri:** None. **M. Cordaro:** None. **R. Siracusa:** None. **E. Esposito:** None. **S. Cuzzocrea:** None.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.04

Topic: C.10. Trauma

Support: VA Merit Grant

SCIRF

Title: Targeted complement inhibition improves recovery in murine spinal cord injury model

Authors: *A. NARANG[1], H. ZHU[2], C. ATKINSON[2], X. F. YANG[2], L. KULIK[3], M. HOLERS[3], S. TOMLINSON[2,4];
[1]Microbiology & Immunol., [2]Med. Univ. of South Carolina, Charleston, SC; [3]Univ. of Colorado, Denver, CO; [4]Ralph H. Johnson Veterans Affairs Med. Ctr., Charleston, SC

Abstract: Spinal cord injury (SCI) initiates a cascade of events including ischemia, excitotoxicity and inflammation. Tissue injury exposes neoepitopes (Damage Associated Molecular Patterns,DAMPs) on the surface of injured cells that elicit an innate immune response following their recognition by natural IgM. We identified two IgM mAbs derived from unmanipulated mice that bind to post-ischemic cell membranes, and used them to investigate the role of natural IgM Abs in propagating SCI. These mAbs, B4 and C2, recognize annexin IV and a subset of phospholipids, respectively. Compared to wild type (wt) mice, Ab-deficient Rag1-/-

mice exhibited less tissue injury and improved locomotor recovery after SCI. However, reconstitution of Rag1-/- mice with B4 or C2 mAb restored injury to that seen in wt animals. Further, IgM was deposited in the spinal cord of wt mice after SCI, and depletion of peritoneal B cells by hypotonic shock reduced IgM and complement (C) deposition and protected mice from injury. The hypotonic shock procedure depletes the majority of B1a B cells (source of natural IgM), but has minimal effect on other components of the immune system, indicating SCI is driven by the binding of specific natural Ab IgM clones. Based on these data, we investigated a strategy to target a C inhibitor to the injured spinal cord. We constructed an anti-annexin-IV single chain (B4scFv) and linked it to Crry, an inhibitor of C3 activation. This construct significantly reduced SCI and improved locomotor recovery. This construct both blocked the binding of pathogenic IgM and inhibited C. This study identifies pathophysiologically important epitopes expressed within the spinal cord after contusion injury, and describes a novel strategy for targeted C inhibition to reduce secondary injury after SCI.

Disclosures: **A. Narang:** None. **H. Zhu:** None. **C. Atkinson:** None. **X.F. Yang:** None. **L. Kulik:** None. **M. Holers:** None. **S. Tomlinson:** None.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.05

Topic: C.10. Trauma

Support: HKSCI

973 program, 2014CB502200

Title: Enhanced regeneration and functional recovery after root avulsion by manipulation of proteoglycan receptor protein tyrosine phosphatase-σ

Authors: H. LI[1], C. W. WONG[2], W. LI[2], C. RUVEN[2], L. HE[2], X. WU[2], B. LANG[3], J. SILVER[3], *W. WU[4];
[1]the Univ. of Hong Kong, Hong Kong SAR, Hong Kong; [2]HKU, HK, Hong Kong; [3]Case Western Reserve Univ., OH, OH; [4]The Univ. Of Hong Kong, Hong Kong SAR, Hong Kong

Abstract: Following root avulsion, spinal nerves are physically disconnected from the spinal cord. Severe motoneuron death, scarring in the CNS-PNS transitional zone (TZ) and long distance for axon regrowth together could lead to inefficient regeneration and devastating motor

dysfunction. Chondroitin sulfate proteoglycan (CSPG) presents a major barrio for axonal extending in the extracellular matrix of scar tissue and it exerts the inhibitory role via its neuronal receptors, including protein tyrosine phosphatase-σ (PTPσ). Previously, a small peptide mimetic of PTPσ wedge motif, namely Intracellular Sigma Peptide (ISP) was generated and its capabilities to target PTPσ and relieve CSPG inhibition were validated. In the present study, in order to promote axonal regeneration and achieve functional recovery, we systematically administrated ISP for 12 weeks into adult rats with ventral root avulsion (the 5th, 6th and 7th cervical roots) and immediate reimplantation (C6 only). We show that 1) ISP treatment enabled up to 80.7% of injured motoneurons to survive, compared with 61.2% of that in vehicle treated reimplanted rats ($p<0.0001$, Chi-square test). 2) By facilitating newly formed axons to navigate through the inhibitory CNS-PNS TZ, ISP intervention nearly doubled the number of axons elongating in the peripheral nerve trajectory ($p<0.0001$, chi-square test). In addition, these axons exhibited bigger axon sizes than those found in vehicle rats ($p<0.05$, student's t test). 3) Muscles atrophy was rescued in ISP rats, reflected by their high similarity to intact ones in muscle fiber diameters and motor endplate morphology. By contrast, vehicle muscles displayed shrunk myocytes ($p<0.01$, z test) and fibrosis. Moreover, number of motor endplates was decreased ($p<0.05$, chi-square test) and they were more likely to fall into smaller area categories, with lower density of acetylcholine receptors, due to delayed or lack of reinnervation. 4) Importantly, motor functional recovery was remarkably enhanced, suggested by increased averaged score of Terzis grooming test ($p<0.05$ at 3- and 6-weeks post injury, Mann Whitney U test) and shortened recovery duration. Electromyography further confirmed that improved behavioral performance in ISP rats was associated with healthier motor units, with less spontaneous potentials recorded. Our results show that modulation of PTPσ is a potential therapeutic strategy for root avulsion injury.

Disclosures: **H. Li:** None. **C.W. Wong:** None. **W. Li:** None. **C. Ruven:** None. **L. He:** None. **X. Wu:** None. **B. Lang:** None. **J. Silver:** None. **W. Wu:** None.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.06

Topic: C.10. Trauma

Support: Onassis Foundation

CSRS

Title: Riluzole attenuates the decompression induced ischemia reperfusion injury and enhances the beneficial impact of decompression in cervical spondylotic myelopathy

Authors: *S. K. KARADIMAS, A. LALIBERTE, W. FOLTZ, M. G. FEHLINGS;
Krembil Discovery Tower, Toronto, ON, Canada

Abstract: INTRODUCTION: Surgical decompression is increasingly recommended as the treatment strategy for CSM and is associated with overall neurological improvement. While beneficial, little is known related to the physiological consequences of decompression in CSM. Here, we hypothesized for the first time that surgical decompression can cause initial harm to the spinal cord due to ischemia reperfusion injury (IRI) and that riluzole can prevent this surgical complication to improve overall functional recovery. METHODS: Here, a rat CSM model was used. Spinal cord blood flow (SCBF) was evaluated *in vivo* before and 6 hours after decompression using the Flow Alternative Inversion Recovery MRI technique. The levels of neuronal oxidative damage were also examined using immunohistochemistry. The potential protective effects of riluzole against the reperfusion induced oxidative damage were evaluated *in vivo* and *in vitro*. The long-term outcomes of combined treatment were also examined. ANOVAs were used for the statistics. RESULTS: FAIR MRI demonstrated a significant increased of SCBF 24 hours after decompression which was associated with an initial neurobehavioral decline. Neurobehavioural analysis further revealed that riluzole administration prevented this immediate neurobehavioural decline. It was also found that surgical decompression induced neuronal oxidative damage demonstrating hallmarks of IRI. Immunohistochemical tissue analysis and mechanistic *in vitro* oxidative stress experiments suggested that riluzole was able to attenuate neuronal oxidative damage. Moreover, this work demonstrated that combinatorial strategy consisting of surgical decompression and riluzole markedly improves hand and gait function. Finally, combined strategy reduces axonal damage, cellular apoptosis and motoneuronal injury. CONCLUSIONS: Here we discover the development of a previously unrecognized complication associated with surgical decompression, the only current treatment for human CSM. This silent enemy may represent a putative mechanism that can account for post-decompression neurobehavioural decline in surgically treated CSM. Finally this work supports and informs the CSM protect clinical trial.

Disclosures: S.K. Karadimas: None. **A. Laliberte:** None. **W. Foltz:** None. **M.G. Fehlings:** None.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.07

Topic: C.10. Trauma

Support: Craig H. Neilsen Foundation (283051)

Cardinal Hill Endowment to Joe Springer

NINDS NS051220 P30 grant to the University of Kentucky

Title: Pharmacological manipulation of macrophage phenotype with azithromycin improves recovery and tissue sparing in spinal cord injury

Authors: W. M. BAILEY, B. ZHANG, K. J. BRAUN, T. J. KOPPER, M. B. ORR, *J. C. GENSEL;
Physiology, Spinal Cord and Brain Injury Res. Ctr., Univ. of Kentucky, Lexington, KY

Abstract: Macrophages persist indefinitely at sites of spinal cord injury (SCI) and contribute to both pathological and reparative processes. While the alternatively activated phenotype (M2) is believed to promote cell protection, regeneration, and plasticity; pro-inflammatory (M1) macrophages persist after SCI and contribute to protracted cell and tissue loss. Thus, identifying non-invasive, clinically viable, pharmacological therapies for altering macrophage phenotype is an important challenge for the SCI field. Azithromycin (AZM), a common clinical antibiotic, increases M2 and decreases M1 activation in rodent models of lung infection, skin inflammation, and sepsis; in alveolar macrophages and human monocytes; and in humans with cystic fibrosis. We hypothesize that treatment with AZM can alter the macrophages in response to SCI and reduce progressive tissue pathology. In accordance with this hypothesis, we determined that mice (C57BL/6J, 3-month-old) receiving daily doses of AZM treatment via oral gavage exhibited significantly increased M2 and decreased M1 macrophage activation in response to moderate thoracic contusion SCI (75 Kdyne Infinite Horizons). In addition, AZM treatment led to improved tissue sparing and recovery of gross and fine locomotor function. Furthermore, AZM treatment altered macrophage phenotype *in vitro* and lowered the neurotoxic potential of pro-inflammatory, M1 macrophages. Taken together, these data suggest that pharmacologically intervening with AZM can alter SCI macrophage polarization towards the alternatively activated phenotype that, in turn, may potentially limit secondary injury processes. Given that M1 macrophage activation is a hallmark of many neurological pathologies and that AZM is non-invasive and clinically viable, these data highlight a novel approach for treating SCI and other maladaptive neuroinflammatory conditions.

Disclosures: W.M. Bailey: None. **B. Zhang:** None. **K.J. Braun:** None. **T.J. Kopper:** None. **M.B. Orr:** None. **J.C. Gensel:** None.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.08

Topic: C.10. Trauma

Title: b cell-targeted therapy with anti-cd20 monoclonal antibody reduced secondary tissue damage and enhanced behavioral recovery following experimental spinal cord injury in mice

Authors: ***S. CUZZOCREA**, D. IMPELLIZZERI, G. BRUSCHETTA, M. CORDARO, R. CRUPI, E. ESPOSITO;
Univ. of Messina, Messina, Italy

Abstract: Traumatic injury to the spinal cord activates B cells, which culminates in the synthesis of autoantibodies. The functional significance of this immune response is unclear. Antibodies produced after SCI caused pathology, in part by activating intraspinal complement and cells bearing Fc receptors. These data indicate that B cells, through the production of antibodies, affect pathology in SCI. There is increasing appreciation of the important role of B cells in spinal cord trauma and consequently, increasing interest in treating these disorders through B cell-depletion therapy. The purpose of this study was to investigate the effects of anti-CD20 mAb B cell depletion therapy within the first 24 hours of SCI. In this study, the T6-T7 vertebrae in three groups of mice were injured by a 50-g clip-induced compression method, and the anti-murine CD20 IgG2a antibody (clone 18B12, 1 mg/kg) was intravenously administered starting 1 hour and 6 hours postinjury. Animals were sacrified at 24 hours. The anti-CD20 antibody treatment caused significant attenuation of leukocyte infiltration, reactive oxygen species-associated enzymes, and secondary tissue damage. Basso-Beattie-Bresnahan (BBB) scores were significantly higher in anti-CD20-treated mice than controls 10 days postinjury. Our data demonstrate an important role of B cells which could possibly lead to B cell-based strategies for the treatment of SCI.

Disclosures: S. Cuzzocrea: None. **D. Impellizzeri:** None. **G. Bruschetta:** None. **M. Cordaro:** None. **R. Crupi:** None. **E. Esposito:** None.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.09

Topic: C.10. Trauma

Support: Department of Neurological Surgery, University of Washinton

Title: Characterization of intraspinal pressure following traumatic rodent spinal cord injury

Authors: Z. KHAING, L. CATES, A. FISCHEDICK, *C. HOFSTETTER;
Neurolog. Surgery, Univ. of Washington, Seattle, WA

Abstract: Traumatic spinal cord injury (SCI) leads to devastating neurological impairment. Currently, the only clinically effective intervention following traumatic spinal cord injury (SCI) is surgical decompression of the spinal cord by removal of impinging bone fragments within 24 hours after injury. In contrast, following traumatic brain injury, intensive care protocols include meticulous pressure monitoring of contused brain tissue that has led to a significant reduction of mortality and morbidity. A recent clinical study suggests that intraspinal pressure is raised following traumatic spinal cord injury (Werndle et al. 2014). There is a lack of data regarding intraspinal pressure in rodent traumatic spinal cord injury models. We investigate intraspinal pressure after a moderate thoracic contusion SCI in rats. Intraspinal pressure was recorded using a Millar Mikro-Tip® catheter placed into the epicenter of the spinal cord parenchyma (tip diameter 250 μm). Our preliminary results suggest that compared to physiological pressure in the intact spine (1.8 ± mmHg), intraspinal pressures increase almost fivefold following SCI. Thus, 30 minutes after injury intraspinal pressure was measured at 3.1 ± 0.9 mmHg, pressure increased steadily until it reached a maximum at approximately 12 hours (10.0 ± 1.5 mmHg), and then declined until the last measurement at 24 hours (6.1 ± 1.2 mmHg). Additionally, preliminary data suggest that the injury area with elevated tissue pressure extends along a rostrocaudal axis with time after injury. Thus, one hour following injury, increased pressure was detected in an approximately 5 mm long segment of the spinal cord while 24 hours after injury elevated pressures were recorded in an area spanning approximately 10 mm. Once pressure monitoring was completed, a durotomy was performed. This intervention decreased ISP by approximately 30% and resulted in intraspinal pressures of 6.2 ± 0.4 mmHg. Results presented here suggest that rat contusion SCI model in combination with novel microcatheters allow measurement of intraspinal pressures after a contusion type SCI. Similarly to traumatic brain injuries, raised tissue pressure following spinal cord injury might effect spontaneous recovery. Moreover, elevated pressures may impact the efficacy of experimental therapeutic interventions that are currently evaluated in rodent contusion models of SCI.

Disclosures: Z. Khaing: None. **L. Cates:** None. **A. Fischedick:** None. **C. Hofstetter:** A. Employment/Salary (full or part-time); University of Washington.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.10

Topic: C.10. Trauma

Support: Advancing a Healthier Wisconsin 5520207

Craig H Neilsen Foundation 297024

NIGMS T32-GM080202

Title: Rapid *in vivo* detection of spinal cord injury severity with advanced diffusion magnetic resonance spectroscopy

Authors: *N. P. SKINNER[1,2], B. D. SCHMIT[4], S. N. KURPAD[3,5], M. D. BUDDE[1,3,5]; [1]Biophysics Grad. Program, [2]Med. Scientist Training Program, [3]Neurosurg., Med. Col. of Wisconsin, Milwaukee, WI; [4]Biomed. Engin., Marquette Univ., Milwaukee, WI; [5]Clement J. Zablocki Veteran's Affairs Med. Ctr., Milwaukee, WI

Abstract: Assessing the severity of spinal cord injury in the acute clinical setting and predicting subsequent outcome are important but unmet challenges. Diffusion Tensor Imaging (DTI), a Magnetic Resonance Imaging (MRI) technique that noninvasively measures water diffusion in tissue as a probe of microstructure, has shown promise as a sensitive marker of injury severity. However, in-vivo DTI of the spinal cord is limited by significant technical barriers, requires imaging durations not often amenable to clinical care, and is complicated by multiple coexistent pathological features. Most prominently, the DTI-derived measures of Mean Diffusivity and Fractional Anisotropy are altered by the presence of acute axonal injury but are also confounded by edema. To overcome these limitations and improve in-vivo characterization of injury pathology, we developed an alternative diffusion weighted MRI method, DwFilt, which has greater specificity for axonal injury, the pathology most related to injury severity and functional outcome. This method is a new pulse sequence that combines a diffusion weighting filter to suppress edema with a conventional diffusion weighting sensitization to selectively probe diffusion properties predominantly in the intra-axonal space. Additionally, the diffusion filter also suppresses signal from non-spinal cord tissues, including cerebrospinal fluid and muscle, which enables rapid detection of signal from the spinal cord only. This technique was evaluated in a rat model of contusion spinal cord injury at the T10 vertebral segment for mild, moderate, severe, and sham injury severities. At the lesion epicenter, the DwFilt method provided a clear separation of the injury severities in approximately 5 minutes of acquisition time. Conversely, DTI at the lesion epicenter in the same animals required approximately 70 minutes for data

acquisition but did not show a clear effect of injury severity, presumably due to the conflicting effects of edema. The DwFilt technique was also related to severity at locations distant from the injury site, including the proximal thoracic cord and the cervical cord, although the effects were less pronounced remote from the lesion, as expected. In summary, the DwFilt technique robustly separates injury severity, has better sensitivity than DTI analysis, and is performed with a considerable reduction in time requirements. These features, combined with being a completely noninvasive method, make the DwFilt technique particularly attractive for evaluation of spinal cord injury in both clinical and pre-clinical settings.

Disclosures: **N.P. Skinner:** None. **B.D. Schmit:** None. **S.N. Kurpad:** None. **M.D. Budde:** None.

Nanosymposium

650. Spinal Cord Injury: Therapeutic Strategies

Location: S102

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 650.11

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: SpinalCure Australia

The National Health and Medical Research Council (NHMRC)

The University of New South Wales (UNSW)

St Vincent's Centre for Applied Medical Research (AMR)

Brain Science UNSW

Title: Dynamics of inflammatory immune response in a mouse model of traumatic spinal cord injury

Authors: *M. HASSANPOUR GOLAKANI[1,2], M. G. MOHAMMAD[1,2], H. LI[1,2], S. N. BREIT[1,2], M. RUITENBERG[3], D. A. BROWN[1,2];
[1]Lab. of Neuroinflam., St Vincent'S Ctr. For Applied Med. Res., Darlinghurst, Australia; [2]The Univ. of New South Wales (UNSW), Sydney, Australia; [3]Queensland Brain Inst., The Univ. of Queensland, Brisbane, Australia

Abstract: Inflammatory responses post spinal cord injury (SCI) may be detrimental or beneficial. However, the dynamics of this inflammatory response are largely unknown. The aim

of this study was to quantify and characterize immune cells in, and around, the injury site, as well as their relationship with locomotor functional recovery after contusive SCI. Mice had a 70 kilo dyne force SCI induced using the Horizon impactor after laminectomy. Locomotor function was assessed, using the Basso Mouse Scale (BMS). At days 7, 14, 21, and 28 post injury, the entire spinal cord was removed and mononuclear cells associated with SCI were isolated. Various immune cell populations were characterized and quantified using multiparameter flow cytometry. Results were validated using both IHC and IF staining and correlated with histological assessment of injury parameters and injury course. Post SCI mice had complete paralysis, with functional recovery to score 3-4 over 28 days post injury (dpi). Smaller mice had significantly less recovery. Peripherally derived immune cells progressively increased over the course of recovery from SCI, most of which were T-cells. Both CD4+ and CD8+ T-cells increased by 4-5 fold at day 28 compared to day 7 dpi. The CD4+ T-cell population was predominantly INFγ+ (Th1), with FoxP3+ (T-regulatory) and IL17+ (Th17) cells being less frequent. Myeloid DCs (mDCs) were the predominant subtype of DCs present. They increased significantly from day 21 to 28 dpi. On the other hand, CD8α+ DCs were the least frequent DC subtypes and significantly decreased by about 3 fold at day 21 and then increased at 28 dpi. Plasmacytoid DC (pDC) frequency was unchanged from 7 dpi. There were also no significant changes in macrophages and B cells over 7-28 dpi, indicating early recruitment. Immunohistology revealed CD11c+ cells and CD3+ T-cells were predominantly confined to the injury core. While GFAP+ astrocytes surrounded the core. Iba-1+ microglia were dispersed throughout the entire spinal cord. White mater surrounding the injury core was substantially demyelinated and myelin was observed in injury core. Functional recovery was positively correlated with the total numbers of injury-associated macrophages and their percentage of CD45+ cells at 28 dpi. Improved recovery was also positively correlated with CD11c+ DCs' percentage of CD45+ cells, mostly consisting of mDCs. On the other hand, pDC numbers were negatively correlated with functional recovery. The changes for T-cells and their subtypes were not significantly related to improvement. These data suggest a role for DCs and macrophages in the resolution of SCI and identify them as a potential therapeutic target.

Disclosures: **M. Hassanpour Golakani:** None. **M.G. Mohammad:** None. **H. Li:** None. **S.N. Breit:** None. **M. Ruitenberg:** None. **D.A. Brown:** None.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.01

Topic: C.14. Gene Therapy

Support: Hannah's Hope Fund Grant

NIH NINDS Grant 1R01NS087175

Title: Development of a first-in-human intrathecal scAAV9 gene therapy for giant axonal neuropathy

Authors: *S. J. GRAY[1,2], R. M. BAILEY[1], D. ARMAO[3], S. NAGABHUSHAN KALBURGI[1]; [1]Gene Therapy Ctr., [2]Ophthalmology, [3]Pathology and Lab. Med., Univ. of North Carolina, Chapel Hill, NC

Abstract: Giant axonal neuropathy (GAN) is a rare pediatric neurodegenerative disorder characterized by progressive sensory and motor neuropathy that presents as early as 2-3 years of age and with ultimate mortality during the second or third decade of life. GAN is caused by autosomal recessive loss-of-function mutations in the GAN gene that encodes for the gigaxonin protein. Gigaxonin plays a role in the organization/degradation of intermediate filaments (IFs), and GAN patients are pathologically characterized by large axonal swellings filled with disorganized aggregates of IFs. While GAN is primarily described as a progressive peripheral neuropathy, diffuse pathology from disorganized IFs is apparent throughout the nervous system and other organ systems. An NIH-sponsored Phase I study (NCT02362438) is underway to test the safety of intrathecal (IT) administration of scAAV9/JeT-GAN to treat the most severe aspects of GAN, namely the motor and sensory neuropathy. Gigaxonin gene transfer is the first proposed therapy for GAN, and to our knowledge this is the first IT delivery of a gene therapy vector in humans. Our group developed the approach and vector to be used in the Phase I clinical trial, which is a self-complementary AAV serotype 9 vector carrying a codon-optimized human GAN transgene whose expression is controlled by the minimal synthetic JeT promoter (scAAV9/JeT-GAN). Preclinical studies show that scAAV/JeT-GAN can restore the normal arrangement of IFs in patient fibroblasts within days in cell culture and by 3 weeks in GAN KO mice. The safety and biodistribution of scAAV9/JeT-GAN was investigated in mice, rats, and non-human primates (NHPs) that received a single IT overdose of scAAV9/JeT-GAN. No safety concerns were apparent from these animal studies at up to a 10-fold overdose, with the longest endpoint at 1 year post-injection. To further support the translation of this approach to human subjects, IT delivery of the scAAV9/JeT-GAN vector in GAN KO mice showed sustained levels of human gigaxonin expression in therapeutically-relevant areas for at least 48 weeks without evidence of toxicity. Furthermore, treated GAN KO mice have improved motor function and preservation of peripheral nerve ultrastructure. In all, the results of our preclinical studies attest to the safety of IT-delivered scAAV9/JeT-GAN and the potential to benefit treated patients.

Disclosures: **S.J. Gray:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asklepios Biopharma. **R.M. Bailey:** None. **D. Armao:** None. **S. Nagabhushan Kalburgi:** None.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.02

Topic: C.03. Parkinson's Disease

Title: A novel TwinkPark mouse model to understand the impact of increased mitochondrial DNA deletions in dopaminergic neurons and Parkinsonism

Authors: *G. CORTOPASSI, L. SONG;
VM: Mol. Biosci., UC DAVIS, Davis, CA

Abstract: Parkinson's disease (PD) is characterized by the loss of dopaminergic (DA) neurons in the substantia nigra (SN). Mitochondrial DNA (mtDNA) deletions accumulate with age to the greatest extent in SN in the brain, and are correlated with death, yet the pathomechanism by which mtDNA deletions trigger DA neurodegeneration remains unclear. Twinkle is a key helicase involved in mtDNA replication and critical for the maintenance of human mtDNA integrity. Twinkle mutations cause multiple mtDNA deletions and neurodegeneration in humans. Previously we constructed mice expressing mutant Twinkle in DA neurons, and found that mutant Twinkle increased mtDNA deletions and mild DA neurodegeneration. Since Parkin deletion may inactivated mitochondrial quality control, we crossed mutant Twinkle (Twinkledup/+ or Twinkledup/dup) mice with Parkin knockout (Parkin-/-) mice to create 'TwinkPark' mice. TwinkPark mice had the highest mtDNA deletion levels, and displayed more behavior deficits (treadscan, beam level and rotarod test) compared to WT, Twinkle dup/+ and Parkin-/- mice at 13 and 19 months. Similarly, Twinkpark mice had the lowest SN dopamine levels, and tyrosine hydroxylase positive neurons at 13 and 19 months. Mitochondrial respiratory function and mitochondrial membrane potential are remarkably lower in midbrain of Twinkledup/+;parkin-/- mice at 3 months. These results demonstrate a new mouse model of the consequences of increased mtDNA deletions in dopaminergic neurons of the SN. This model could provide insights into the mechananism by which increased DA mtDNA deletions promote DA neurodegeneration.

Disclosures: G. Cortopassi: None. **L. Song:** None.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.03

Topic: C.14. Gene Therapy

Title: Towards gene therapy in the brain: Delivery to the NHP CNS using AAV-5

Authors: *B. BLITS[1], L. SAMARANCH[2], J. BRINGAS[2], W. SAN SEBASTIAN[2], K. BANKIEWICZ[2], H. PETRY[1];
[1]Uniqure, Amsterdam, Netherlands; [2]Neurolog. Surgery, Interventional Neuro Center, Univ. of California San Francisco, San Francisco, CA

Abstract: This study was performed to investigate the delivery of AAV vectors into the putamen, thalamus, or CSF of nonhuman primates (n=12). The vectors were delivered to the targeted brain regions by MRI guided convection enhanced diffusion. Intrathecal injections were performed at the lumbar region. Special attention was given to the analysis of directional axonal transport. Recombinant AAV is an excellent candidate for delivery of therapeutic molecules to the central nervous system to target neurodegenerative diseases. UniQure has succeeded in developing a proprietary platform manufacturing technology that allows safe, effective, cGMP-compliant, economically feasible and commercially scalable manufacturing of AAV. UniQure's novel approach is based on the use of a combination of recombinant baculoviruses and insect cells. Using our production platform, two AAV stocks encoding GDNF or GFP were generated. At eight weeks following infusion into the thalamus (approximately 200 µL/site), for instance, massive transduction of the thalamus, cortex, striatum and substantia nigra was observed indicating both anterograde and retrograde transduction. Following injection of a lower volume, into the putamen (51-127 µL/site), transduction only in the Putamen and the substantia nigra suggested pure anterograde transduction. At the site of injection, transduction was both glial and neuronal, whereas off site transduction was mainly neuronal. These data suggest a dose dependent anterograde or retrograde transduction mechanism. For CSF delivery, we injected various concentrations of AAV5 (1E+14, 1E+13 and 1E+12 vg/mL) into CSF via lumbar routes (5 mL/site) in naïve NHP and studied vector distribution and cellular transduction 8 weeks after CSF delivery. We found a dose-dependent increase in transduction with strong levels of cell transduction and distribution throughout cortex and along the spinal cord at the highest doses and no signal in the low-dose group. These results suggest a dose threshold when delivering into CSF, most likely due to a dilution of the viral particles. These data together show that production of AAV using the (scalable) baculovirus-based platform results in an effective vector that is able to mediate expression patterns that can be used to develop and tailor an AAV-mediated therapeutic strategy to treat neurodegenerative diseases.

Disclosures: **B. Blits:** None. **L. Samaranch:** None. **J. Bringas:** None. **W. San Sebastian:** None. **K. Bankiewicz:** None. **H. Petry:** None.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.04

Topic: C.19. Drug Discovery and Development

Support: NIH, NIA Grant AG029777

Title: Drug discovery for Alzheimer's and related tauopathies targeting a novel proteolytic mechanism intrinsic to tau oligomers

Authors: G. PAPIANI, P. LOPEZ, D. ROMERO, P. KRISHNAMURTHY, *E. J. DAVIDOWITZ, J. G. MOE;
Oligomerix, Inc., New York, NY

Abstract: The particular structure and mechanisms by which tau oligomers exert their deleterious effects are an important focus of current research. The oligomeric forms of tau accumulate in AD brain and appear to be most closely associated with neuronal loss and memory impairment in mouse models of tauopathy. Importantly, extracellular tau oligomers have been shown to impair memory formation and inhibit long-term potentiation in hippocampal slices. Tau oligomers are also thought to transmit tau pathology from diseased to healthy neurons during disease progression. We have made the interesting observation that when tau forms oligomeric structures tau itself becomes an active protease ("tau protease") truncating itself and cleaving other proteins. Here, we present work characterizing tau protease activity and assays for screening small molecule inhibitors. Recombinant human tau oligomers were purified and incubated to generate autoproteolytic fragments. N-terminal sequencing of isolated fragments was used to determine cut sites in tau. Peptides spanning a cut site were used as a substrate for assaying tau protease activity and for screening inhibitors *in vitro*. A range of protease inhibitors were used to classify tau protease. Antibodies specific for autoproteolytic tau fragments were developed. Truncated constructs and mutagenesis were used to localize the active-site region of tau. Cell assays are being developed to screen inhibitors of tau protease activity. A point mutation in tau blocks tau cleavage in a cell assay for tau protease. A platform for drug discovery targeting tau protease is being assembled to enable screening of focused libraries of small molecule protease inhibitors.

Disclosures: **G. Papiani:** A. Employment/Salary (full or part-time); Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **P. Lopez:** A. Employment/Salary (full or part-time); Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **D. Romero:** A. Employment/Salary (full or part-time); Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **P. Krishnamurthy:** A. Employment/Salary (full or part-time); Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **E.J. Davidowitz:** A. Employment/Salary (full or part-time); Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **J.G. Moe:** A. Employment/Salary (full or part-time); Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc..

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.05

Topic: C.03. Parkinson's Disease

Title: Synuclein strains cause distinct synucleinopathies *in vivo*

Authors: W. PEELAERTS[1], L. BOUSSET[2], A. VAN DER PERREN[1], A. MOSKALYUK[3], R. PULIZZI[3], M. GIUGLIANO[3], C. VAN DEN HAUTE[1], R. MELKI[2], *V. BAEKELANDT[1]; [1]KU Leuven, Lab. for Neurobio. and Gene Therapy, Leuven, Belgium; [2]Paris-Saclay Inst. of Neurosci., Gif-sur-Yvette, France; [3]Theoretical Neurobio. & Neuroengineering Lab., Antwerp, Belgium

Abstract: Misfolded protein aggregates represent a continuum with overlapping features in neurodegenerative diseases but differences in protein components and affected brain regions. The molecular hallmark of synucleinopathies such as Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA) are mega-dalton α-synuclein-rich deposits suggestive of one molecular event causing distinct disease phenotypes. Glial α-synuclein (αSYN) filamentous deposits are prominent in MSA while neuronal αSYN inclusions

are found in PD and DLB. The discovery of αSYN assemblies with different structural characteristics or 'strains' has led to the hypothesis that strains could account for the different clinico-pathological traits within synucleinopathies. In this study we show that αSYN strain conformation and seeding propensity lead to distinct histopathological and behavioral phenotypes. We assess the properties of structurally well-defined αSYN assemblies (oligomers, ribbons and fibrils) after injection in rat brain. We prove that αSYN strains amplify *in vivo*. Fibrils appear as the major toxic species resulting in progressive motor impairment and cell death, while ribbons cause a distinct histopathological phenotype displaying PD and MSA traits. Additionally, we show that αSYN assemblies cross the blood-brain barrier and distribute to the central nervous system after intravenous injection. Our results demonstrate that distinct αSYN strains display differential seeding capacities inducing strain-specific pathology and neurotoxic phenotypes.

Disclosures: W. Peelaerts: None. **L. Bousset:** None. **A. Van der Perren:** None. **A. Moskalyuk:** None. **R. Pulizzi:** None. **M. Giugliano:** None. **C. Van den Haute:** None. **R. Melki:** None. **V. Baekelandt:** None.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.06

Topic: C.14. Gene Therapy

Support: NIH NINDS

The Legacy of Angels Foundation

Title: Aav9 delivery of galactosyl-ceramidase attenuates neuronal and myelin disease in a mouse model of krabbe's disease

Authors: *M. S. MARSHALL[1], B. JAKUBAUSKAS[1], Y. ISSA[1], S. M. KARUMUTHIL[2], M. S. SANDS[3], S. J. GRAY[2], E. R. BONGARZONE[1];
[1]Anat. and Cell Biol., Univ. of Illinois at Chicago Col. of Medic, Chicago, IL; [2]Gene Therapy Ctr., Univ. of North Carolina, Chapel Hill, NC; [3]Medicine, Genet., Washington Univ., St. Louis, MO

Abstract: Infantile Krabbe disease is a devastating genetic disorder, which causes progressive demyelination of the central and peripheral nervous system, neurosensory deficits, muscle

atrophy, and early death. Krabbe disease is due to loss-of-function mutations in the gene encoding for the lysosomal enzyme Galactosylceramidase (GALC). This results in the toxic accumulation of one of its lipid substrates, galactosyl-sphingosine (or psychosine). Current therapy for patients afflicted with Krabbe is limited to Hematopoietic Stem Cell Transplantation (HSCT) from healthy donors, which has the ability to extend lifespan, but still results in many debilitating disabilities. In this study, we developed and optimized a gene therapy strategy using the adeno-associated virus serotype 9 (AAV9) vector to correct for the deficiency of GALC activity in combination with HSCT. Using the Twitcher mouse model of Krabbe disease, we show that AAV9 gene therapy restored GALC activity in CNS, PNS, and systemic organs, thereby significantly reducing the accumulation of psychosine. Immunohistology demonstrated transduction of central neurons and astrocytes. When combined with neonatal HSCT, AAV9 gene therapy resulted in nearly complete correction of the clinical phenotype and extended lifespan significantly. Histopathological analysis showed the reversal of demyelination, neuro-inflammation and gliosis, and neuropathy in treated mice. These results reveal the profound benefit AAV9 gene therapy could have on human Krabbe's patients when used in conjunction with current therapies.

Disclosures: **M.S. Marshall:** None. **B. Jakubauskas:** None. **Y. Issa:** None. **S.M. Karumuthil:** None. **M.S. Sands:** None. **S.J. Gray:** None. **E.R. Bongarzone:** None.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.07

Topic: C.19. Drug Discovery and Development

Title: Metal ion chelation enhances tissue plasminogen activator (tPA)-induced thrombolysis: an *in vitro* and *in vivo* study

Authors: X. YU[1], *Y. V. LI[2,2];
[1]Biol. Grad. Program, [2]Biomed. Sci., Ohio Univ., Athens, OH

Abstract: Stroke is the third leading cause of death in the United States and the leading cause of adult disability. Despite enormous research efforts including many clinical trials, very little is known about the mechanisms that govern stroke recovery. There is not yet an effective treatment for stroke, and effective therapy has remained elusive. Tissue plasminogen activator (tPA) remains the only FDA-approved treatment for acute ischemic stroke. Unfortunately, only 1-3% of stroke patients in the US receive this therapy because of the narrow time window and severe

side effects for using tPA. The most deadly and damaging side effect of tPA is the risk of intracranial bleeding or hemorrhage. For that reason, the dose of tPA and its overall administration are under tight control, while the effect of thrombolysis may be compromised. Studies have been focused on improving efficacy of tPA for higher rate of reperfusion, and for enhancement of safety and less adverse bleeding episode. In the present study, we investigated the effect of zinc and iron on tPA-induced thrombolysis *in vitro* and *in vivo*, and proposed a method to improve thrombolysis. Results showed that Zn2+, Fe3+ and Fe2+ inhibited tPA-induced thrombolysis, with Zn2+ and Fe2+ being the most potent. Ion chelation of EDTA significantly increased the efficacy of tPA-induced thrombolysis. Our study shows effective zinc and iron chelation facilitates tPA-induced thrombolysis and reduces the necessary dose of tPA treatment. The smaller dose of tPA when it was applied with the chelator achieved a higher rate of reperfusion. Taken together, our results suggest that the co-application of tPA and a chelator targeting zinc and iron improves the efficacy, potency, and safety of tPA in thrombolysis.

Disclosures: **X. Yu:** None. **Y.V. Li:** None.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.08

Topic: C.14. Gene Therapy

Support: NIH R01 DC06908

NIH R01 GM095501

Howard Hughes Medical Institute

Title: Restoration of hearing in the Pmca2 deafness mouse model by protein delivery and CRISPR/Cas9-medated hair cell genome editing

Authors: ***Z.-Y. CHEN**[1], Y. TAO[2], X. GAO[3], J. ZURIS[3], D. LIU[3];
[1]Mass Eye & Ear Infirmary, Boston, MA; [2]Otology & Laryngology, Massachusetts Eye & Ear Infirmary, Harvard Med. Sch., Boston, MA; [3]Harvard University, HHMI, Boston, MA

Abstract: 1 in 500 newborns suffer from genetic hearing loss. Over 100 loci have been linked to and hundreds more genes are likely to be responsible for genetic hearing loss when mutated. Approaches including AAV-mediated gene therapy, anti-sense oligos and shRNA have been developed as potential treatment. Due to the limitations of each method, new approach is needed

for the treatment of different forms of genetic hearing loss. CRSIPR/Cas9-mediated genome editing has been increasingly explored as new type of potential treatment due to the permanent editing results. However most CRISPR/Cas9 has been performed in germline or *in vitro* by viral vectors or DNA, which raises long-term safety concerns. Further the *in vivo* efficiency has been generally low. We have recently demonstrated that Cas9 with guide RNAs can be effectively delivered into mammalian inner ear *in vivo* by cationic lipid formulation, resulting in efficient genome editing in the sensory hair cells. To develop potential treatment based on CRISPR/Cas9-mediated genome editing for genetic hearing loss, we studied the delivery of Cas9 with gRNAs against mutant Pmca2, a plasma-membrane calcium pump, which is associated with human and mouse progressive deafness. Direct *in vivo* local injection of Cas9 protein with Pmca2 guide RNA targeting the mutation led to restoration of hearing in the Pmca2 Oblivion mutant mouse demonstrated by auditory brainstem response (ABR) and distortion product otoacoustic emissions (DPOAE). Long-term hearing restoration was achieved. Cas9:gRNA mediated genome editing recovers the function of outer hair cells, promotes hair cell survival and preserves neurites of auditory ganglion neurons. Thus transient *in vivo* inner ear delivery of Cas9 and gRNA complex is sufficient to induce genome editing and restore hearing in a genetic deaf mouse model. Similar approach can be applied to treat other genetic hearing loss in the animal models with the implication in the treatment of human genetic hearing loss.

Disclosures: Z. Chen: None. **Y. Tao:** None. **X. Gao:** None. **J. Zuris:** None. **D. Liu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Editas Medicine.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.09

Topic: C.14. Gene Therapy

Support: Italian Ministry of Health grant GR-2010-2309229

Title: Gene therapy rescues disease phenotype in a spinal muscular atrophy with respiratory distress type 1 (SMARD1) mouse model

Authors: M. NIZZARDO[1], C. SIMONE[1], F. RIZZO[1], S. SALANI[1], P. RINCHETTI[1], R. DEL BO[1], S. DAMETTI[1], K. FOUST[2], B. K. KASPAR[2,3], N. BRESOLIN[1], *G. P. COMI[4], S. CORTI[1];
[1]Univ. of Milan, Milan, Italy; [2]The Ohio State Univ., Columbus, OH; [3]The Res. Inst. at

Nationwide Children's Hosp., Columbus, OH; [4]Univ. of Milan, Ospedale Maggiore Policlinico, Milan, Italy

Abstract: Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is an autosomal recessive motor neuron disease affecting children that is caused by mutations in the IGHMBP2 gene (11q13) and lacks a cure. Recently, adeno-associated virus serotype 9 (AAV9)-mediated gene therapy rescued the phenotype of animal models of another lower motor neuron disorder, spinal muscular atrophy 5q, and a clinical trial with this strategy is ongoing. In this study, we report rescue of the disease phenotype in a SMARD1 mouse model following therapeutic delivery of an AAV9 construct encoding the wild-type IGHMBP2 via systemic injection to replace the defective gene. AAV9-IGHMBP2 administration restored protein levels and rescued motor function, neuromuscular physiology, and lifespan (450% increase), ameliorating pathological features in the CNS, muscles, and heart. To test this strategy in a human model, we transferred wild-type IGHMBP2 into human SMARD1 induced pluripotent stem cell-derived motor neurons; these cells exhibited increased survival and axonal length in long-term culture. Our data support the translational potential of AAV-mediated gene therapies for SMARD1, opening the door for AAV9-mediated therapy in human clinical trials.

Disclosures: **M. Nizzardo:** None. **C. Simone:** None. **F. Rizzo:** None. **S. Salani:** None. **P. Rinchetti:** None. **R. Del Bo:** None. **S. Dametti:** None. **K. Foust:** None. **B.K. Kaspar:** Other; Avexis. **N. Bresolin:** None. **G.P. Comi:** None. **S. Corti:** None.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.10

Topic: C.14. Gene Therapy

Support: NIH 5T32 GM8243-28

Title: A potential choroid plexus-directed gene therapy with AAV5 in MPS IIIB mice

Authors: ***S.-H. KAN**, S. Q. LE, Q. D. BUI, P. I. DICKSON;
LA BioMed At Harbor-UCLA Med. Ctr., Torrance, CA

Abstract: Mucopolysacccharidosis (MPS) IIIB is an inherited lysosomal storage disorder caused by the deficiency of a lysosomal enzyme, alpha-N-acetylglucosaminidase (NAGLU). The disease is characterized by mild somatic features but severe neurologic manifestations with high

mortality, associated with storage of heparan sulfate. Intracerebroventricular enzyme replacement therapy (ERT) with IGF-II fusion protein has been shown to be a feasible treatment for Sanfilippo B in mice [1] to overcome two impediments to ERT: the absence of mannose 6-phosphate (M6P) on recombinant human NAGLU (rhNAGLU) and the blood brain barrier. In this study, hNAGLU-IGF-II and hNAGLU cDNA were cloned into an adeno-associated virus (AAV) vector plasmid and the recombinant AAV serotype 5 (rAAV5) was generated by triple transfection. Recombinant AAV5 expressing either hNAGLU-IGF-II or hNAGLU targets the choroid plexus epithelium to express and secrete the missing enzyme into the cerebrospinal fluid (CSF) of MPS IIIB mice. 2.5x10E9 vector genomes (v.g.) of rAAV5 for either constructs or vehicle was administered to MPS IIIB mice at postnatal day 2 by injection into both lateral ventricles. Biochemical and histological analyses were performed on mouse brains 10 weeks after rAAV5/vehicle injection and compared with control (heterozygous) mice. NAGLU enzyme activity reached 3.68 and 0.13 times the control level in the brain section around the injection site of mice treated by rAAV5-hNAGLU and rAAV5-hNAGLU-IGF2, respectively. β-Hexosaminidase activity, which is elevated in MPS IIIB, was reduced in the rAAV5-rhNAGLU treated mice to the carrier level throughout the brain except cerebellum/brain stem area. Tissue evaluations by immunohistochemistry showed hNAGLU-IGF-II or hNAGLU expression in the choroid plexus epithelium in lateral ventricles; Lamp1 expression was significantly reduced around the injection sites (hippocampus, frontal cortex) in the rAAV5-hNAGLU treated mice. Although no NAGLU enzyme activity was detected in liver samples, but β-hexosaminidase activity was reduced half way to the normal level. Our results suggest that the choroid plexus-targeted viral gene therapy with rAAV5 NALGU may overcome the major obstacles for ERT with proper M6P modification as a permanent, efficient distribution of NAGLU throughout the brain. 1.Kan et al., (2014) Proc Natl Acad Sci U S A. 111(41):14870-5.

Disclosures: **S. Kan:** None. **S.Q. Le:** None. **Q.D. Bui:** None. **P.I. Dickson:** None.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.11

Topic: C.14. Gene Therapy

Support: NS072446-01

NS081374-01

Title: Behavioral outcome of X-ALD mouse after rAAV9-ABCD1 treatment

Authors: *Y. GONG, D. MU, J. REN, C. MAGUIRE, F. EICHLER;
MGH, Charlestown, MA

Abstract: X-linked adrenoleukodystrophy(X-ALD) is a devastating neurological disorder caused by mutations in the ABCD1 gene that encodes a peroxisomal ATP-binding cassette (ABC) transporter. We previously reported successful transduction of central nervous system cells *in vitro* and *in vivo* using recombinant adeno-associated virus serotype 9 (rAAV9) vector for delivery of the human ABCD1 gene (ABCD1). Here we report first results of long term experiments to evaluate the therapeutic effect of AAV9-ABCD1 in a mouse model of X-ALD that develops motor and sensory symptoms around 18 months of age. rAAV9 encoding ABCD1 (rAAV9-ABCD1) was delivered to Abcd1-/- mouse CNS by stereotactic intraventricular (ICV) injection at young (4 months) and old (12 months) age, while intravenous (IV) injection was tested at only old age (12 months). Mouse body weight was monitored every month, while mouse behavior including hind limb reflex extension (scoring system 0-4, paralysis to normal), mechanical sensitivity (von Frey testing) and motor function (rotarod testing and beam walking) were recorded starting from 15 months of age. No changes in body weight occurred regardless of delivery route or age injected, suggesting no obvious toxicity of the rAAV9-ABCD1 vector. ICV injection at both young and old age showed significant improvement upon mouse hind limb reflex extension after 15 months of age. Scores of hind limb reflex extension in untreated Abcd1-/- mice dropped to 1.75 at 18 months of age (wild type mice: 3.5), whereas Abcd1-/- mice treated via ICV at an old age retained scores around 3.25 ($p<0.05$). ABCD1-/- mice treated via ICV at a young age had an average score of 3.5 at 15 months (compared to untreated Abcd1-/- mice: 2.4; $p<0.05$). IV injection at old age showed mild but not significant improvement. Motor function tested by beam walking show significant improvement by IV injection at old age. Mechanical sensitivity also improved after both ICV injection at young age and IV injection at old age but not ICV injection in old Abcd1-/- mice. We conclude that rAAV9-mediated ABCD1 gene transfer is safe and efficacious at improving behavior of a known X-ALD mouse model including mouse hind limb reflex extension and mechanical sensitivity. However timing and delivery route are crucial determinants of efficacy and need to be independently assessed.

Disclosures: Y. Gong: None. **D. Mu:** None. **J. Ren:** None. **C. Maguire:** None. **F. Eichler:** None.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.12

Topic: C.14. Gene Therapy

Support: FP7 EU Commission Award number: 233147

Title: Motor neuron targeted αCAR-IGF-1 lentiviral vector is neuroprotective in model of ALS

Authors: *I. ELEFTHERIADOU[1], I. MANOLARAS[2], E. IRVINE[3], N. D. MAZARAKIS[2]; [1]MEDICINE, IMPERIAL COLLEGE LONDON, London, United Kingdom; [2]Med., [3]Insitute of Clin. Sci., Imperial Col. London, London, United Kingdom

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a lethal, adult onset progressive neurodegenerative disorder, characterized by the combined degeneration of upper and lower motor neurons that reside in the spinal cord, brain stem and cortex. No effective ALS treatment is available at present. Retrograde viral delivery of Insulin-like Growth Factor 1 (*IGF-1*) from the muscle to spinal cord motor neurons, has been reported to prolong survival in transgenic mouse ALS model. In order to overcome the limitations of existing viral vectors for non-invasive CNS delivery, we have engineered HIV-1 vectors with tropism to spinal cord Motor Neurons (MNs) delivered via the Neuromuscular Junction (NMJ). We have described the generation of HIV-1 based coxsackievirus and adenovirus receptor (αCAR)-targeted vector, and shown that *in vivo* intramuscular (i.m.) delivery of αCAR-targeted vector in mouse leg muscles results in specific retrograde transduction of lumbar MNs. Utilizing the αCAR-targeted vector we investigated *in vivo* the neuroprotective effects of lentivirally expressed *IGF-1* for inducing neuronal survival and ameliorating the neuropathology and behavioral phenotypes associated with the $SOD1^{G93A}$ mouse model of ALS. Human *IGF-1* was cloned into HIV-1 based lentiviral vectors (LV) under the full CMV promoter and expression was assessed via Western Blot analysis. Utilizing cell factories, we produced high titer preparations of therapeutic αCAR *IGF-1* LVs. We also produced Vesicular Stomatitis Virus glycoprotein (VSV-G) pseudotyped LVs expressing *IGF-1* to assess neuroprotection resulting from retrogradely transported muscle-produced *IGF-1*. Single bilateral delivery of either αCAR-targeted or VSV-G pseudotyped LVs expressing *IGF-1* into key muscle groups of both male and female $SOD1^{G93A}$ mice was performed pre disease onset at day 28. Motor performance, coordination and gait analysis were assessed weekly from day 65 onwards, for both *IGF-1* treated and control groups. We observed substantial therapeutic efficacy *in vivo* with αCAR *IGF-1* LV pretreatment with up to 23% extension of survival compared to VSV-G IGF-1 LV and non- treated controls. Efficacy was linked to improved motor performance, as αCAR *IGF-1* treated animals retained muscle tone and motor function during their prolonged survival. Histological analysis of lumbar and thoracic spinal cord samples at end point revealed that intramuscular delivery of αCAR *IGF-1* LV increases motor neuron survival compared to age-matched non-treated controls. These data support that αCAR *IGF-1* LV is a good candidate for non- invasive neuroprotective gene therapy of ALS.

Disclosures: **I. Eleftheriadou:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); N Mazarakis and I Eleftheriadou are named inventors on a submitted UK patent no: 1308772.1. **I. Manolaras:** None. **E. Irvine:** None. **N.D. Mazarakis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); named inventor on a submitted UK patent no: 1308772.1.

Nanosymposium

651. Neurodegeneration Drug Discovery: Gene Therapy and others

Location: S403

Time: Wednesday, October 21, 2015, 8:00 AM - 11:15 AM

Presentation Number: 651.13

Topic: C.19. Drug Discovery and Development

Title: Small molecules targeting tau aggregation demonstrate correlated efficacy in an *in vivo* tauopathy model

Authors: O. ADOLFSSON, F. CAPOTOSTI, N. SREENIVASACHARY, J. MOLETTE, E. GABELLIERI, Y. VARISCO, H. KROTH, D. T. HICKMAN, W. FROESTL, A. PFEIFER, *A. MUHS;
AC Immune SA, Lausanne, Switzerland

Abstract: The microtubule associated protein tau is being explored as a therapeutic target in multiple tauopathies, including Alzheimer's disease. Misfolded forms of tau are thought to form the basis of neurotoxic oligomeric tau and be involved in the spread of tau inclusions. To target oligomeric tau, we designed and synthesized a series of low molecular weight compounds that inhibit tau aggregation and demonstrated therapeutic effects in a transgenic model of aggressive tauopathy. We have employed a set of rationally designed non-dye compounds of our proprietary MorphomerTM platform to interact with the β-sheet conformation present in misfolded oligomeric tau protein. The most potent compounds were selected based on a series of functional and cell-based assay results, as well as pharmacokinetic properties. Two compounds, C1 and C2, were selected for an *in vivo* efficacy study in Tg4510 mice, a model of aggressive tauopathy expressing human tau carrying the P301L mutation of frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Compounds C1 and C2 were selected using a multitude of *in vitro* assays to screen for effects on tau aggregation and cellular toxicity. Both compounds exhibited good potency in reducing the β-sheet content of synthetic human tau, as well as in reversing the toxicity of β-sheet rich tau multimeric structures. Compound C2 was significantly more potent than C1 in reducing the size of tau aggregates, in reducing the

cytotoxicity of tau paired helical filaments (PHF) enriched from AD brains, and in reducing intracellular tau aggregation and phosphorylation in neuroblastoma cells overexpressing tau with the P301L mutation. When tested for efficacy in the Tg4510 tauopathy model, C1 treatment resulted in a dose-dependent improvement of memory. In the same behavioral test, C2 displayed an even better potency on spatial learning and memory performance. Histological evaluation showed cortical atrophy in vehicle-treated mice. Treatment with C1 resulted in a dose-dependent trend for reduced brain atrophy, whereas C2 treatment led to significantly less atrophy compared to control mice. Interestingly, C2-treated mice also had a significant reduction in misfolded tau and a trend for reduced tau aggregation. In conclusion, we have shown that compounds designed to target and prevent tau aggregation, and selected using specific assays *in vitro*, demonstrate therapeutic efficacy in an aggressive model of tauopathy. These results further establish the concept of prevention of tau propagation as a promising strategy for the development of therapeutic compounds targeting tauopathy indications.

Disclosures: **O. Adolfsson:** A. Employment/Salary (full or part-time); AC Immune SA. **F. Capotosti:** A. Employment/Salary (full or part-time); AC Immune SA. **N. Sreenivasachary:** A. Employment/Salary (full or part-time); AC Immune SA. **J. Molette:** A. Employment/Salary (full or part-time); AC Immune SA. **E. Gabellieri:** A. Employment/Salary (full or part-time); AC Immune SA. **Y. Varisco:** A. Employment/Salary (full or part-time); AC Immune SA. **H. Kroth:** A. Employment/Salary (full or part-time); AC Immune SA. **D.T. Hickman:** A. Employment/Salary (full or part-time); AC Immune SA. **W. Froestl:** A. Employment/Salary (full or part-time); AC Immune SA. **A. Pfeifer:** A. Employment/Salary (full or part-time); AC Immune SA. **A. Muhs:** A. Employment/Salary (full or part-time); AC Immune SA.

Nanosymposium

652. Auditory System: Temporal, Frequency, and Spectral Processing

Location: N226

Time: Wednesday, October 21, 2015, 8:00 AM - 10:00 AM

Presentation Number: 652.01

Topic: D.02. Auditory System

Support: BB/J01835X/1

Issac Newton Trust

Title: A feature detection circuit for song pattern recognition in the cricket brain

Authors: *B. HEDWIG[1], S. SCHOENEICH[2], K. KOSTARAKOS[3];
[2]Zoology, [1]Univ. of Cambridge, Cambridge, United Kingdom; [3]Zoology, Karl-Franzens Univ., Graz, Austria

Abstract: From human language to birdsong and the chirps of insects, acoustic communication is based on amplitude and frequency modulation of sound signals. Whereas frequency-processing starts at the level of the hearing organs, temporal features of the sound amplitude like rhythms or pulse rates require processing by central auditory neurons. Besides several theoretical concepts, the brain circuits that detect temporal features of the signal are poorly understood. We show how five neurons in the brain of female field crickets form an auditory feature-detector circuit for the pulse pattern of the male calling song. Auditory responses to the calling song are forwarded towards the brain via a single ascending interneuron. A small circuit of identified local brain neurons recognizes the species-specific sound pulse pattern and exhibits properties fundamental to a feature detection circuit based on delay-line and coincidence-detection mechanism. A constant internal delay that matches the pulse period of the calling song is provided by a non-spiking brain neuron. Upon acoustic stimulation it receives a transient inhibition that triggers postinhibitory rebound depolarization. Direct and delayed excitatory responses converge in a coincidence detector neuron. The coincidence detector neuron responds best to the pulse pattern of the species-specific calling song when the rebound activation of the non-spiking neuron temporally coincides with the response of the ascending interneuron to the subsequent sound pulse. The output of the coincidence detector neuron is further processed by a feature detector neuron that receives an additional inhibitory input to suppress unselective responses and background activity. The sparse but highly pattern selective spike response of the feature detector neuron closely matches the pulse period tuning of the phonotactic behavior. The circuit provides the basis for auditory mate recognition in field crickets and reveals principal mechanisms of sensory processing underlying the perception of temporal patterns.

Disclosures: B. Hedwig: None. **S. Schoeneich:** None. **K. Kostarakos:** None.

Nanosymposium

652. Auditory System: Temporal, Frequency, and Spectral Processing

Location: N226

Time: Wednesday, October 21, 2015, 8:00 AM - 10:00 AM

Presentation Number: 652.02

Topic: D.02. Auditory System

Title: Specific neuronal populations in the dorsal cochear nucleus that responds to sound can be controlled using optogenetic and chemogenetic proteins

Authors: *T. B. MALFATTI, M. M. HILSCHER, R. N. LEAO, K. E. LEAO;
Brain Inst. of the Federal Univ. of Rio G, Natal, Brazil

Abstract: Tinnitus is the perception of a sound in the absence of a corresponding physical stimulus. It is not clear yet what are the mechanisms involved in tinnitus and how it starts and/or becomes chronic. Due to the relationship between tinnitus and somatosensory trauma/stimuli, the dorsal cochlear nucleus (DCN), a region known to integrate somatosensory and auditory pathways, has been identified as a potential key structure in the generation of phantom sound perception. Here, we target specific neuronal populations in the DCN to investigate how this region may contribute to the generation of tinnitus signals that spread to other auditory areas. We examined the expression of optogenetic proteins (Channelrhodopsin 2 - ChR2; and Archaerhodopsin3 - Arch3) and chemogenetic proteins (Designer Receptors Exclusively Activated by Designer Drugs - DREADDs; more specifically Gq-coupled human M3 DREADD - hM3Dq, and Gi-coupled human M4 DREADD - hM4Di), targeting neurons expressing Calmoduline Kinase II alpha (CaMKIIa) promoter in wild-type C57/Bl6 mice and neurons expressing nicotinic acetylcholine receptor subunit alpha-2 promoter (ChRNA2) in ChRNA2-Cre transgenic C57/Bl6 mice, using local virus injection, verified by fluorescence microscopy. Unit responses were differentiated based on their electrophysiological response to sound. We then investigated if firing of neurons expressing optogenetic or chemogenetic tools can be controlled *in vivo* and if the same neurons also fire action potentials in response to precisely timed sound stimulation. Both *in vivo* and *in vitro* data shows that neurons expressing ChR2 that responds to sound can respond to light stimulation with a stable and similar waveform. Also, preliminary *in vivo* data suggests that neurons expressing Arch3.0 that responds to sound decrease their firing rate using light stimulation. By applying these optogenetic and chemogenetic tools we aim to test tinnitus theories by producing an increased firing rate, trying to mimic tinnitus; or inhibiting increased spontaneous firing rate on animals with noise-induced or salycilate-induced tinnitus.

Disclosures: T.B. Malfatti: None. **M.M. Hilscher:** None. **R.N. Leao:** None. **K.E. Leao:** None.

Nanosymposium

652. Auditory System: Temporal, Frequency, and Spectral Processing

Location: N226

Time: Wednesday, October 21, 2015, 8:00 AM - 10:00 AM

Presentation Number: 652.03

Topic: D.02. Auditory System

Support: Wellcome Trust 084364/Z/07/Z

Title: Mind the gap: two dissociable mechanisms of temporal processing in the auditory system

Authors: *J. F. LINDEN, L. A. ANDERSON;
Univ. Col. London, London, United Kingdom

Abstract: High temporal acuity of auditory processing underlies perception of speech and other rapidly varying sounds. A common measure of auditory temporal acuity in humans is the threshold for detection of brief gaps in noise. Gap-detection deficits, observed in developmental disorders, are considered evidence for "sluggish" auditory processing. Here we show, in an animal model of developmental disorder, that deficits in auditory brain sensitivity to brief gaps in noise do not imply a general loss of central auditory temporal acuity. Extracellular recordings in three different subdivisions of the auditory thalamus in anaesthetised BXSB/MpJ-Yaa mice revealed a stimulus-specific, subdivision-specific deficit in thalamic sensitivity to brief gaps in noise in experimental animals relative to controls. Neural responses to brief gaps in noise were reduced, but responses to other rapidly changing stimuli unaffected, in lemniscal and non-lemniscal (but not polysensory) subdivisions of the medial geniculate body. Through experiments and modelling, we demonstrate that the observed deficits in thalamic sensitivity to brief gaps in noise arise from reduced neural population activity following noise offsets, but not onsets. These results reveal dissociable sound-onset-sensitive and sound-offset-sensitive channels underlying auditory temporal processing, and suggest that developmental disorders specifically affect the sound-offset-sensitive channel.

Disclosures: **J.F. Linden:** None. **L.A. Anderson:** None.

Nanosymposium

652. Auditory System: Temporal, Frequency, and Spectral Processing

Location: N226

Time: Wednesday, October 21, 2015, 8:00 AM - 10:00 AM

Presentation Number: 652.04

Topic: D.02. Auditory System

Support: NIH NIMH T32 MH017168-31

NIDCD R01DC014479

NIDCD R03DC013660

Klingenstein Award in Neuroscience

Human Frontier in Science Young Investigator Award RGY0073/2014

Burroughs Wellcome Career Award at Scientific Interface

NARSAD Young Investigator Award

Title: Two types of interneurons differentially modulate tone-evoked responses in the primary auditory cortex

Authors: *J. BLACKWELL, M. AIZENBERG, L. MWILAMBWE-TSHILOBO, S. JONES, R. G. NATAN, M. N. GEFFEN;
Otorhinolaryngology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: The ability to discriminate between tones of different frequencies is fundamentally important for everyday hearing. Primary auditory cortex (A1) regulates behaviors that rely on frequency discrimination (Aizenberg and Geffen, 2013), but the underlying neural mechanisms are poorly understood. Frequency tuning of cortical excitatory neurons is shaped by the balance of excitatory and inhibitory inputs. In the cortex, the two most common classes of inhibitory interneurons are parvalbumin-positive (PV) interneurons and somatostatin-positive (SOM) interneurons. PV and SOM interneurons differ morphologically and may therefore differentially affect tone-evoked responses of excitatory neurons. We found that photo-activation of parvalbumin-positive (PV) interneurons enhanced tone-evoked responses of excitatory neurons. By contrast, photo-activation of SOMs diminished tone-evoked responses in the excitatory neurons, by suppressing tone-evoked responses more than spontaneous activity. Furthermore, photo-activation of SOMs decreased the frequency tuning width of excitatory neurons. Combined, we find that different types of interneurons exert a differential effect on frequency responses of excitatory neurons. PVs and SOMs may therefore carry out functionally different roles in auditory processing.

Disclosures: J. Blackwell: None. **M. Aizenberg:** None. **L. Mwilambwe-Tshilobo:** None. **S. Jones:** None. **R.G. Natan:** None. **M.N. Geffen:** None.

Nanosymposium

652. Auditory System: Temporal, Frequency, and Spectral Processing

Location: N226

Time: Wednesday, October 21, 2015, 8:00 AM - 10:00 AM

Presentation Number: 652.05

Topic: D.02. Auditory System

Support: NIH Grant NS073874

Kleberg Foundation Grant

Title: Functional architecture of mouse auditory cortex in response to tones and sweeps

Authors: *J. B. ISSA, B. D. HAEFFELE, M. ZHANG, E. D. YOUNG, D. T. YUE;
Johns Hopkins Univ., Baltimore, MD

Abstract: Many studies of cortex rely on assumptions of the underlying functional organization of the region being studied. However, our understanding of cortical organization has typically been established by methods which record activity at a single spatial scale, limiting our ability to generalize to what extent the functional organization observed by large scale methods is reflective of the spatial organization at the level of single neurons. To bridge this gap, we employ a Ca^{2+} imaging approach in transgenic mice expressing genetically encoded Ca^{2+} indicators to record activity at multiple scales of spatial resolution. Our multiscale approach establishes a 'global' view at the millimeter scale by utilizing transcranial widefield imaging and provides reliable landmarks based on large scale functional organization for registration across animals. Next a 'local' view, via two-photon imaging, allows us to monitor activity in populations of individual neurons across several hundred microns of cortex. Specifically, we apply this technique to study the functional organization of auditory cortex in awake mice. At the global scale, we uncover a finely detailed tonotopic structure in both primary and secondary fields and regions of cortex responsive to frequency modulated (FM) sweeps but not to pure tones. Further, this functional organization is preserved at a local scale, with single neuron activity within a 100-200 micron region matching the corresponding functional properties observed at the global scale. Together these results indicate that rich organizational features are present within small regions of mouse auditory cortex, which in turn may reflect the functional specialization of those regions for the processing of sound.

Disclosures: J.B. Issa: None. **B.D. Haeffele:** None. **M. Zhang:** None. **E.D. Young:** None. **D.T. Yue:** None.

Nanosymposium

652. Auditory System: Temporal, Frequency, and Spectral Processing

Location: N226

Time: Wednesday, October 21, 2015, 8:00 AM - 10:00 AM

Presentation Number: 652.06

Topic: D.02. Auditory System

Title: Adaptive estimation of sparse point process models enhances resolution of spectrotemporal receptive field plasticity analysis

Authors: A. SHEIKHATTAR[1], J. B. FRITZ[2], S. A. SHAMMA[2], *B. BABADI[1];
[1]Dept. of Electrical and Computer Engin., [2]Inst. for Systems Res., Univ. of Maryland, College Park, MD

Abstract: Studies of neuronal plasticity have revealed that receptive fields undergo rapid changes in their characteristics during attentive behavior in order to capture salient stimulus modulations. Hence, dynamic analysis of receptive field plasticity from spike recordings provides valuable insights into the dynamics of the underlying neural system. Most of the existing estimation techniques (e.g., reverse correlation) provide static estimates of the receptive field. Moreover, they do not systematically capture the inherent sparsity manifested in the receptive field characteristics. We address these issues for the problem of estimating spectrotemporal receptive fields (STRF) from multi-unit recordings in the ferret primary auditory cortex (A1). We model the neuronal dynamics by a point process with a sparse time-varying kernel governed by a logistic-link conditional intensity. We estimate the kernel parameters using a novel sparse adaptive filtering algorithm based on recursive L1-regularized maximum likelihood estimation, where recursive estimation is efficiently carried out using a proximal algorithm. We evaluate the performance of our proposed algorithm on simulated as well as real multi-unit spike data recorded from ferret A1 during passive stimulus presentation and during performance of a click rate discrimination task. Our simulation studies reveal that the proposed adaptive filtering algorithm significantly outperforms existing filtering algorithms in terms of goodness-of-fit, mean square error and trackability. Furthermore, application of our algorithm to real data provides new insights into the time course of attention-driven STRF plasticity, with a thousand-fold increase in temporal resolution from minutes to centiseconds, while capturing the underlying sparsity in a robust fashion.

Disclosures: A. Sheikhattar: None. **J.B. Fritz:** None. **S.A. Shamma:** None. **B. Babadi:** None.

Nanosymposium

652. Auditory System: Temporal, Frequency, and Spectral Processing

Location: N226

Time: Wednesday, October 21, 2015, 8:00 AM - 10:00 AM

Presentation Number: 652.07

Topic: D.02. Auditory System

Support: Rothberg Research Award

Title: Topographic representation of frequency-selective attention in human auditory cortex

Authors: F. K. DICK[1], M. LEHET[2], *L. L. HOLT[2];
[1]Birkbeck College/UCL Ctr. for Neuroimaging, London, United Kingdom; [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Humans and other mammals are very sensitive to changes in the salience, task-relevance, and composition of the acoustic dimensions of complex and ecologically important sounds. Listeners appear to be able to shift attention across multiple simultaneously-present acoustic dimensions to home in on the ones that are diagnostic in guiding behavior. In particular, psychoacoustic experiments have shown that both endogenously and exogenously cued attention to a particular frequency or spectral band can enhance detection of auditory targets and sharpen sensitivity to multiple features within the attended band. Electrophysiological work in non-human animals has begun to uncover the mechanics of this process (Fritz et al., 2007; 2010) while a pair of fMRI studies in humans (da Costa et al., 2013; Paltoglou et al., 2009) have shown that attention to high or low frequency bands drives responses across auditory cortex in a way that is predicted by tonotopic mapping in the same participants. However, it is unclear how fine-grained this mapping is, how it differs across auditory fields, how it relates to the underlying myeloarchitecture of auditory cortex, and how other cortical regions drive or modulate 'attention-o-tonotopic' maps. In the current study, we use a novel fMRI paradigm to drive sustained attention to multiple frequency bands; in the same participants, we obtained quantitative MR data (to estimate cortical myelination) along with tonotopic mapping in order to localize auditory areas (Dick et al., 2012). Across participants, we found that multiple auditory fields showed 'attention-o-tonotopic' mapping that was closely aligned with tonotopic maps (which can be quite differently organized across participants and even over hemispheres). We also characterized the relationship of attention-o-tonotopic fields to putative the cortical myeloarchitectonic maps, both in the auditory core as well as non-core fields, and found interesting and reliable (cross-scan) patterns of individual variation. These results have implications for understanding how human listeners direct attention to behaviorally-relevant auditory dimensions in listening to complex sounds like speech and music and provide groundwork for understanding how experience may modulate these maps.

Disclosures: F.K. Dick: None. **M. Lehet:** None. **L.L. Holt:** None.

Nanosymposium

652. Auditory System: Temporal, Frequency, and Spectral Processing

Location: N226

Time: Wednesday, October 21, 2015, 8:00 AM - 10:00 AM

Presentation Number: 652.08

Topic: D.02. Auditory System

Support: Centre for Chronic Diseases and Disorders/Wellcome Trust

Title: Effects of sensorineural hearing loss on cortical entrainment to auditory temporal envelopes

Authors: *R. E. MILLMAN[1], G. PRENDERGAST[2], S. L. MATTYS[3];
[1]York Neuroimaging Centre, Univ. of York, York, United Kingdom; [2]Sch. of Psychological Sci., Univ. of Manchester, Manchester, United Kingdom; [3]Dept. of Psychology, Univ. of York, York, United Kingdom

Abstract: Sensorineural hearing loss (SNHL) enhances the neural coding of the temporal envelope of sounds (e.g. Moore et al., 1996; Kale & Heinz, 2010). This enhanced temporal envelope coding is thought to have a detrimental effect on the ability of hearing-impaired listeners to understand speech in the presence of fluctuating background noise. Here we used magnetoencephalography (MEG) to test the hypothesis that cortical temporal envelope coding is enhanced in SNHL listeners who struggle more than normal-hearing (NH) listeners to understand speech in fluctuating backgrounds. Cortical entrainment to a 2-Hz square-wave-gated noise was measured in older listeners with either normal-hearing or a mild-to-moderate, symmetrical SNHL. NH listeners were selected on the basis of their ability to "listen in the dips" of a fluctuating background, i.e. a 2-Hz square-wave-gated noise masker relative to an unmodulated noise masker. Conversely SNHL listeners were selected if they were less able to benefit from "listening in the dips" of the square-wave-gated noise masker. Ordinary least squares linear modelling was applied to MEG beamformer-based analyses to inform about both the amplitude (model β) and fidelity (model r^2) of temporal envelope coding in "good dip listeners" (NH) and "poor dip listeners" (SNHL). In accordance with the Asymmetric Sampling in Time model (e.g. Poeppel, 2003), entrainment to the temporal envelope of the square-wave-gated noise was lateralised to areas in right auditory cortex within both listener groups. Temporal envelope coding was enhanced in poor dip listeners (SNHL) listeners, when compared with good dip listeners (NH); however, this enhancement was more evident in right auditory cortex. Our results demonstrate a degree of functional lateralization in cortical temporal processing in the poorer dip listeners, which may have important translational implications for auditory prostheses. The poor dip listeners demonstrated a superior ability to entrain to the temporal structure of the square-wave-gated noise, suggesting that poor dip listeners are able to accurately identify when the "dips" occur in fluctuating backgrounds: Their difficulties in understanding speech presented against noisy backgrounds may stem instead from an inability to use the information present in the "dips" of fluctuating background noise. References Kale, S. & Heinz, M.G. (2010). Journal of the Association for Research in Otolaryngology, 11: 657-673 Moore, B.C.J., Wojtczak, M & Vickers, D.A. (1996).Journal of the Acoustical Society of America. 100: 481-489. Poeppel, D. (2003). Speech Communication 41: 245-255.

Disclosures: **R.E. Millman:** None. **G. Prendergast:** None. **S.L. Mattys:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.01

Topic: D.14. Cerebellum: Central Physiology

Support: NINDS/NIH (R01 NS040863)

The Hand Embodied (THE) (Integrated Project, EU FP7, project no. 248587)

The Swedish Research Council (VR Medicine

Title: The specifik relationship between excitatory inputs and climbing fiber receptive fields in deep cerebellar nuclear neurons

Authors: *F. L. BENGTSSON, H. JORNTELL;
Univ. of Lund, BMC F10, Lund, Sweden

Abstract: Many mossy fiber pathways to the neurons of the deep cerebellar nucleus interpositus anterior (AIN) originate from the spinal motor circuitry. For cutaneously activated spinal neurons, the receptive field is a tag indicating the specific motor function the spinal neuron has. Similarly, the climbing fiber receptive field of the AIN neuron reflects the specific motor output function of the neuron. To explore the relationship between the motor information the AIN neuron receives and the output it issues, we made *in vivo* patch clamp recordings of cell responses in the AIN to tactile skin stimulation of the forelimb. The excitatory responses were organized according to a general principle, where the excitatory mossy fiber responses became stronger the closer the skin site was located to its climbing fiber receptive field. The findings represent a novel functional principle of cerebellar connectivity, with crucial importance for our understanding of the function of the cerebellum in movement coordination.

Disclosures: F.L. Bengtsson: None. **H. Jorntell:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.02

Topic: D.14. Cerebellum: Central Physiology

Support: NIH Grant EY018585

NIH Grant RR-00166

Title: Parallel fibers that cross the midline in the oculomotor vermis are not critical to saccade deceleration

Authors: *F. R. ROBINSON[1], E. BUZUNOV[2], A. MUELLER[4], J. OJEMAN[3];
[2]Dept of Bio Structure, [3]Neurosurg., [1]Univ. Washington, Seattle, WA; [4]Neurobio., Standord Univ., Stanford, CA

Abstract: The activity of neurons in the caudal part of the cerebellum's medial, or fastigial, nucleus strongly influences the horizontal component of saccades. The timing of saccade-related bursts of action potentials depends on saccade direction. For example, a few milliseconds (ms) before a rightward saccade, neurons in the left caudal fastigial nucleus (CFN) fire a burst of action potentials. A little later, a few ms after the saccade has started, neurons in the right CFN fire a burst of action potentials. The early bursts in the left CFN help accelerate the rightward saccade by inhibiting antagonist muscles. The late bursts in the right CFN decelerate the saccade by inhibiting agonist muscles so that they do not continue to rotate the eye near the end of the saccade. The late decelerating bursts probably originate in the cerebellum. No brain structure outside the cerebellum fires bursts after saccade onset except structures that receive CFN input. We proposed a mechanism that the cerebellum could use to generate these late bursts. Saccade-related signals from the superior colliculus and frontal eye field enter the cerebellum on the side contralateral to saccade direction and elicit the early burst in CFN neurons. The signals then enter the cerebellar cortex in the oculomotor vermis (OMV) and travel across the midline in parallel fibers. These fibers synapse onto Purkinje cells that project to the CFN ipsilateral to saccade direction and elicit a burst there. This burst occurs later because of the travel time of the signal in the parallel fibers. We tested this proposal in three rhesus monkeys trained to make saccades by making a parasagittal cut through the OMV near the midline in an aseptic surgery. This cut interrupted crossing OMV parallel fibers. If our proposal is correct, then the deceleration of both leftward and right ward saccades would be impaired without damaging acceleration. Our cuts were 0.4, 1.0 and 1.4 mm left of the midline. They impaired leftward saccades much more than rightward saccades. We concluded that our proposal was wrong. Signals in parallel fibers are not critical to normal saccades. We propose that a parasagittal region of Purkinje cells damaged by our cut is critical. This region is within 1 mm of the midline. The cut at 1.4 mm had little effect on saccades. This finding may improve surgery to remove tumors in the IVth ventricle under the cerebellum. To remove these tumors surgeons often cut down the middle of the OMV which damages eye movements. If they cut lateral to the narrow saccade-related area revealed in our animals then they might spare eye movements.

Disclosures: **F.R. Robinson:** None. **E. Buzunov:** None. **A. Mueller:** None. **J. Ojeman:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.03

Topic: D.14. Cerebellum: Central Physiology

Support: NIH Grant 5R01DC00415413

NIH Grant 5R01NS07240605

Katherine McCormick postdoctoral fellowship

NSF GRFP grant DGE-114747

NSF IGERT Award 0801700

Title: Synaptic plasticity tuned for behaviorally relevant timing

Authors: ***A. SUVRATHAN**, H. L. PAYNE, J. L. RAYMOND;
Neurobiology, Stanford Univ., Stanford Univ., Stanford, CA

Abstract: Synapses can alter their strength in response to specific patterns of input. The local rules governing this process at each synapse within a neural circuit define the algorithm the circuit uses to learn, yet our understanding of these rules is still primitive. We investigated these local rules in the context of behavioral function, by studying a tractable form of motor learning, and integrating analyses at the behavioral, circuit and cellular levels. It is widely assumed that the rules for plasticity are uniform across a given, anatomically defined synapse type, particularly in brain structures like the cerebellum, which has a remarkably uniform cytoarchitecture. In striking contrast, our results demonstrate that in different regions of the cerebellum, the same types of synapses are governed by different rules for plasticity - and these rules are tuned to the behavior that each region supports. In the cerebellum, behavioral performance errors are signaled by climbing fibers, which are known to trigger plasticity at parallel fiber to Purkinje cell synapses. *In vivo* electrophysiological recordings during learning revealed that individual climbing fiber spikes induced changes in the responses of cerebellar Purkinje cells that were precisely timed to compensate for the feedback delay in the error signals carried by climbing fibers. *In vitro*, a climbing fiber delay precisely matched to that observed during learning *in vivo* was effective at inducing plasticity. In addition, plasticity at parallel fiber

synapses in different parts of the cerebellum was tuned to different time intervals, which could reflect a tuning of the plasticity mechanisms for the behavior supported by that specific microcircuit.

Disclosures: A. Suvrathan: None. **H.L. Payne:** None. **J.L. Raymond:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.04

Topic: D.06. Eye Movements

Title: Can the transfer of short-term saccadic adaptation to new directions be led back to changes in the responses of purkinje cell simple spikes?

Authors: *A. SHARMA[1], K. MARCINIAK[2], P. W. DICKE[2], P. THIER[2];
[2]Cognitive Neurol., [1]Hertie Inst. For Clin. Brain Res., Tuebingen, Germany

Abstract: The improvement of motor behavior, based on experience, is a form of learning that is critically dependent on the cerebellum. A well-studied example of cerebellar motor learning is short-term saccadic adaptation (STSA). In STSA, information on saccadic amplitude errors is used to improve the amplitude of future saccades. The information optimizing saccade metrics is conveyed by oculomotor vermis (OMV) Purkinje cells simple spikes (PC-SS) because they are the critical input to the premotor circuits for saccades. We have previously shown that individual OMV PC-SS of monkeys undergoing STSA show highly idiosyncratic changes of their discharge during STSA whereas a PC-SS population signal, based on the collective activity of larger groups of PC exhibits changes that closely parallel changes of saccade kinematics (Catz et al., PNAS, 2008). STSA transfers to new saccade directions by an amount that decreases with distance from the adapted direction (Noto et al., J Neurophysiology, 1999). Here we asked if the properties of the transfer can be led back to adaption-related changes in PC-SS discharge that show the same direction dependence. In order to address this question we tested two monkeys on a typical inward adaptation task in three continuous blocks in which the target stepped back during the saccade with decreasing probabilities (1, 0.8 and 0.6 respectively). In the complementary trials in blocks 2 and 3 the target was presented at the same primary eccentricity, yet without the later inward step, and in new directions, drawn at random from a pool of 7 vertical target locations at varying distance from the adaptation direction. The monkeys exhibited clear inward adaptation. The transfer of adaptation to the new directions reflected the adaptation of the horizontal component of the saccades made in the oblique adaptation direction. As the

contribution of the horizontal component decreased with angular distance from the adaptation direction, so decreased the adaptation transfer. This result is fully compatible with a model assuming a transfer of Cartesian components. Single PC-SS showed the well-known, individually very different PC-SS discharge changes for the adaptation direction. Changes were also observed in the transfer directions, when compared to the responses of saccades in these directions before adaptation. We are currently examining if these changes could explain the adaptation transfer observed. Acknowledgement: Supported by DFG FOR 1847-A3

Disclosures: **A. Sharma:** None. **K. Marciniak:** None. **P.W. Dicke:** None. **P. Thier:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.05

Topic: D.14. Cerebellum: Central Physiology

Support: BBSRC UK Grant BB/J017116/1

Title: The human cerebellar cortex and the instrumental control of learned behaviour

Authors: G. P. D. ARGYROPOULOS, J. L. MILLS, ***N. RAMNANI**;
Royal Holloway Univ. of London, Egham, United Kingdom

Abstract: The associative and neural properties of conditioned and unconditioned stimuli (CS, US) have been widely studied using simple forms of cerebellar-dependent motor learning, such as classical eyeblink conditioning. Such studies have reported CS- and US-evoked changes in cerebellar activity. This is consistent with computational accounts that explain cerebellar memory formation in terms of the decreasing efficacy between cerebellar cortical neurons and their inputs. In contrast, instrumental learning often requires the use of cognitive operations, and engages the prefrontal cortex. It involves learning the contingencies between CSs, actions and outcomes, such that CSs can be used to select actions to obtain desired outcomes. Cerebellar circuits have recently been implicated in instrumental processing, but their specific roles are not clear. Here, we used functional MRI to record CS- and outcome-evoked activity in the human cerebellum as subjects learned arbitrary associations between CSs, oculomotor actions and outcomes through trial-and-error. We were able to isolate CS- and outcome-specific activity in separate studies without contamination from other trial elements (controls: (i) non-arbitrary stimuli with no associative properties, which directly specified the same responses; (ii) arbitrary stimuli which were followed by incorrectly executed responses), and test hypotheses about parts

of the cerebellar cortex (lobule HVIIa) that communicate with the prefrontal cortex. We found activity time-locked to CSs and outcomes in lobule HVIIa. CSs that were arbitrarily paired with correctly selected actions evoked activity in a set of areas within lobule HVIIa. CS-related activity amplitude decreased from trial-to-trial as learning progressed. We observed similar decreases in the nucleus accumbens, which has a well-established role in instrumental learning. Separately, we periodically altered CS-action mappings so that new mappings would replace previously acquired response rules. Our statistical model predicted decreasing outcome-related activity with each successive correctly selected response, but reverted to high, pre-learning levels on presentation of new mappings. We report such activity in parts of lobule HVIIa. Our findings show that cerebellar responses to instrumental CSs and outcomes can be specific to those that acquire associative properties, and change as a function of instrumental learning. They are consistent with the view that the cerebellar mechanisms which support information processing in simple forms of motor learning may be similar to those that support instrumental forms of learning.

Disclosures: G.P.D. Argyropoulos: None. **J.L. Mills:** None. **N. Ramnani:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.06

Topic: D.14. Cerebellum: Central Physiology

Support: Franco-German PROCOPE funding

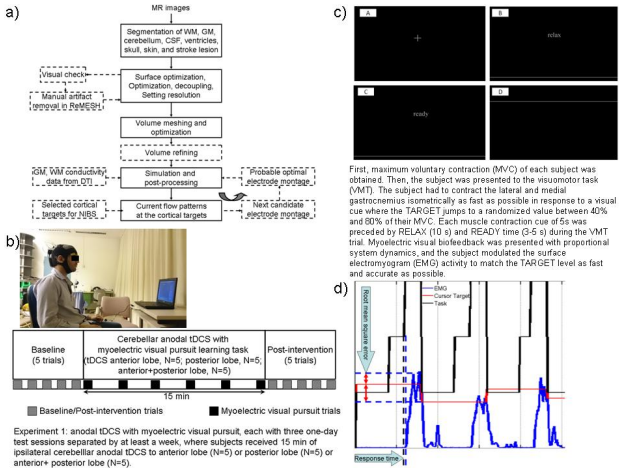
DAAD funding

Title: Optimizing cerebellar transcranial direct current stimulation for visuomotor learning - anterior versus posterior lobe of cerebellum

Authors: *A. DUTTA;
Inst. Natl. De Recherche En Informatique Et En Automatique (INRIA), Montpellier, France

Abstract: INTRODUCTION This study sought to investigate two-electrode montages for anodal transcranial direct current stimulation (atDCS) over ipsilateral cerebellar hemisphere during visuomotor learning of myoelectric visual pursuit task (VMT) using electromyogram (EMG) from gastrocnemius (GAS) muscle. The atDCS montages were selected based on computational modeling to target electric field strength at the anterior lobe (AL) or posterior lobe (PL) or

AL+PL of the cerebellum. METHODS *A. Computational modeling* Two-electrode montages were selected from prior works using a software pipeline, shown in Figure 1a, that was partly based on SCIRun. Here, we used the Intensity Contour tool of the FreeSurfer to extract the cerebellum. *B. Cerebellar atDCS* This study on 15 healthy volunteers was conducted to investigate the effects of 15min of atDCS (current density=0.526A/m^2; electrode size 25 cm^2) of ipsilateral AL, PL, AL+PL on response time (RT) and root mean square error (RMSE) during isometric contraction of the dominant GAS for VMT, i.e., 'ballistic EMG control' (see Figure 1b,c,d). RESULTS AND DISCUSSION AL atDCS (Grimaldi and Manto montage) resulted in a statistically significant ($p<0.05$) decrease in RT post-intervention than baseline when compared to PL atDCS (Pope and Miall montage) and AL+PL atDCS (Galea et al. montage). However, only AL+PL atDCS resulted in a statistically significant ($p<0.05$) decrease in RMSE post-intervention than baseline. Here, optimizing the direction of the electric field relative to the cerebellar peduncles may also be relevant. REFERENCES 1. Ferrucci, R., Cortese, F. & Priori, A. Cerebellum Lond. Engl. 14, 27-30 (2015). 2. Dutta, A., Paulus, W. & Nitsche, M. A. J. Neuroengineering Rehabil. 11, 13 (2014). 3. Dannhauer, M., Brooks, D., Tucker, D. & MacLeod, R. Conf. Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Conf. 2012, (2012). 4. Grimaldi, G. & Manto, M. Ann. Biomed. Eng. 41, 2437-2447 (2013). 5. Pope, P. A. & Miall, R. C. Brain Stimulat. 5, 84-94 (2012). 6. Galea, J. M., Jayaram, G., Ajagbe, L. & Celnik, P. J. Neurosci. 29, 9115-9122 (2009).



Disclosures: A. Dutta: None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.07

Topic: D.14. Cerebellum: Central Physiology

Title: Bidirectional modulation of motor skill learning by non-invasive cerebellar stimulation

Authors: *T. POPA[1,3], F. GHEYSEN[4,5], G. LASNE[6], M. PÉLÉGRINI-ISSAC[6], G. ALBOUY[7,8], S. MEUNIER[3,2], H. BENALI[6], J. DOYON[7,8];
[1]Human Motor Control Section, [2]NIH/NINDS/HMCS, Bethesda, MD; [3]Inserm U975, CNRS UMR 7225, Univ. Pierre et Marie Curie – Univ. Paris6 UMR S975, Inst. du Cerveau et de la Moëlle Epiniere (ICM), Paris, France; [4]Dept. of Movement and Sport Sci., [5]Dept. of Exptl. Psychology, Ghent Univ., Ghent, Belgium; [6]Lab. d'Imagerie Biomédicale, Sorbonne Universités, UPMC Univ. Paris 06, CNRS, INSERM,, Paris, France; [7]Geriatric Institute, Functional Neuroimaging Unit, [8]Dept. of Psychology, Univ. of Montreal, Montreal, QC, Canada

Abstract: Motor skill learning implies synergistic activations of different brain structures that change over time. Such co-activations include the cerebellum, the hippocampus, and the basal ganglia during the initial phases of learning, while the nodes within the basal ganglia take over during the retention phase (Doyon & Benali, 2005). However, little is known about the interaction between the cerebellum and the basal ganglia within the initial (fast) learning phase of a new motor skill. We have demonstrated recently that repetitive magnetic stimulation of the associative cerebellar cortex can modulate (either boost or suppress) the associative plasticity of the motor cortex (Popa et al., 2013). It is conceivable that such stimulation can similarly influence other connected structures and processes that are dependent on associative cortical plasticity. Here we assessed whether cerebellar stimulation can modulate motor learning-related plasticity underlying skill performance and also the neural activity in the supporting networks. We used functional 3T MRI to track the BOLD activity correlated with the single-session acquisition of an explicit five element sequence of left hand finger movements, in 5 groups of healthy right-handed volunteers (total: 119). One control group was free from any external interference (N=52). In the four others, the cortex of the right or left cerebellar hemisphere was either inhibited or facilitated with continuous or intermittent theta-burst stimulation targeting posterior parts of cerebellar hemispheres ($cTBS_{right}$ N=18; $iTBS_{right}$ N=19; $cTBS_{left}$ N=15; $iTBS_{left}$ N=15) Subjects in all groups acquired the explicit motor sequence following a three-phase pattern within a single training session: an early-phase of rapid learning, followed by a mid-phase of slower learning, and a late-phase of quasi-asymptotic performance. With respect to controls, the learning pattern remained unchanged following left cerebellar stimulation, but was either accelerated in the early-phase of learning by the right cerebellar inhibition or slowed down in the late-phase by the right cerebellar excitation. In the control group, the performance-correlated BOLD activity shifted progressively from the hippocampus in early-phase to the bilateral striatum in late-phase, while in the $cTBS_{right}$ group, enhanced bilateral striatal activity was triggered already from the end of the early-phase. We conclude that artificial modulation of the cerebellar hub output can significantly alter the dynamics of the connected networks (like the

basal ganglia – cortical circuits), which subsequently translates in bidirectional modulation of motor skill learning.

Disclosures: **T. Popa:** None. **F. Gheysen:** None. **G. Lasne:** None. **M. Pélégrini-Issac:** None. **G. Albouy:** None. **S. Meunier:** None. **H. Benali:** None. **J. Doyon:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.08

Topic: D.14. Cerebellum: Central Physiology

Support: NIH K01 DA030442

Title: The interaction between working memory and motor performance in cerebellar ataxia

Authors: ***S. I. KRONEMER**, C. L. MARVEL;
Dept. of Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Background: The cerebellum is important for coordinating movement. Recent studies suggest that the cerebellum is also involved in coordinating a variety of cognitive functions, such as working memory (WM). Spinocerebellar ataxia (SCA) is a hereditary disorder that leads to progressive degeneration of the cerebellum. If the cerebellum is involved in the coordination of motor and cognitive functions, performing both simultaneously should lead to impairments in one or both domains. In SCA patients, impairments in one or both domains could become even more severe. It is unclear, however, how motor and cognitive functions interact when competing for cerebellar resources, especially in SCA patients who have limited cerebellar functionality. For example, when both functions are performed simultaneously, is motor function prioritized over cognition (or vice-versa)? In this pilot study, we compared motor and cognitive functions performed separately and together in 9 SCA patients recruited from the Johns Hopkins Ataxia Center and 10 age-equated controls. Methods: Subjects were tested on a novel paradigm that consisted of three tasks: (1) Motor: subjects drew figure 8s continuously for 5 seconds (8 trials); (2) Cognitive: subjects heard a letter sequence (increasing each trial from 3 to 8 letters), and repeated the letter sequence 5 seconds later; and (3) Cognitive-Motor Dual Task: subjects heard a letter sequence (increasing from 3 to 8 letters), then drew figure 8s, and then repeated the letter sequence aloud 5 seconds later. Results: In controls and SCA patients, drawing speed increased across trials. However, drawing speed was slower for SCA patients, with a smaller rate of increase across trials than for controls. In controls only, drawing speed continued to increase

when combined with shorter letter sequences but then began to slow down when combined with longer letter sequences. By contrast, in SCA patients, motor learning stopped altogether when combined with any letter sequence length. For both groups, accuracy of letter recall declined as a function of sequence length. Accuracy declined markedly when combined with drawing. Conclusions: These preliminary results suggest that, normally, when motor and cognitive functions are performed simultaneously, motor function is prioritized over cognition. Only under high cognitive demands does motor function also become affected. However, for SCA patients, cognitive function and motor function impact each other directly, leading to low performance in both domains. This suggests that, whenever possible, SCA patients should perform motor and cognitive tasks independently to achieve optimal performance.

Disclosures: S.I. Kronemer: None. **C.L. Marvel:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.09

Topic: D.14. Cerebellum: Central Physiology

Support: ISIS 07PHR04

HERMES 10PHR03

Title: Altered microstructural connectivity of the cerebellar peduncles is related to motor dysfunction: a longitudinal DTI study in stroke patients

Authors: *A. JAILLARD[1], C. HUBER[2], L. LAMALLE[4], M. G. HOMMEL[3], F. RENARD[5]; [1]Univ. Hosp. Grenoble, Grenoble, France; [2]Neurol., [3]research, CHU Grenoble, Grenoble, France; [4]Unité IRM 3T - Recherche, IRMaGe - Inserm US 17 CNRS UMS 3552, Grenoble, France; [5]AGIM, Univ. Joseph Fourier, Grenoble, France

Abstract: Neuroplasticity is involved in post-stroke restorative neurorehabilitation and can be facilitated with transcranial direct current stimulation (tDCS) intervention. However, lack of agreement in methods using tDCS intervention limits its clinical translation for stroke rehabilitation. Cerebellar tDCS processes of acquisition during adaptive motor learning may promote post-stroke motor recovery. To further perform neurophysiological testing in cerebellar regions using tDCS, we tested diffusion tensor imaging (DTI) for determining cerebellar structural reserve. The goal was to correlate motor impairment with the microstructural integrity

of cerebellar peduncles (CP) by using DTI method, to further use it as a marker of structural reserve. MATERIALS AND METHODS: 29 patients (21 males; age range 27-67 years) with ischemic anterior stroke (19 with left stroke; mean lesion volume =100cm3±63) were scanned at 1 month and 6 months (± 1 week) post stroke. 29 healthy controls (17 males; age range 19-67 years) were enrolled in this study. The MRI protocol performed using a 3-T Philips magnet included anatomic T1 images (1 mm3) and diffusion-weighted EPI sequence (70 slices 60 directions; b-value 1000 s/mm2; voxels 1.67x1.67x2 mm). DTI outcome measurements, fractional anisotropy (FA), for the superior (SCP), middle (MCP), inferior CP (ICP) and cortical spinal tract (CST) were estimated using the Diffusionnist toolkit. The Fugl-Meyer motor score was used for assessing motor functions. RESULTS: Compared to the controls, patients had a significantly lower FA in bilateral SCP, MCP ICP and CST. There was a significant positive correlation between the Fugl Meyer motor scores at 1 and 6 months and FA in ipsilateral SCP, MCP and ICP in the patients group. In addition, significant correlation of FA value was found between the CST and the cerebellar pathways. CONCLUSIONS: These findings suggest that microstructure impairment of cerebellar peduncles may contribute to the motor dysfunction related to stroke at all times and serve as a marker of cerebellar reserve for assessing tDCS in stroke patients. Moreover, the correlations we found between CST and cerebellar pathways confirm the disconnection between the motor cortex and the cerebellum in stroke patients.

Disclosures: **A. Jaillard:** None. **C. Huber:** None. **L. Lamalle:** None. **M.G. Hommel:** None. **F. Renard:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.10

Topic: D.14. Cerebellum: Central Physiology

Support: NIH/NCATS KL2 TR000102 to PET

Title: Cerebellar contributions to language: A combined TDCS-FMRI study

Authors: ***C. J. STOODLEY**[1], A. M. D'MELLO[1], D. SHOOK[1], W. HAYWARD[2], P. E. TURKELTAUB[2,3];
[1]Psychology, American Univ., Washington, DC; [2]Neurol., Georgetown Univ. Med. Ctr., Washington, DC; [3]Res. Div., MedStar Rehabil. Hosp., Washington, DC

Abstract: The right posterolateral cerebellum is structurally and functionally connected to language regions of the cerebral cortex. Clinical, neuroimaging, and neuromodulation studies suggest that the cerebellum is involved in many aspects of language, but the specific mechanisms underlying the cerebellar contributions to language remain unknown. It has been proposed that the cerebellum is important in the acquisition and training of internal models that enable prediction. Consistent with this, both damage to and neuromodulation of the right posterolateral cerebellum impair performance on language prediction tasks. Our aim was to examine the effects of cerebellar transcranial direct current stimulation (tDCS) on neural activation patterns and predictive language processing. We hypothesized that right cerebellar tDCS would modulate neural activation patterns throughout the language network, specifically affecting performance and activation patterns during predictive trials. We combined 20min of 1.5 mA anodal or sham tDCS over the right posterolateral cerebellum with functional MRI in healthy adults (n=12; μ=26.5 years). Functional images were acquired pre- and post-tDCS while participants viewed a series of four words and decided which possible fifth word best completed the sentence. In some sentences the final word was highly predictable based on the preceding context, while other sentences were non-predictive. Anodal tDCS, relative to sham, decreased activation in right cerebellar Crus I/II. TDCS modulated cortical activation throughout the reading/language network, including left occipito-temporal gyrus and supramarginal gyrus. These preliminary results are consistent with the proposed role of the right posterolateral cerebellum in optimizing performance during predictive language processing, and suggest that right cerebellar tDCS modulates supratentorial language networks.

Disclosures: C.J. Stoodley: None. **A.M. D'Mello:** None. **D. Shook:** None. **W. Hayward:** None. **P.E. Turkeltaub:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.11

Topic: D.14. Cerebellum: Central Physiology

Title: Delineating a role for the cerebellum in sensory processing during vocal behavior in patients with cerebellar ataxia

Authors: *Z. K. AGNEW[1], J. GILL[1], S. NAGARAJAN[1], R. IVRY[3], J. F. HOUDE[2]; [2]OHNS, [1]UCSF Med. Sch., San Francisco, CA; [3]UC Berkeley, Berkeley, CA

Abstract: It has been proposed that the cerebellum serves to generate predictions about the sensory consequences of future movements. Complete, or over reliance on sensory feedback is thought to result in unstable movements. Patients with cerebellar ataxia are known for their deficits in visually guided movement and their movements are known to improve in the absence of visual feedback. Thus it is suggested that patients with damage to the cerebellum are less able to make accurate predictions about the sensory consequences of movements and have to rely on reafferent information which ultimately leads to unstable movements. Here we report a series of behavioural tasks identifying a clear role for the cerebellum in feedback processing during vocal behaviour and a theta burst experiment confirming this in healthy controls. The present study aimed to investigate the nature of auditory feedback processing in patients with cerebellar degeneration by measuring various aspects of vocal behaviour. Two sets of patients were tested on a battery of vocal assessments designed to probe different aspects of vocalisation: we investigated ability to produce spontaneous voicing, pitch tracking of a moving pitch target and pitch perturbation. We investigated the hypothesis that reducing auditory feedback during vocalisation would improve vocal stability, showing that under auditory masking conditions, variability in vocal pitch is significantly reduced in patients with cerebellar damage. In order to investigate this idea further, a third experiment was carried out where we investigated how patients responded to perturbations in pitch production whereby auditory feedback is pitch shifted during vocalisation. As predicted, patients with cerebellar damage displayed significantly altered responses to the pitch shift compared to healthy age matched controls indicating an alteration in the way reafferent information is utilised. Finally continuous theta burst stimulation to cerebellar cortex in healthy controls confirmed a role for cerebellar processing in compensation for an imposed shift in auditory feedback. Together, these experiments provide compelling evidence in favour of the idea of the cerebellum as a prediction system, the dysfunction of which leads to over reliance on sensory feedback and hence unstable auditorily guided vocal movements. These data will be discussed in relation to the function of the cerebellum in the neural control of vocal behaviour and current models of speech production.

Disclosures: Z.K. Agnew: None. **J. Gill:** None. **S. Nagarajan:** None. **R. Ivry:** None. **J.F. Houde:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.12

Topic: D.14. Cerebellum: Central Physiology

Title: Cerebro-cerebellar circuitry for body language reading

Authors: *A. A. SOKOLOV[1,3], M. ERB[4], F. E. POLLICK[5], W. GRODD[6], K. SCHEFFLER[6], R. S. J. FRACKOWIAK[2], K. J. FRISTON[3], M. A. PAVLOVA[4];
[2]Dept. des Neurosciences Cliniques, [1]Ctr. Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [3]The Wellcome Trust Ctr. for Neuroimaging, Univ. Col. London, London, United Kingdom; [4]Dept. of Biomed. Magnetic Resonance, Univ. of Tübingen Med. Sch., Tübingen, Germany; [5]Sch. of Psychology, Univ. of Glasgow, Glasgow, United Kingdom; [6]Max Planck Inst. for Biol. Cybernetics, Tübingen, Germany

Abstract: Body language reading is essential for social cognition and interaction. Healthy individuals readily recognize emotions conveyed by body motion, yet the underlying brain circuitry remains largely unknown. Here, we conducted a functional MRI (3T Trio, Siemens Medical Solutions, Erlangen, Germany) in 17 healthy adults during recognition of different emotional expression in dynamic displays of knocking on a door. Data pre-processing and analysis were conducted with Statistical Parametric Mapping (SPM12, Wellcome Institute of Cognitive Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm). Positive knocking elicited higher activations in the right basal ganglia and superior temporal sulcus (STS), as compared to neutral displays. The left inferior insula, anterior and medial cingulate cortex were more activated by negative emotion. Neutral contrasted to emotional body language engaged left cerebellar lobule IX and right amygdala. In a nutshell, the outcome indicates a distributed cerebro-cerebellar network for visual processing of emotional body language. Midline cerebellar structures and the amygdala may interact in signalling a lack of emotional expression. This is in line with recent data on cerebellar involvement in visual processing of body motion, and may open a window for future research on the role of cerebellum in neuropsychiatric disorders such as schizophrenia and autistic spectrum disorders.

Disclosures: **A.A. Sokolov:** None. **M. Erb:** None. **F.E. Pollick:** None. **W. Grodd:** None. **K. Scheffler:** None. **R.S.J. Frackowiak:** None. **K.J. Friston:** None. **M.A. Pavlova:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.13

Topic: D.14. Cerebellum: Central Physiology

Support: National Ataxia Foundation

Cerebellar Research Consortium for the Spinocerebellar Ataxias (RC1 NS068897-02)

Birmingham Foundation

Mindlink Foundation

Title: The cerebellar contribution to social cognition - a Lasso regression analysis

Authors: *F. HOCHE[1], X. GUELL[1], J. C. SHERMAN[2], M. G. VANGEL[3], J. D. SCHMAHMANN[1];
[1]Massachusetts Gen. Hosp., Boston, MA; [2]Massachusetts Gen. Hospital, Psychology Assessment Ctr., Boston, MA; [3]Massachusetts Gen. Hospital, Martinos Ctr. for Biomed. Imaging, Boston, MA

Abstract: Background: Neuroimaging and brain lesion studies suggest that the cerebellum is incorporated into neural substrates for social cognition, including tests of emotion attribution (EA). We recently confirmed this notion and showed that EA is impaired in patients with cerebellar pathology (Hoche et al., 2014). Social cognitive deficits are viewed as part of the spectrum of affective impairments in patients with the cerebellar cognitive affective syndrome (CCAS), characterized by deficits in executive function, linguistic processing, visual spatial cognition, and affect regulation (Schmahmann and Sherman, 1998). The EA task may require cognitive processing dependent on CCAS domains, such as visual-spatial reasoning as well as executive functions, attention, working memory or language skills (Byom and Mutlu, 2013). Further, it has been suggested that social cognitive performance *per se* is ameliorated by co-operationalization of cognitive networks in addition to recruitment of a social cognitive core circuitry (Haxby *et al*., 2000). We hypothesized that cerebrocerebellar cognitive networks that are disrupted in cerebellar pathology leading to the CCAS also contribute to loss of function on EA tasks in patients with cerebellar disease. Methods: We performed standard neuropsychological tests and the Reading the Mind in the Eyes test (RMET) (Baron-Cohen, 2001) in patients with cerebellar pathology (n=57) and healthy controls (n=57), and implemented least absolute shrinkage and selection operator (LASSO) regression to evaluate effects of cognitive performance on accuracy of decoding facial expressions. Cognitive domains that contributed to performance on the RMET were selected by LASSO, which identifies efficient sets of variants influencing the outcome measure (RMET). Results: Impairments in cerebellar patients were found on EA skills as well as on CCAS domains (p<.000 respectively). LASSO revealed that performance on a variety of tests evaluating domains of the CCAS (executive function, visual spatial reasoning, and language) were included in a predictive model of EA in controls (parsimonious model; r^2=1.000) but not in the cerebellar cohort (r^2=0.731, F=8.685, p<0.001). Discussion: Social cognition as measured by EA is impaired in cerebellar patients. LASSO regression in healthy controls shows that EA is dependent on the cognitive domains that are core features of the CCAS in cerebellar lesioned patients. We conclude that cerebellar pathology disrupts cerebellar interconnections with cerebral associative and paralimbic regions,

resulting in the CCAS and impairing co-operationalization of cognitive domains necessary for EA.

Disclosures: F. Hoche: None. **X. Guell:** None. **J.C. Sherman:** None. **M.G. Vangel:** None. **J.D. Schmahmann:** None.

Nanosymposium

653. Cerebellum: Learning and Cognition

Location: S402

Time: Wednesday, October 21, 2015, 8:00 AM - 11:30 AM

Presentation Number: 653.14

Topic: D.14. Cerebellum: Central Physiology

Support: Sidney R. Baer Jr. Foundation

NCATS NIH 8KL2TR000168-05

Title: Cerebellar transcranial magnetic stimulation to impact network connectivity in schizophrenia

Authors: *M. A. HALKO[1], I. GONSALVEZ[1], A. STERN[2], J. SCHMAHMANN[3], A. PASCUAL-LEONE[1];
[1]Neurol., [2]Psychiatry, Beth Israel Deaconess Med. Ctr., Boston, MA; [3]Massachusetts Gen. Hosp. / Harvard Med. Sch., Boston, MA

Abstract: Growing evidence suggests that symptoms of neurological and psychiatric illness may arise from deficient neural network function. Resting state functional connectivity has emerged as a tool to identify deficient neural network function within disease populations. The cerebellum is incorporated into neural systems subserving sensorimotor, cognitive and limbic domains, and cerebellar lesions produces deficits in intellect and emotion. We hypothesized that cerebellar connections with cerebral cortex may provide access for cortical network modulation. We delivered intermittent theta-burst transcranial magnetic stimulation (TMS) to the cerebellar vermis and assessed network functional connectivity using three 6-minute resting state fMRI runs. Healthy participants (n=9) participated in single session studies comparing functional connectivity before TMS to a second fMRI session immediately following TMS. In schizophrenia patients (n=16) in a double-blind, randomized trial of TMS efficacy, stimulation was delivered twice a day for 5 days. Resting state functional connectivity was assessed at baseline and 1 week following the last TMS session. In healthy participants, stimulation resulted in increased functional connectivity within the dorsal attention network. Similar patterns of

increased connectivity within the dorsal attention network in the intraparietal sulcus were found in patients who received real stimulation. No changes in functional connectivity were observed in a control network analysis within the default network, or in patients receiving sham stimulation. Baseline PANSS ratings on the negative and general scales correlated with baseline functional connectivity (r=0.46 and r=0.41, respectively). These baseline ratings were not correlated with functional connectivity within the default network (r=-0.08 and -0.12). These results suggest that functional connectivity may be shaped by TMS, and that this change can last multiple days following repeated stimulations. Our findings suggest that therapeutic interventions may be guided towards functional connectivity endpoints to establish treatment efficacy, which may then correspond to clinical improvement. Cerebral cortical network modulation appears to be possible via cerebellar stimulation.

Disclosures: **M.A. Halko:** None. **I. Gonsalvez:** None. **A. Stern:** None. **J. Schmahmann:** F. Consulting Fees (e.g., advisory boards); Dr. Schmahmann serves as a consultant to Takeda Pharmaceuticals. **A. Pascual-Leone:** F. Consulting Fees (e.g., advisory boards); Dr. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, and Neosync; and is listed as an inventor on several issued and pending patents.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.01

Topic: D.15. Basal Ganglia

Support: CTSA grant UL1 TR000064

CTSA grant KL2TR000065

Title: Gene expression, dendrite morphology, and neuronal activation of indirect basal ganglia pathway nuclei in a mouse model of repetitive behavior

Authors: ***A. MUEHLMANN**[1], L. CURRY-POCHY[1], M. MAHMOOD[1], M. KING[2], M. H. LEWIS[1];
[1]Psychiatry, [2]Univ. of Florida, Gainesville, FL

Abstract: Restricted, repetitive behaviors are continuous and invariant behaviors such as motor stereotypies, insistence on sameness, rituals, and compulsions and are common phenotypic traits of many psychiatric, neurological, and neurodevelopmental disorders. Despite the high incidence

of these disruptions of adaptive behavior, the neurobiological basis is relatively unknown and pharmacological targets for treatment have not been adequately studied. Previous work using the Peromyscus maniculatus mouse model identified hypoactivation of the subthalamic nucleus in mice with high rates of repetitive behavior. Furthermore, drug cocktails designed to selectively increase the function of the indirect basal ganglia pathway (circuitry that includes the subthalamic nucleus) significantly reduce repetitive behavior in mouse models. We have extended this line of research to the C58 inbred mouse model, which also exhibits high rates of repetitive behavior. Gene expression analyses using commercially available PCR arrays (SABiosciences) identified significant alterations in receptor subunit and transporter genes that mediate the excitatory/inhibitory balance in the subthalamic nucleus of C58 mice, compared to the closely related C57Bl/6 mice, which do not exhibit high rates of repetitive behavior. These genes include GABA receptor subunits, the GABA transporter, and mGluR3, which regulates glutamate release in the substantia nigra pars reticulata. We are now expanding on these analyses using RNA-seq to catalog all gene expression differences in the globus pallidus and subthalamic nucleus between C58 and C57Bl/6 mice. In addition, we found significantly lower dendritic spine density in the globus pallidus and subthalamic nucleus neurons in C58 mice relative to C57Bl/6 mice. This is consistent with our finding that neuronal activation, as measured by cytochrome oxidase histochemistry, is also reduced in the subthalamic nucleus of C58 mice. No differences in globus pallidus neuronal activation were found, though this may be a limitation of the histochemistry technique in this highly striated brain region. Taken together, these data suggest repetitive behavior is a function of hypoactivation of the subthalamic nucleus, which is mediated by enhanced inhibitory tone provided by the globus pallidus. This is consistent with the role of the indirect basal ganglia pathway, of which both the globus pallidus and subthalamic nucleus are exclusively involved, to suppress motor behavior.

Disclosures: **A. Muehlmann:** None. **L. Curry-Pochy:** None. **M. Mahmood:** None. **M. King:** None. **M.H. Lewis:** None.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.02

Topic: D.15. Basal Ganglia

Support: NSERC PDF-438487-2013

1ZIAAA000416-09

Title: Real-time *in vivo* plasticity of corticostriatal afferent activity during skill learning

Authors: D. A. KUPFERSCHMIDT[1], G. CUI[2], D. M. LOVINGER[1];
[1]NIH/NIAAA, Rockville, MD; [2]Natl. Inst. of Envrn. Hlth. Sci., Research Triangle, NC

Abstract: Dynamic changes in cortico-basal ganglia circuit function underlie action learning. How changes in discrete, connectivity-specified circuits manifest *in vivo* during such learning remains a fundamental question in neuroscience. Using *in vivo* fiber photometry, we assessed real-time activity and plasticity of distinct cortical inputs to the striatum during motor skill learning. Emx1Cre mice expressing Cre recombinase in excitatory cortical neurons were injected with adeno-associated viruses encoding a Cre-dependent form of the calcium indicator, GCaMP6s, into the motor cortex (M1) or medial prefrontal cortex (mPFC). An optical fiber was implanted into the dorsolateral striatum of M1-injected mice to target sensorimotor corticostriatal inputs, and the medial striatum of mPFC-injected mice to target associative corticostriatal inputs. Activity-dependent fluorescent calcium dynamics were assessed in presynaptic elements of these inputs as a proxy for projection activity as mice were trained on the accelerating rotarod. Sensorimotor inputs were engaged by performance on the rotarod, and their activity scaled flexibly with rotarod velocity. Velocity-correlated activity persisted across training, despite a progressive decrease in overall engagement of this pathway. Associative projection activity was also engaged in a velocity-correlated manner during early rotarod performance, but was markedly reduced with extended training. Our work describes a novel approach to observe real-time activity dynamics in discrete corticostriatal inputs, and reveals projection-specific plasticity that likely underlies motor skill learning.

Disclosures: D.A. Kupferschmidt: None. **G. Cui:** None. **D.M. Lovinger:** None.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.03

Topic: F.02. Animal Cognition and Behavior

Support: Swartz Foundation Fellowship

NIH R01 MH062349

Office of Naval Research Grant N00014- 13-1-0297

Title: A cortico-basal ganglia-thalamocortical circuit model for executive control and working memory

Authors: *W. WEI[1], X.-J. WANG[1,2];
[1]New York Univ., New York, NY; [2]NYU Shanghai, Shanghai, China

Abstract: Whereas "cognitive-type" cortical circuits (such as the prefrontal cortex) have been much emphasized, their interactions with the corresponding subcortical structures have been less studied. To make progress, we developed a physiologically-based network of spiking neurons endowed with feedback mechanisms at three levels: local cortical microcircuit, thalamocortical loop and cortico-basal ganglia (BG)-thalamocortical system. We tested our circuit model for executive control in a stop-signal task in which a subject is required to suppress a planned action upon the occurrence of an unexpected stop signal. A stop signal enters the BG through the subthalamic nucleus (STN) and is transmitted along two routes that impact the output of the BG. The fast route is from the STN directly to the output nucleus of the BG, the substantia nigra pars reticulata (SNr) or internal segment of the globus pallidus (GPi), which quickly increases the SNr/GPi inhibitory output to the thalamus. The slower route is from the STN to the external segment of globus pallidus (GPe); the model is capable of accounting for the experimental observations from a stop-signal task, provided that the GPe sends feedback inhibition to striatum (a newly reported pathway), through which the stop signal could interrupt ramping activity in the striatum. We found that decreasing the weight of the direct pathway enhances the inhibitory function, reflected by an enhanced probability of action cancellation and a reduced stop signal reaction time (SSRT), an important measure for the effectiveness of inhibitory control. We further applied the same model to a perceptual decision making process in a random-dots motion direction discrimination task, where the only difference in implementation of these two tasks is the specific form of external input. The model turns out to be capable of not only this choice task, but also a combined perceptual decision and stop-signal task. The SSRT is insensitive to the task difficulty in the perceptual decision making process, indicating a functional independence of the two processes in our model, consistent with the finding from a recent monkey experiment. Importantly, for our model to perform properly, attractor dynamics underlying the required computations, as well as persistent activity in working memory, must not originate solely from local recurrent connections within the cortex; instead it should reply on either the thalamocortical or cortico-BG-thalamocortical closed loop. Therefore, our model supports a distributed mechanism for persistent activity, and provides a unified framework for investigating inhibitory control, decision-making and working memory.

Disclosures: W. Wei: None. **X. Wang:** None.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.04

Topic: D.15. Basal Ganglia

Title: Neural correlates of bidirectional kinetic control and reinforcement in the basal ganglia

Authors: *E. A. YTTRI[1], J. T. DUDMAN[2];
[1]Neurobio., [2]Janelia - HHMI, Ashburn, VA

Abstract: For voluntary actions such as singing or pitching a baseball it is critical that we can learn to modify the underlying movements (e.g. the pitch of a note or velocity of the arm) to improve the outcomes of the action. The basal ganglia are an evolutionarily conserved subcortical circuit, composed of two opponent pathways, direct and indirect, that promote actions that elicit positive outcomes or oppose actions that do not, respectively. This circuitry plays an indispensible role in selecting actions based upon their expected outcomes; however, it is unknown whether basal ganglia circuits are also sufficient to control the specification of movement parameters such as velocity through reinforcement. Furthermore, the mechanism by which action selection is shaped (change in gain, recruitment of neurons from specific populations, etc) is not known. We used cell-type specific stimulation delivered in closed-loop during movement to demonstrate that activity in either pathway is sufficient to produce sustained, opposing changes in specific movement kinetics without generalized changes in action selection or motivation. During stimulation sessions, mice increased or decreased the probability of rapid velocity movements in order to trigger more direct pathway stimulation or less indirect pathway stimulation, independent of the direction of the kinetic modulation. These behavioral changes accumulated over tens of trials, persisted after the cessation of stimulation, and were abolished in the presence of dopamine antagonists. We then elucidated the changes in the population dynamics of striatal direct pathway, indirect pathway, and substantia nigra cell activity using multichannel electrode arrays and paired recordings between areas. Our results demonstrate and characterize how the direct and indirect pathway is each sufficient to selectively reinforce parameters of movements that underlie reward-seeking actions through coordinated changes in activity, demonstrating an unprecedented combination of specificity and flexibility in the control of volition by the basal ganglia.

Disclosures: E.A. Yttri: None. **J.T. Dudman:** None.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.05

Topic: F.02. Animal Cognition and Behavior

Support: 2012KIP506

XDB02010005

2011CBA00404

Title: Neural mechanisms of sustained attention in rats despite of sensory modalities

Authors: ***D. WU**, H. DENG, Z.-R. WANG;
Inst. of Neurosci., Shanghai, China

Abstract: Sustained attention is a brain function of focusing limited cognitive resources on the most significant ongoing task to deal with the complicated internal and external environment. Sustained attention could be steadily elicited when the upcoming target stimulus is uncertain. With this principle, we developed a training system which could be used to train both sustained visual and olfactory attention in rats. Existing evidence has shown that anterior cingulate cortex (ACC) is one of the critical brain regions for the sustained attention. Therefore, we first tested the potential causal relationship between ACC and attention by damaging the ACC in the well-trained rats. The results showed that lesion of partial ACC could lead to retrievable function loss of sustained attention in both visual and olfactory attention, suggesting that ACC is most likely related to executive function which is sustained attention but not memory function in the present task. Then we investigated the neuronal activities in ACC during sustained attention using extracellular recording method. The results showed that the activity intervals of some neurons were coincident with the time window of sustained attention, suggesting that these neurons might be the critical neurons that maintained the function of sustained attention. Then we verified this hypothesis by controlling most of the potential interferences including the target modality, animal behavioral pattern, and external sensory inputs. Besides, we found that the trial-to-trial variability of population activities in ACC was the most reduced during sustained attention in both visual and olfactory task. Further analyses in local field potential (LFP) showed that gamma band was related to sustained attention, suggesting that brain state was stabilized by focusing cognitive resources. In summary, the present study first reported the substitutive executive function of partial ACC, first clarified the critical role of ACC neurons in sustained attention by strict control studies, and first reported that sustained attention could reduce trial-to-trial variability in population activity despite modality. These novel findings are theoretically important because the sustained attention is at the center of all types of attention, as well as practically significant because they could be used to guide us to cure the disorders in attention

system such as attention-deficit/hyperactivity disorder (ADHD) and guide us to design new generation of artificial intelligence.

Disclosures: **D. Wu:** None. **H. Deng:** None. **Z. Wang:** None.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.06

Topic: F.02. Animal Cognition and Behavior

Support: Simons Collaboration on the Global Brain

Title: Optimal context dependent decision making with probabilistic population codes

Authors: *D. ROBLES LLANA, A. POUGET;
Univ. Med. Ctr. (CMU) - Dept. of Basic Neurosci., Univ. of Geneva, Geneve, Switzerland

Abstract: To maximize their chances of survival, animals need to make optimal decisions regulating complex interactions with their environment. Most of these decisions involve multiple, or even a continuum, of possible alternatives, and depend on contextual factors of the environment in which the animal finds itself. Unfortunately, existing theoretical models of decision-making fail to simultaneously address the three aspects of the decision-making process outlined above. Optimal multi-alternative decision making models have been considered before, but they fail to address context, whereas models which built in context dependence ignore optimality and are generally limited to binary choice tasks. Here we present a biologically plausible neural model that performs context dependent, multi-alternative decision making optimally. Momentary sensory evidence is coded by linear probabilistic population codes which allow for a whole continuum of perceptual values to be encoded simultaneously. Likelihood evidence is then accumulated in time by a continuous attractor network whose dynamical state can be adjusted according to the relevant context. We derive theoretical relationships between the sensory input kernels encoding the statistics of the input populations and the geometric quantities that characterize the attractor dynamics. We show how these should be adjusted in such a way that evidence is accumulated optimally. Our model for evidence accumulation reduces to a multidimensional drift diffusion model. As opposed to other works, this is not postulated abstractly but comes directly from the dynamics of the neural model. Drift and uncertainty can be unambiguously related to intrinsic properties of the network and the firing statistics of the populations.

Disclosures: **D. Robles Llana:** None. **A. Pouget:** None.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.07

Topic: F.02. Animal Cognition and Behavior

Support: Japan Grant KAKENHI 23120010

Japan Grant KAKENHI 26290009

Japan Grant KAKENHI 15K14320

Japan Grant KAKENHI 20700293

Japan Grant KAKENHI 24700425

Title: Roles of the centromedian nucleus of thalamus and its projection to the striatum in cognitive and behavioral biases

Authors: ***M. KIMURA**[1], K. YAMANAKA[2], T. MINAMIMOTO[3], Y. HORI[3], Y. UEDA[4]; [1]Brain Sci. Institute, Tamagawa Univ., Tokyo, Japan; [2]Dept. of Physiol., Juntendo University, Fac. of Hlth. and Sports Sci., 1-1 Hiragagakuendai, Inzai, Chiba, Japan; [3]Mol. Neuroimaging, Natl. Inst. of Radiological Sci., 4-9-1 Anagawa, Inage-ku, Chiba, Japan; [4]Dept. of Physiol., Kansai Med. Univ., 2-3-1 Shinmachi, Hirakata, Osaka, Japan

Abstract: The centromedian (CM) and parafascicular (PF) nuclei are posterior cell groups of intralaminar thalamus which receive inputs from the basal ganglia, cerebral cortex and brain stem and project mainly to the striatum and partly to frontal cortical areas. Little is known how the CM and PF are involved in cognitive and motor functions although suggestions were made to participate in stimulus-driven attention and action selection, in contrast to well-studied cortico-basal ganglia loop structures which are suggested to participate in representation of value of actions and response bias as differential reinforcement of high- and low-value actions before action initiation. To understand underlying mechanisms of CM/PF thalamus and its projection to the striatum, we recorded neurons in the CM nucleus of two macaque monkeys performing instructed choice tasks under response bias (biased task) and sensory guidance (cued task). In the biased task, long-latency facilitation (LLF, n=29) neurons responded to large-reward GO with shorter latency than that after small-reward GO, suggesting motivational salience representation.

Non-sensory facilitation (NSF, n=68) neurons generated pre-GO activity reflecting response bias. After switching from the biased to cued task, the GO responses of LLF and short-latency facilitation (SLF, n=5) neurons stopped immediately, and the CUE responses of SLF neurons declined over a few trials, suggesting a surprise signal. Reversal of action-outcome combination induced SLF neuron responses in the first few trials, while LLF and NSF neurons slowly developed motivational and response bias signals, respectively. LLF neurons were electrophysiologically identified to project to the putamen. These results suggest roles of the CM nucleus of thalamus and its projection to the striatum in cognitive and behavioral biases.
Supported by grants by 23120010, 26290009, 15K14320, 20700293 and 24700425.

Disclosures: M. Kimura: None. **K. Yamanaka:** None. **T. Minamimoto:** None. **Y. Hori:** None. **Y. Ueda:** None.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.08

Topic: F.02. Animal Cognition and Behavior

Support: CIHR Postdoctoral Fellowship

Title: Microendoscopic imaging of cell-type specific neuronal activity in the basal forebrain of awake behaving mice

Authors: *T. C. HARRISON, L. PINTO, Y. DAN;
Mol. and Cell Biol., Univ. of California Berkeley, Berkeley, CA

Abstract: The basal forebrain contains the somata of corticopetal cholinergic neurons and is involved in the regulation of brain states, including transitions between sleep and wake. Recent work has demonstrated that direct activation of basal forebrain cholinergic neurons can modulate cortical activity and enhances behavioral performance on sensory discrimination tasks1. The natural pattern of activity of basal forebrain neurons during behavior is incompletely characterized, particularly with respect to neuronal identity. The basal forebrain comprises a mixture of cell types, including glutamatergic, GABAergic and cholinergic neurons, all of which extend projections to cortex2. To examine the activity of these cell types in awake mice, we performed microendoscopic calcium imaging in the basal forebrain using a miniature integrated fluorescence microscope. Imaging was conducted both in freely moving mice exhibiting spontaneous natural behavior in their home cages and in head-fixed mice performing a go/no-go

auditory discrimination task. Glutamatergic, cholinergic, and gabaergic neurons all displayed responses to sensory and motor events occurring on a timescale of seconds. These observations suggest that the functional roles of the basal forebrain are not limited to relatively slow changes in arousal such as between sleep and wake, but may also include the modulation of widespread brain regions on a rapid, behaviorally-relevant timescale. References: 1.Pinto, L. et al. Fast modulation of visual perception by basal forebrain cholinergic neurons. Nat. Neurosci. 16, 1857-1863 (2013). 2.Zaborszky, L. et al. Neurons in the Basal Forebrain Project to the Cortex in a Complex Topographic Organization that Reflects Corticocortical Connectivity Patterns: An Experimental Study Based on Retrograde Tracing and 3D Reconstruction. Cereb. Cortex N. Y. N 1991 (2013)

Disclosures: T.C. Harrison: None. **L. Pinto:** None. **Y. Dan:** None.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.09

Topic: F.02. Animal Cognition and Behavior

Support: CIHR

Title: A novel rat probabilistic choice task models the effects of losses disguised as wins: implications for gambling disorder

Authors: *C. A. WINSTANLEY[1], J.-M. N. FERLAND[2], S. MURCH[2], L. CLARK[2]; [1]Psychology, Univ. British Columbia, Vancouver, BC, Canada; [2]Psychology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Understanding the reinforcing aspects of gaming behaviour is essential in determining what may contribute to gambling disorder. Casino games such as multiple-line slot machines use a variety of reward outcomes to incentivize play. One such outcome, when the return to player is less than that of the wager placed, or a loss disguised as a win (LDW), is thought to invigorate play. Indeed, LDWs have been found to produce similar physiological responses (i.e. skin conductance responses) as true wins, are less likely to be recognized as losses, and are thought to be more rewarding than losses despite negative net outcome. Animal models capable of capturing the impact of LDWs on probabilistic decision-making would be useful in improving our understanding of the phenomenological and neurobiological basis of the LDW effect. Using 24 male Long-Evans rats, we piloted a novel rat operant task to model LDWs and investigate

their impact on decision-making. Rats were trained during 15-minute sessions that took place in standard 5-hole operant boxes with two retractable levers. During the first 5 sessions of training, animals were presented with forced-choice trials with one lever extended at a time, each lever associated with a different reward contingency. After initiating a trial, the animal was presented with either the "safe" lever, resulting in 100% chance of winning two sugar pellets, or the "risky" lever, resulting in 50% chance of winning four sugar pellets. Following forced-choice sessions, animals were presented with the safe and risky levers simultaneously and were allowed to freely choose between the two levers. Upon the demonstration of stable choice (10 sessions), LDWs were then presented to subjects on risky lever choices as a three sugar pellet “win” for 30% of true win trials and were then increased to 40% of true win trials. Each probability contingency was maintained for 10 sessions. Results indicated that most animals shifted choice towards the safe option as the probability of LDWs increased. However, a subgroup of animals (n=6) were insensitive to the LDWs, resulting in continued choice of the risky option. This subgroup may represent a vulnerable population that is insensitive to loss, making them more likely to choose risky options despite the lowered return to player. With this novel task, we will be able to investigate the neurobiological bases of these individual differences and may be able to further determine how LDWs affect the propensity to gamble.

Disclosures: **C.A. Winstanley:** F. Consulting Fees (e.g., advisory boards); Shire. **J.N. Ferland:** None. **S. Murch:** None. **L. Clark:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; British Columbia Lottery Corporation. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); British Columbia Lottery Corporation. F. Consulting Fees (e.g., advisory boards); Cambridge Cognition.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.10

Topic: F.02. Animal Cognition and Behavior

Support: NIH grant NS076416

UW RRF grant

NIH grant T32 DA07278-20

Title: Lateral habenula inactivation impairs cued switching performance in rats

Authors: *P. M. BAKER, S. A. RAYNOR, S. J. Y. MIZUMORI;
Psychology, Univ. of Washington, Seattle, WA

Abstract: The ability to rapidly switch behaviors when cues in the external environment signal a change in outcomes is critical to survival. While these cued switches in behavior are routine for the majority of people, various psychopathologies including major depression, generalized anxiety disorder, drug addiction, and obsessive compulsive disorder result in an impairment in this form of behavioral flexibility. Recently, research examining reward predictive cues has identified the lateral habenula (LHb) as a locus for anti-reward signals projecting to both the dopamine and serotonin systems. These systems in turn are known to influence behavioral flexibility in many areas throughout the brain. However, a number of recent results have suggested that the LHb may be involved in reward processing beyond an anti-reward signal, e.g. subjective choice preferences. This raises the possibility that the LHb is also involved when cues may be used proactively to switch behaviors. To test this possibility, male Long-Evans rats were trained to flexibly switch between two egocentric choices on a t shaped maze based on auditory cues (high or low pitched tones). These cues were switched every 3-6 trials requiring rats to maintain a high level of behavioral flexibility while also allowing the establishment of an ongoing choice pattern. Once animals established proficiency on the task, they were implanted with guide cannula aimed at the LHb for subsequent injection with the GABA agonists, baclofen and muscimol (50ng/0.2μL). Once criterion was again reached, animals were injected 2 times each with either baclofen and muscimol or saline vehicle in alternating order. Results indicate that inactivation of the LHb results in a profound deficit in the ability of rats to perform the cued switching task. Specifically, animals' performance fell from 75% accuracy to chance levels representing an increase in multiple error types. Ongoing experiments are currently aiming to address whether this deficit is due to memory impairments or due to the difficultly of repeatedly switching within a single session. Overall, these findings support the hypothesis that the LHb is involved in cognitive flexibility tasks beyond a role in negative reward prediction error signaling.

Disclosures: P.M. Baker: None. **S.A. Raynor:** None. **S.J.Y. Mizumori:** None.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.11

Topic: F.02. Animal Cognition and Behavior

Support: Grants-in-Aid for Scientific Research (KAKENHI) from MEXT (no. 22115013)

KAKEN-HI No. 255413 from MEXT

Title: The underlying mechanism of individual variation in sensory-guided probabilistic decision making

Authors: *T. KURIKAWA[1], T. HANDA[2], T. FUKAI[1];
[1]RIKEN, Brain Sci. Inst., Wako City, Saitama, Japan; [2]Res. center Caesar, Bonn, Germany

Abstract: Animals are often required to adequately respond to novel stimuli on the basis of their previous sensory experiences. To investigate the neural mechanism underlying this sensory-guided decision making, we conducted multiunit recordings from the rats performing a two-alternative choice task. The rats were trained to make a LEFT or a RIGHT choice in response to two auditory cues, and then their behavior was tested for these familiar cues and other novel cues. Their choice probabilities generally varied in a graded manner such that the probability of choosing an option changed gradually according to frequency differences between familiar and novel cues (gradual behavior). However, we also observed large variability in choice behavior across rats: choice probabilities for novel cues were near the chance level in some rats (flat behavior). We elucidated the mechanism underlying such decision behavior and the possible origin of individual behavioral differences by constructing a model and comparing its behavior with experimental data. Our model is viewed as a reservoir network and learns to associate two familiar cues with two alternative choices through reinforcement learning with eligibility trace. Our model successfully replicated both type of experimentally observed behavior: the gradual and flat behaviors. We revealed that which type is provided is dependent on trial-by-trial overlaps between the familiar trajectories and novel-cue-evoked trajectories in models as well as rats. We, further, found that if input neurons are highly sensitive to external stimuli, that is, if the width of their frequency tuning curves is broad, the model network likely shows gradual choice behavior through trial-by-trial overlaps. In contrast, the model with more sensitive input neurons (with broader tuning curves) tends to generate near-random choice behavior. We compared choice behavior between the models and the rats by introducing quantitative measures and found that the behavioral tendency of our model is consistent with that of the rats. These results may suggest that some individual differences in decision-making behavior emerge from neural population dynamics rather than differences in higher-level behavioral strategies.

Disclosures: **T. Kurikawa:** None. **T. Handa:** None. **T. Fukai:** None.

Nanosymposium

654. Basal Ganglia and Basal Forebrain: Behavioral Control

Location: S401

Time: Wednesday, October 21, 2015, 8:00 AM - 11:00 AM

Presentation Number: 654.12

Topic: F.02. Animal Cognition and Behavior

Support: CIHR Grant

NSERC Grant

Title: Neural correlates of anticipatory spatial attention using local field potential recordings with 5-choice serial reaction time task in rats

Authors: *V. LJUBOJEVIC[1], P. LUU[2], P. R. GILL[3], L.-A. BECKETT[2], K. TAKEHARA-NISHIUCHI[2], E. DE ROSA[1];
[1]Cornell Univ., Ithaca, NY; [2]Univ. of Toronto, Toronto, ON, Canada; [3]Rambus Labs, Sunnyvale, CA

Abstract: Previous work has suggested that cholinergic projections from the nucleus basalis magnocellularis (NBM) to the neocortex contribute to attention. In particular, acetylcholine (ACh) input the sensory cortices plays a role in attentional enhancement of target detection via bottom-up modulation (Sarter et al., 2005). However, less is known of cholinergic influence on top-down attentional modulation. In particular, it is not known how NBM cholinergic modulation of higher attentional centres, such as prefrontal (PFC) and posterior parietal cortices (PPC), affects stimulus detection. In the present study, we examined how cholinergic deafferentation of the PFC and the PPC affects both the behaviour and local field potential (LFP) activity associated with detection of visual and olfactory targets. We trained 19 male Long-Evans rats on both visual and olfactory versions of the 5-choiceserial reaction time task (5-CSRTT), a paradigm that involves the detection of target stimuli presented after a brief delay period. Following the training, the rats underwent either a selective cholinergic lesion of the NBM reducing frontoparietal cortical ACh input (N=10), or a sham lesion surgery (N=9). Then, rats were implanted with cortical electrodes into the prelimbic PFC and the PPC and tested on the 5-CSRTT. Histological analyses confirmed both the neurochemical and neuroanatomical specificity of the lesions and the accuracy of electrode placement. Post-surgery, ACh-NBM-lesioned rats performed comparably to sham-lesioned rats under baseline conditions (target duration, TD=1sec), but had less correct responses and more omissions under conditions of increased attentional demand (TD=0.5sec and TD=0.25sec). This pattern of deficit was observed on both the visual and olfactory version of the task. In sham-lesioned rats, behavioural performance on both versions of the task was associated with increased LFP coherence in the beta range between the PFC and the PPC, and with increased beta power measured from the PPC. These changes were observed immediately prior to the target's appearance (within 1 sec) and may reflect a top-down, anticipatory attentional process. Importantly, these task-associated changes in brain activity were attenuated in the ACh-NBM-lesioned group. These results suggest

that the PFC and PPC are involved in top-down control of target detection by modulation of anticipatory attention and that this function of frontoparietal cortices is ACh-dependent. Additionally, these frontoparietal neural processes are modality independent, suggesting an existence of an amodal mechanism for top-down control of target detection.

Disclosures: V. Ljubojevic: None. **P. Luu:** None. **P.R. Gill:** None. **L. Beckett:** None. **K. Takehara-Nishiuchi:** None. **E. De Rosa:** None.

Nanosymposium

655. New Insight into Neural Circuitry Controlling Inflammation

Location: N230

Time: Wednesday, October 21, 2015, 8:00 AM - 9:45 AM

Presentation Number: 655.01

Topic: E.02. Neuroimmunology

Support: SFARI

DOD

NARSAD

Title: Probing the contribution of maternal antibodies to Autism Spectrum Disorder

Authors: *L. BRIMBERG, S. MADER, V. JEGANATHAN, P. HUERTA, B. VOLPE, B. DIAMOND;
Ctr. for Autoimmune and Musculoskeletal Dis., The Feinstein Inst. for Med. Res., Manhasset, NY

Abstract: Maternal brain-reactive antibodies have been associated with increased risk for Autism Spectrum Disorders (ASD) in the offspring. This is due to the fact that maternal brain-reactive antibodies can affect the fetal brain before the development of a competent blood brain barrier that prevents exposure to antibody. Several studies have indicated that mothers with an ASD child have significantly higher levels of anti-brain antibodies in the serum compared to mothers of typically developed children and women of child bearing age. Previous studies have used polyclonal serum to study maternal antigenic specificities, and their postnatal effects. We developed a method to generate monoclonal brain-reactive antibodies to study the antigenic specificities of brain-reactive antibodies and to determine which contribute to ASD pathogenesis. We show in a mouse model that exposure in-utero to a monoclonal brain-reactive antibody isolated from a mother of an ASD child induces neurodevelopmental effects in the offspring that can be observed already during the embryonic stage. We identified brain-reactive B cells in

blood of women with brain-reactive IgG and a child with ASD and generated monoclonal (Mab) brain-reactive antibodies by single cell cloning and expression. One Mab, C6 was found to target Caspr2, a protein that is part of the voltage gated potassium channel complex and is encoded by a known autism associated gene. When this Mab was administrated to pregnant mice at E13, male but not female mice showed thinning of the cortical plate and fewer mitotic cells at E15 compared to embryos of mice injected with a non brain-reactive Mab. Two week old mice showed reduced dendrite complexity in the CA1 region of the hippocampus which continued into the adulthood. Adult mice also showed reduced GABAergic neurons in the same region. In parallel, in adulthood, male mice exposed to C6 showed increased stereotypic behavior, reduced sociability and inflexibility in a learning paradigm. This work demonstrates that anti-brain antibodies cloned from a mother of an ASD child lead to in -vivo to structural and behavior alterations. Identifying pathogenic brain-reactive Mabs may translate into future protection studies.

Disclosures: **L. Brimberg:** None. **S. Mader:** None. **V. Jeganathan:** None. **P. Huerta:** None. **B. Volpe:** None. **B. Diamond:** None.

Nanosymposium

655. New Insight into Neural Circuitry Controlling Inflammation

Location: N230

Time: Wednesday, October 21, 2015, 8:00 AM - 9:45 AM

Presentation Number: 655.02

Topic: E.02. Neuroimmunology

Title: Characterization of stimulation parameters that activate the cholinergic anti-inflammatory pathway and fiber types mediating this effect in rodents, canines, and RA patients

Authors: ***Y. A. LEVINE**, A. DRAKE, A. CARAVACA, M. FALTYS, R. ZITNIK; Setpoint Med. Corp., Valencia, CA

Abstract: The inflammatory reflex regulates innate and adaptive immunity. Activation of its efferent arm (the cholinergic anti-inflammatory pathway [CAP]) by vagus nerve stimulation (VNS) reduces systemic inflammation and ameliorates disease in many animal models (Andersson, Annu Rev Immunol 2012; 30:313). Our understanding of the nerve fiber type mediating the CAP, and optimal stimulus characteristics for CAP activation was incomplete. Additionally, whether this pathway was operant in humans was not known. Here, we characterize the fibers involved in the CAP activation through dose titration and evoked potential studies in rats and canines. We then show that VNS activates the CAP and improves clinical manifestations in rheumatoid arthritis (RA) patients. Rats and canines underwent VNS or sham

surgery, and TNF levels were measured in lipopolysaccharide (LPS)-exposed blood before and after cervical VNS. In select animals, evoked potentials were measured distally on the cervical (canine) or subdiaphragmatic (rat) vagus. Patients with active RA (N=18) were enrolled in a study where after a baseline visit and implantation with a cervical VNS system, output current was escalated based on tolerability to a maximum of 2.0 mA, and 1-4 min of daily stimulation (10 Hz, 0.25 ms pulse width) was delivered through day 42. Stimulation was then withdrawn for 14 days, reinitiated and maintained through day 84. TNF levels were measured in LPS-exposed blood samples at baseline and throughout the study. In rat and canine, the threshold stimulus for inhibition of cytokine production was ~0.25mA, with minimal additional reduction at higher intensities. Potentials evoked in this range had conduction velocities typical of larger myelinated fibers, suggesting they mediate this anti-inflammatory effect. In humans, the mean output current delivery achieved at day 42 was 1.43 mA (SD 0.38) and was associated with a significant reduction in TNF levels in LPS-exposed blood at days 42 and 84 compared to pre-implant baseline. TNF reduction correlated with the RA disease activity score (DAS28). Both DAS and TNF improved significantly during the period of active VNS, worsened during treatment withdrawal, and then improved again once VNS was reinitiated. Together these data provide evidence that VNS mediates CAP activation through larger myelinated fibers in rats and canines. A similar population of neurons likely mediate the effect in humans but more work is needed to determine this definitively. Further studies will determine the pathway activation threshold in humans and may demonstrate VNS efficacy in larger controlled studies in RA and other chronic inflammatory diseases.

Disclosures: **Y.A. Levine:** A. Employment/Salary (full or part-time); SetPoint Medical Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SetPoint Medical Inc. **A. Drake:** A. Employment/Salary (full or part-time); SetPoint Medical Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SetPoint Medical Inc. **A. Caravaca:** A. Employment/Salary (full or part-time); Setpoint Medical Corp. **M. Faltys:** A. Employment/Salary (full or part-time); SetPoint Medical Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SetPoint Medical Inc. **R. Zitnik:** A. Employment/Salary (full or part-time); SetPoint Medical Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SetPoint Medical Inc..

Nanosymposium

655. New Insight into Neural Circuitry Controlling Inflammation

Location: N230

Time: Wednesday, October 21, 2015, 8:00 AM - 9:45 AM

Presentation Number: 655.03

Topic: E.02. Neuroimmunology

Support: AAP INSERM-DGOS

Title: Vagus nerve stimulation as an innovative treatment in inflammatory bowel diseases

Authors: *B. L. BONAZ[1,2], V. SINNIGER[1,2], S. PELLISSIER[2,3], D. HOFFMANN[4], N. MATHIEU[1], C. TROCMÉ[5], L. VERCUEIL[6], D. CLARENÇON[2];
[1]Dept of Gastroenterology and Liver Dis., Grenoble Cedex 09, France; [2]Grenoble Inst. of Neurosciences (GIN, INSERM U836), Grenoble, France; [3]Univ. of Savoie Mont-Blanc, Dept. of Psychology, Chambéry, France; [4]Dept. of Neurosurg., Grenoble, France; [5]Dept. of Biol., Grenoble, France; [6]Dept. of Neurol., Grenoble, France

Abstract: Introduction: The vagus nerve (VN) has an anti-inflammatory effect through the cholinergic anti-inflammatory pathway by inhibiting the release of pro-inflammatory cytokines, such as TNFα, by peripheral macrophages and the spleen. We have previously shown that VN stimulation (VNS) improves an experimental model of Crohn's disease (CD) in rats. We have also shown that patients with CD have a blunted VN activity, as recorded by heart rate variability (HRV). In a translational approach, we are running a pilot study (Clinical Trials.gov NCT01569503) of VNS in patients with active CD. The main goal was to evaluate the safety and efficacy of VNS as well as its efficacy at the clinical, biological and endoscopic level. Methods: Six patients with active CD were included and equipped with a VNS device (Cyberonics Inc.). Stimulation parameters were 10 Hz, 500 μs, 0.5-1.5 mA, 30 s ON, 5 min OFF. Three main types of markers were measured during a one-year follow-up: clinical (Crohn's disease activity index, CDAI), biological (C-reactive protein, CRP, and fecal calprotectin, FC), autonomic (heart rate variability, HRV), and endoscopic (ileo-colonoscopy). Currently, the study is still running and only the six first month of follow-up are presented herein. Results: Four patients had an improvement of their: 1) clinical state, marked by a decrease in CDAI, 2) parasympathetic tone (HRV), which returned to a homeostatic level, 3) biological state, with a decrease in CRP and FC, 4) endoscopic appearance with a mucosal improvement/healing. VNS was well tolerated. Conclusions: these results show, for the first time, that VNS is safe and well tolerated in patients with active CD. Moreover, long-term VNS induces an effective improvement over the six first months and further next results will show us if this improvement is maintained over the one year of follow-up. VNS, devoid of problem of compliance, could be of interest as a non-drug alternative treatment to classical pharmacological therapies.

Disclosures: B.L. Bonaz: None. **V. Sinniger:** None. **S. Pellissier:** None. **D. Hoffmann:** None. **N. Mathieu:** None. **C. Trocmé:** None. **L. Vercueil:** None. **D. Clarençon:** None.

Nanosymposium

655. New Insight into Neural Circuitry Controlling Inflammation

Location: N230

Time: Wednesday, October 21, 2015, 8:00 AM - 9:45 AM

Presentation Number: 655.04

Topic: E.02. Neuroimmunology

Title: Tumor necrosis factor induces a cytokine specific sensory vagus neurogram

Authors: *H. A. SILVERMAN[1,2], S. ROBBIATI[3], B. E. STEINBERG[1], A. STIEGLER[4], T. TSAAVA[1], E. A. BATTINELLI[1,2], P. T. HUERTA[3], K. J. TRACEY[1,2], S. S. CHAVAN[1]; [1]Lab. of Biomed. Science, Ctr. for Biome, Manhasset, NY; [2]Hofstra North Shore-LIJ Sch. of Med. at Hofstra Univ., Hempstead, NY; [3]Lab. of Immune and Neural Networks, Feinstein Inst. for Med. Res., Manhasset, NY; [4]Circulatory Technology, Inc., Oyster Bay, NY

Abstract: The vagus nerve plays an essential role in communicating physiological, metabolic, and hemodynamic status of the animal to the central nervous system. The sensory vagus also senses the immunological status and transmits the information to the brain stem to initiate the reflex control of inflammation. Here, we have mapped changes in vagus nerve activity in response to changes in peripheral immunological status in adult Balb/c mice. Animals displayed consistent low baseline vagus nerve activity (7.6±1.6Hz). In contrast, intraperitoneal administration of the proinflammatory cytokine, Tumor Necrosis Factor (TNF) induced changes in vagus nerve within 3 minutes. Physiologically high levels of TNF (50 µg/mouse) induced significant increases in vagus activity (35.9±5.2Hz), whereas lower levels of TNF showed a dose dependent response. The specificity of TNF-specific responses was confirmed by administration of trypsin-digested TNF, which failed to induce any vagus activity. Next, we confirmed that TNF-induced signals are mediated in a TNF-receptor specific manner. TNF receptor knock out animals developed significant increases in vagus activity in response to IL1, but not TNF administration. These results indicate that the vagus nerve senses changes in the peripheral inflammatory status in mediator-specific, receptor-restricted, and a dose dependent manner. This defines a mechanism of inflammation sensing by the brain.

Disclosures: H.A. Silverman: None. **S. Robbiati:** None. **B.E. Steinberg:** None. **A. Stiegler:** None. **T. Tsaava:** None. **E.A. Battinelli:** None. **P.T. Huerta:** None. **K.J. Tracey:** None. **S.S. Chavan:** None.

Nanosymposium

655. New Insight into Neural Circuitry Controlling Inflammation

Location: N230

Time: Wednesday, October 21, 2015, 8:00 AM - 9:45 AM

Presentation Number: 655.05

Topic: E.02. Neuroimmunology

Support: GCRC MO1 RR018535 NCRR

NIAMS-1RC2AR059092

Wenner-Gren Foundation

Title: Prolonged suppression of tnf release in macrophages following transient electrical vagus nerve stimulation

Authors: *P. S. OLOFSSON[1], M. W. TUSCHE[2], C. REARDON[2], M. ROSAS-BALLINA[3], Y. A. LEVINE[4], L. K. HUDSON[3], W. R. PARRISH[3], M. FALTYS[4], P. K. GREGERSEN[3], B. DIAMOND[3], T. W. MAK[2], U. ANDERSSON[5], K. J. TRACEY[5];
[1]Dept. of Med., Ctr. For Mol. Medicine, L8:03, Stockholm, Sweden; [2]The Campbell Family Inst. for Breast Cancer Res., Univ. Hlth. Network, Toronto, ON, Canada; [3]The Feinstein Inst. for Med. Res., Manhasset, NY; [4]SetPoint Medical, Inc., Valencia, CA; [5]Dept. of Women's and Children's Hlth. (KBH), K6, Karolinska Institutet, Stockholm, Sweden

Abstract: Bioelectronic medicine, the use of neuromodulating devices to modulate therapeutic molecular mechanisms, is a promising opportunity for improved treatment of inflammatory disease. For example, in the inflammatory reflex, signals in the cholinergic vagus nerve suppress cytokine release by activation of the alpha7 nicotinic acetylcholine receptor subunit (a7nAChR) on macrophages in spleen. We previously noted that a single 250 μs pulse of electrical vagus nerve stimulation significantly reduces systemic TNF release in endotoxemia for at least 24 hours, and a minute-long daily stimulation significantly reduces progression of experimental arthritis. However, the kinetics and mechanism for this prolonged effect have been unknown. Here, we report that a brief vagus nerve stimulation reduced TNF release significantly in experimental endotoxemia for ≥24 h, but this effect was absent in a7nAChR deficient mice. The corresponding signal transduction mechanism in macrophages was blocked by pharmacological blocking of adenylyl cyclase, suppression of adenylyl cyclase 6 or cfos expression by siRNA or cellular overexpression of a phosphorylation defective cAMP response element binding protein (CREB). These observations indicate that electrical stimulation of the vagus nerve result in a prolonged change in macrophage activation behavior, and that the a7nAChR-mediated signal in macrophages is mediated by a cAMP-dependent signaling pathway. This mechanism of neural control of immunity has important implications for the development of novel strategies to treat inflammatory diseases using bioelectronic medicine.

Disclosures: P.S. Olofsson: None. **M.W. Tusche:** None. **C. Reardon:** None. **M. Rosas-Ballina:** None. **Y.A. Levine:** A. Employment/Salary (full or part-time); SetPoint Medical,

Inc.. **L.K. Hudson:** None. **W.R. Parrish:** None. **M. Faltys:** None. **P.K. Gregersen:** None. **B. Diamond:** None. **T.W. Mak:** None. **U. Andersson:** None. **K.J. Tracey:** None.

Nanosymposium

655. New Insight into Neural Circuitry Controlling Inflammation

Location: N230

Time: Wednesday, October 21, 2015, 8:00 AM - 9:45 AM

Presentation Number: 655.06

Topic: E.02. Neuroimmunology

Support: Elmezzi Foundation

Title: Activation of viral immune pathways in the ICV-STZ model: Considerations for the pathogenesis of cognitive disorders

Authors: *R. SANKOWSKI[1,4], C. D'ABRAMO[2], P. T. HUERTA[3], Y. AL-ABED[1];
[1]Ctr. for Mol. Innovation, [2]The Litwin-Zucker Res. Ctr. for the Study of Alzheimer's Dis., [3]Lab. of Immune & Neural Networks, Feinstein Inst. For Med. Res., Manhasset, NY; [4]Elmezzi Grad. Sch. for Mol. Med., Manhasset, NY

Abstract: Intracerebroventricular (ICV) injection of streptozotocin (STZ) in rodents has been widely used as a non-transgenic (Tg) model for cognitive impairment. Moreover, the ICV-STZ model has been studied for its potential to reproduce major hallmarks of Alzheimer's disease (AD), such as tau phosphorylation, neuroinflammation and cognitive dysfunction in mice and rats. We treated 6-mo-old C57BL/6 mice (101 males, 45 females) with ICV-STZ (3mg per kg) and studied immune, histochemical and behavioral changes compared to control mice injected with saline (SAL). We found no differences in survival (mortality: SAL, 1 out of 82; STZ, 1 out of 64), and no gross neurological abnormalities in ICV-STZ mice when compared to SAL controls. As previously shown, ICV-STZ induced robust astrogliosis within days of injection, particularly in hippocampal and cortical regions. However, in contrast to previous reports, we did not observe increases in tau phosphorylation within the brain following ICV-STZ (n = 30, up to 6 mo post-injection), a result that was further confirmed in human tau Tg mice (n = 8). *In vitro* studies showed that incubation of microglia with STZ led to the induction of MAP kinase and antiviral immune pathways (TBK-IRF3 cascade). Behavioral assessment of ICV-STZ mice (n = 15), 3 mo post-injection, revealed clear impairments in reference memory and working memory when tested in the clockmaze task. We conclude that our results challenge the notion of ICV-STZ injection as a reliable AD model. Nevertheless, ICV-STZ offers a platform to study the interplay of immune activation and cognitive dysfunction.

Disclosures: **R. Sankowski:** None. **C. D'Abramo:** None. **P.T. Huerta:** None. **Y. Al-Abed:** None.

Nanosymposium

655. New Insight into Neural Circuitry Controlling Inflammation

Location: N230

Time: Wednesday, October 21, 2015, 8:00 AM - 9:45 AM

Presentation Number: 655.07

Topic: E.02. Neuroimmunology

Support: NIH grant R01GM089807

Title: From selective cholinergic pharmacology to device-generated brain neuromodulation for controlling peripheral inflammation

Authors: ***V. A. PAVLOV**[1], H. A. SILVERMAN[1], M. DANCHO[1], A. REGNIER-GOLANOV[3], M. OCHANI[1], W. HANES[1], S. S. CHAVAN[1], E. GOLANOV[4], Y. AL-ABED[2], N. M. NATHANSON[5], V. F. PRADO[6,7], M. A. M. PRADO[6,7], K. J. TRACEY[1];
[1]Ctr. for Biomed. Sci., [2]Ctr. for Mol. Innovation, The Feinstein Inst. for Med. Res., Manhasset, NY; [3]Pediatrics-Neurology, Baylor Col. of Med., Houston, TX; [4]The Houston Methodist Res. Inst., Houston, TX; [5]Dept. of Pharmacol., Univ. of Washington, Seattle, WA; [6]Robarts Res. Inst., London, ON, Canada; [7]Dept. of Physiol. and Pharmacology, Dept. of Anat. & Cell Biol., The Univ. of Western Ontario, London, ON, Canada

Abstract: Brain muscarinic acetylcholine receptor (mAChR) signalling plays an important role in the neural control of peripheral cytokine release and inflammation via vagus nerve-based circuitry (Nat Rev Endocrinol, 2012, 8:743). This signalling can be activated by pharmacological treatments including M1 mAChR agonists and centrally-acting acetylcholinesterase inhibitors, including galantamine. However, the specific role of the M1 mAChR and brain cholinergic pathways in controlling peripheral cytokine responses is poorly understood. To provide insight we first administered benzyl quinolone carboxylic acid (BQCA) - a centrally-acting, highly selective positive allosteric modulator of the M1 mAChR to endotoxemic mice. Peripheral (i.p.) administration of BQCA significantly suppressed serum TNF (75%, $P<0.005$) and improved survival in endotoxemic mice. These effects were abolished in M1 mAChR knockout (KO) mice, indicating that the M1 mAChR is required for the regulation of the systemic TNF response. Administration of BQCA to mice exposed to cecal ligation and puncture-induced sepsis significantly increased survival (85.7% BQCA vs 50% vehicle controls, $P<0.05$). This protection exerted by BQCA was abolished in M1 mAChR KO mice. To assess the role of basal forebrain cholinergic pathways to brain regions, including the cortex and hippocampus where the M1

mAChR is predominantly located, we utilized cre-lox technology in mice and ablated the vesicular acetylcholine transporter - an important determinant of acetylcholine release in the basal forebrain cholinergic neurons. Administration of endotoxin to these selective KO mice resulted in higher serum TNF levels (2.9-fold, $P<0.05$) and lower serum IL-10 levels (57%, $P<0.05$), as compared to control mice. The suppression of serum TNF by peripheral (i.p.) administration of galantamine was abrogated in the KO endotoxemic mice. Furthermore, electrical stimulation of the medial septum, an important component of the basal forebrain cholinergic system significantly suppressed serum TNF (79%, $P<0.01$) and other pro-inflammatory cytokine levels as compared to sham stimulation during murine endotoxemia. Together these results indicate a previously unrecognized anti-inflammatory function of basal forebrain cholinergic signalling through M1 mAChRs. Together, they also suggest new therapeutic approaches, including device-generated brain neuromodulation in treating peripheral inflammation. This study was funded in part by NIH/NIGMS.

Disclosures: **V.A. Pavlov:** None. **H.A. Silverman:** None. **M. Dancho:** None. **A. Regnier-Golanov:** None. **M. Ochani:** None. **W. Hanes:** None. **S.S. Chavan:** None. **E. Golanov:** None. **Y. Al-Abed:** None. **N.M. Nathanson:** None. **V.F. Prado:** None. **M.A.M. Prado:** None. **K.J. Tracey:** None.

Nanosymposium

656. Human Brain Networks

Location: N228

Time: Wednesday, October 21, 2015, 8:00 AM - 10:15 AM

Presentation Number: 656.01

Topic: F.01. Human Cognition and Behavior

Support: NSF GSF DGE-1106400

Title: Dynamic modularity and integration during spontaneous neural activity

Authors: *M. A. BERTOLERO[1], B. T. T. YEO[2], D. J. LURIE[1], M. D'ESPOSITO[1];
[1]Univ. of California, Berkeley, Berkeley, CA; [2]Natl. Univ. of Singapore, Signapore, Singapore

Abstract: Graph theoretic analyses of spontaneous activity (fMRI, no cognitive task administered) suggest the brain's modular and integrative functional architecture--tightly interconnected brain regions form functionally autonomous modules; "provincial hubs" have many connections within a module and "connector hubs" integrate across the modules via diverse connections. We previously developed an ontology of cognitive functions ("cognitive components"), which are represented by their engagement in each task in the BrainMap database

and their probability of activity across the brain. Follow up analysis demonstrated a high spatial correlation between the component's spatial maps and graph theoretic modules, suggesting that each module executes a discrete cognitive function. Further, while many brain areas have a high probability of activation by only one component, some have high probabilities for many components. These "flexible" regions show high spatial correlation with connector hubs, but not provincial hubs. Crucially, we found that flexible areas and connector hubs exhibit increased activity in BrainMap tasks that engage more cognitive functions, as they must integrate information across more cognitive functions. Conversely, activity at areas dedicated to discrete cognitive functions (non-flexible areas, provincial hubs) is not effected by how many other cognitive functions are engaged, suggesting that cognitive functions operate autonomously. In this study, we analyzed 1500 individual's (Harvard GSP) spontaneous activity. We used the components' spatial maps to estimate the probability that each component was engaged at every time point of a 12 minute fMRI scan. We found that all components became engaged during spontaneous activity, and there was variability in which and how many components were engaged at each time point. This dynamic engagement and disengagement of cognitive functions allowed for an analysis in individual subjects of integration at flexible areas and any interactions between cognitive functions while cognitive functions dynamically engage and disengage. In line with our previous analyses, we found that activity at individuals' flexible areas is proportional to the number of cognitive functions engaged at each time point, suggesting that flexible areas constantly change their activity as integration demands change. Moreover, even on short time scales during individuals' spontaneous activity, the additional engagement of a cognitive function does not effect the activity of other engaged cognitive functions, which further supports the autonomous operation of cognitive functions.

Disclosures: **M.A. Bertolero:** None. **B.T.T. Yeo:** None. **D.J. Lurie:** None. **M. D'Esposito:** None.

Nanosymposium

656. Human Brain Networks

Location: N228

Time: Wednesday, October 21, 2015, 8:00 AM - 10:15 AM

Presentation Number: 656.02

Topic: F.01. Human Cognition and Behavior

Support: JS McDonnell Foundation

CIHR

TKF Foundation

Title: Structural topology lends stability to a dynamic functional landscape

Authors: K. SHEN[1], R. HUTCHISON[2], B. MISIC[3], M. BERMAN[4], S. EVERLING[5], *A. R. MCINTOSH[1];
[1]Baycrest Ctr., North York, ON, Canada; [2]Harvard Univ., Cambridge, MA; [3]Indiana Univ., Bloomington, IN; [4]Univ. of Chicago, Chicago, IL; [5]Univ. of Western Ontario, London, ON, Canada

Abstract: A growing number of resting-state fMRI studies have reported how functional connectivity (FC) varies significantly across timescales. Interestingly, a particular subset of connections, those between corresponding regions in opposite hemispheres (i.e., homotopic connections) are exceptionally stable over time despite the presence of dynamic FC across both intrahemispheric and other interhemispheric (i.e., heterotopic) connections. Conversely, regions that are topologically positioned to serve flexible and integrative roles across different functional subnetworks (i.e., hubs) are highly variable over time. The underlying structural connectivity is thought to constrain the range of interactions between different regions and may shape ongoing information processing. We explored the extent to which the brain's structural network influences 1) long-range interhemispheric coordination, and 2) rich club hub interactions by comparing FC obtained using BOLD-fMRI to structural connectivity derived from axonal tract tracing studies. First, homotopic FC was most stable across time and conditions and this stability was facilitated by direct anatomical projections. Importantly, temporal stability varied with the change in conductive properties of callosal axons along the anterior-posterior axis. These data suggest a notable role for the corpus callosum in maintaining stable functional communication between hemispheres. Second, FC within the structurally-defined rich club core exhibited the greatest stability over time, inconsistent with previous findings. We reconcile these inconsistencies by first replicating previous findings of high functional variability with high functional embedding. However, by taking into account the range of interactions within which each region could operate, we found that this normalized variability decreased with increasing functional embeddedness. These data suggest that, although hubs are flexible in function, they explore only a limited range of all possible configurations afforded by the available synaptic and polysynaptic pathways. Together, these findings suggest a notable role for structural topology in maintaining stable functional communication and they further elucidate how large-scale dynamic functional coordination exists within a fixed structural architecture.

Disclosures: K. Shen: None. **R. Hutchison:** None. **B. Misic:** None. **M. Berman:** None. **S. Everling:** None. **A.R. McIntosh:** None.

Nanosymposium

656. Human Brain Networks

Location: N228

Time: Wednesday, October 21, 2015, 8:00 AM - 10:15 AM

Presentation Number: 656.03

Topic: F.01. Human Cognition and Behavior

Support: K01MH099232

Title: Exploring the dynamic organization of the human brain at rest

Authors: *J. M. REINEN[1,2], B. YEO[3], R. HUTCHISON[4], J. T. BAKER[5], J. L. ROFFMAN[6], J. W. SMOLLER[6], A. J. HOLMES[2];
[1]Psychology, Columbia Univ., New York, NY; [2]Psychology, Yale Univ., New Haven, CT; [3]Natl. Univ. of Singapore, Singapore, Singapore; [4]Harvard Univ., Cambridge, MA; [5]McLean Hosp., Boston, MA; [6]Massachusetts Gen. Hosp., Boston, MA

Abstract: Traditional static descriptions of network coupling have provided foundational discoveries, characterizing core aspects of brain function. However, recent work has demonstrated dynamic fluctuations in network coupling. Relations linking brain and behavior will benefit from the characterization of dynamically unfolding network configurations. Here we explore the dynamic organization of large-scale cortical networks in healthy young adults using resting-state functional connectivity MRI (fcMRI; n=2,007). We used an established cortical functional parcellation method that decomposes the brain into 17 distinct networks (Yeo et al., 2011). Dynamic functional connectivity was then computed through sliding window analyses. K-means clustering was used to characterize discrete functional connectivity states (Liu et al., 2013; Allen et al., 2014). The stability and spatial properties of the resulting dynamic network solutions were explored in relation to varying sliding window sizes, standard quality control metrics, and sample size. Reliability was assessed in a subset of test-retest participants (n=87). The network architecture of these states and associated implications for cognition and behavior will be discussed, as well as technical artifacts that may provide the illusion of network changes (e.g., non-neuronal physiological variation, head motion).

Disclosures: J.M. Reinen: None. **B. Yeo:** None. **R. Hutchison:** None. **J.T. Baker:** None. **J.L. Roffman:** None. **J.W. Smoller:** None. **A.J. Holmes:** None.

Nanosymposium

656. Human Brain Networks

Location: N228

Time: Wednesday, October 21, 2015, 8:00 AM - 10:15 AM

Presentation Number: 656.04

Topic: F.01. Human Cognition and Behavior

Support: VENI Grant (#451-12-001) Netherlands Organization for Scientific Research (NWO)

Fellowship of the Brain Center Rudolf Magnus

Fulbright Grant

Title: Neural hubs leading the dance: a Kuramoto model simulation of dynamic synchrony in the human connectome

Authors: *R. SCHMIDT, K. J. R. LAFLEUR, M. A. DE REUS, L. H. VAN DEN BERG, M. P. VAN DEN HEUVEL;
Brain Ctr. Rudolf Magnus, UMC Utrecht, Utrecht, Netherlands

Abstract: The topological organization of the wiring of the human brain cortex plays an important role in shaping the functional dynamics of large-scale neural activity. Due to their central embedding in the network, high degree hub regions and their connections (an ensemble often referred to as the 'rich club') have been hypothesized to facilitate intermodular neural communication and global integration of information by means of synchronization. Here, we examined the role of neural hubs and their wiring in theoretical brain dynamics. The Kuramoto model was used to simulate the interaction and synchronization between cortical brain areas by modeling brain regions as phase oscillators that are coupled according to the healthy connectome encompassing all macroscale white matter pathways interconnecting cortical areas. An average connectome map was reconstructed on the basis of T1- and diffusion weighted images of 40 healthy subjects. In order to distinguish between intra- and intermodular synchrony patterns, brain regions were assigned a functional module based on empirically determined resting-state functional MRI data. Our simulations show distinct synchronization patterns for hub regions, with synchrony among hub regions higher than any module's intramodular synchrony ($p < 10\text{-}4$), suggesting that hub regions lead the functional modules in the process of synchronization. Furthermore, computing the region-wise impact on oscillatory behavior of the modules, hub regions were observed to gain the most influence ($p < 0.04$) in the onset of global synchrony. Directly targeting the hub regions by suppressing the coupling among hub regions resulted in an elevated modular state ($p < 0.003$) indicating that hub-to-hub connections are critical in intermodular synchronization. Targeting the hub regions again, now leaving the coupling intact but perturbing their intrinsic oscillatory behavior, prevented functional modules from synchronizing. Taken together, our results converge on anatomical hubs having a leading role in intermodular synchronization and integration in the human brain.

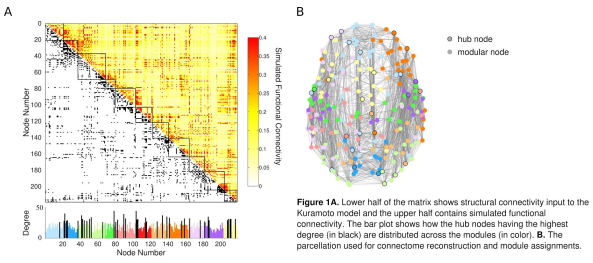


Figure 1A. Lower half of the matrix shows structural connectivity input to the Kuramoto model and the upper half contains simulated functional connectivity. The bar plot shows how the hub nodes having the highest degree (in black) are distributed across the modules (in color). **B.** The parcellation used for connectome reconstruction and module assignments.

Disclosures: R. Schmidt: None. **K.J.R. LaFleur:** None. **M.A. de Reus:** None. **L.H. van den Berg:** F. Consulting Fees (e.g., advisory boards); travel grants and consultancy fees from Baxter; on scientific advisory boards for Prinses Beatrix Spierfonds, Thierry Latran Foundation, Cytokinetics and Biogen Idec.. **M.P. van den Heuvel:** None.

Nanosymposium

656. Human Brain Networks

Location: N228

Time: Wednesday, October 21, 2015, 8:00 AM - 10:15 AM

Presentation Number: 656.05

Topic: F.01. Human Cognition and Behavior

Title: Functional brain modules reconfigure at multiple scales across the human lifespan

Authors: *R. F. BETZEL[1], B. MISIC[1], Y. HE[2,3], J. RUMSCHLAG[1], X.-N. ZUO[2], O. SPORNS[1,4];
[1]Psychological and Brain Sci., Indiana Univ., Bloomington, IN; [2]Univ. of Chinese Acad. of Sci., Beijing, China; [3]Key Lab. of Behavioral Sci. and Magnetic Resonance Imaging Res. Center, Inst. of Psychology, Beijing, China; [4]Indiana Univ. Network Sci. Inst., Bloomington, IN

Abstract: The human cerebral cortex can be represented as a complex network of cortical regions that interact with one another over time and space. Here we uncover the community structure of functional brain networks across multiple scales and track the formation, evolution, and dissolution of communities across the human lifespan. We find that the community structure of the cerebral cortex exhibits scale-specific changes as a function of age. Communities detected at coarse scales become progressively more segregated with age, while the segregation of communities detected at finer scales decreases. The composition of communities also exhibits scale-specific age-dependent changes. At coarse scales, regions associated with executive control, default mode, attention, and visual networks change their community assignments early in life. At fine scales the most changes involve regions associated with the default mode network in younger brains moving into new communities in older brains. We show that, with age, regions

in the default mode network, specifically the retrosplenial cortex, maintain an increasing proportion of functional connections to their own community across scales, while regions associated with the somatomotor and saliency/ventral attention networks distribute their links more evenly across communities.

Disclosures: **R.F. Betzel:** None. **B. Misic:** None. **Y. He:** None. **J. Rumschlag:** None. **X. Zuo:** None. **O. Sporns:** None.

Nanosymposium

656. Human Brain Networks

Location: N228

Time: Wednesday, October 21, 2015, 8:00 AM - 10:15 AM

Presentation Number: 656.06

Topic: F.01. Human Cognition and Behavior

Support: McDonnell Foundation Collaborative Activity Award (SEP)

NIH R01NS046424 (SEP)

NIH T32NS007205-33 (CG)

NIH F32S092290-01 (CG)

Title: Properties that contribute to functional connectivity differences between task and rest

Authors: ***C. GRATTON**, T. O. LAUMANN, E. M. GORDON, B. ADEYEMO, S. E. PETERSEN;
Washington Univ. in St Louis, Saint Louis, MO

Abstract: Past studies suggest that similar large-scale brain networks are present in humans during rest and various task states. However, reliable task-rest differences are present for subsets of network connections. Here, we examine which properties drive connection differences between rest and task. Specifically, we examined whether differences occur primarily at (a) regions that are activated by a given task, or (b) regions that interconnect different networks (connector hubs), as suggested by models of communication in complex systems. We examine this question by measuring fMRI functional connectivity (FC) in 29 healthy adult subjects during rest and during 3 tasks with widely varying demands: a semantic task, a mental rotation task, and a coherence task. FC was measured as correlations among 264 cortical and subcortical regions of interest. A mixed-block/event-related finite impulse response model was used to estimate evoked activations in each task. Importantly, these modeled activations were removed from the task time

series in order to avoid biasing subsequent task FC measurements. The connector hub status of regions was estimated with the participation coefficient metric (PC; a measure of the distribution of connections across networks). As in past work, we found that FC was largely similar between task and rest states. However, small-magnitude differences were present both within- and between- networks, and were consistent across subjects and tasks, despite differing task demands. Critically, both highly activated and high PC regions modified their FC (especially between-networks) more than regions that showed low activation or PC. Across tasks, highly activated connector hub regions were consistently localized to known control systems. Despite their common properties, hierarchical clustering found that subsets of these regions demonstrated distinct patterns of change in FC. Specifically, we identified 3 clusters: (1) a dorsal attention cluster, (2) a cinguloopercular/salience cluster, and (3) an anterior insula and dorsolateral prefrontal cortex cluster. These clusters showed increased FC both to other control networks and to relevant processing regions, and decreased FC to the default mode network. This evidence suggests that both the function of a region and its network role determine whether FC will change in a task context, suggesting mechanisms by which relevant control and processing networks may interact. This research may shed light on how networks flexibly reorganize in the service of high-level goals.

Disclosures: **C. Gratton:** None. **T.O. Laumann:** None. **E.M. Gordon:** None. **B. Adeyemo:** None. **S.E. Petersen:** None.

Nanosymposium

656. Human Brain Networks

Location: N228

Time: Wednesday, October 21, 2015, 8:00 AM - 10:15 AM

Presentation Number: 656.07

Topic: F.01. Human Cognition and Behavior

Support: NSF GRFP

NIMH BRAINS R01MH094639-01

Title: Functional diversity and specialization of brain areas associated with behavioral, social, and emotional dysfunction

Authors: ***D. J. LURIE**[1], Z. SHEHZAD[4], M. A. BERTOLERO[1], B. T. T. YEO[5,6], M. D'ESPOSITO[1,2,3], M. P. MILHAM[7,8];
[1]Psychology, [2]Helen Wills Neurosci. Inst., [3]Henry H. Wheeler Jr. Brain Imaging Ctr., Univ. of California, Berkeley, Berkeley, CA; [4]Psychology, Yale Univ., New Haven, CT; [5]Electrical and

Computer Engin., [6]Clin. Imaging Res. Ctr. and Singapore Inst. for Neurotechnology, Natl. Univ. of Singapore, Singapore, Singapore; [7]Ctr. for the Developing Brain, Child Mind Inst., New York, NY; [8]Ctr. for Advanced Brain Imaging, Nathan S. Kline Inst. for Psychiatric Res., Orangeburg, NY

Abstract: Human experience is complex and multidimensional, and there are many different domains of functioning and well-being in which a person can experience impairment or distress. These problems often co-occur, forming symptom clusters which have traditionally been characterized using binary diagnoses. Efforts to understand the biological basis of psychopathology have shown some success, but are limited by the application of these hard categories to continuous phenomena. Here, we used a fully data-driven exploratory analysis to identify brain regions associated with continuous variation in symptom severity across multiple domains of social, emotional, and behavioral functioning. We then used a novel probabilistic reverse inference analysis to estimate their involvement in different cognitive processes. From a large community sample, we analyzed data from 261 subjects ages 18-59. Subjects completed a 10 minute "resting" fMRI scan and the Adult Self Report (ASR; Achenbach and Rescorla, 2003), a standardized clinical assessment of behavioral, emotional, and social problems which. From raw ASR item scores, we calculated scores for 10 empirically derived syndrome scales, each of which characterizes the severity of a particular set of frequently co-occurring symptoms. For each of the ASR syndrome scales, we used Multivariate Distance Matrix Regression (MDMR; Shehzad et al. 2014) to identify brain areas whose whole-brain functional connectivity differed as a function of symptom severity. Significant connectivity differences were observed for 7 of the 10 ASR syndrome scales, and these differences occurred in a diverse set of cortical, subcortical, and cerebellar regions. Following work by Yeo and colleagues (Yeo et al., in press), we estimated for each of the MDMR syndrome scale maps the probability of engagement by 12 "cognitive components" derived from Bayesian modeling of task information and activation foci from the BrainMap meta-analysis database. Despite their distinctive symptomatology and spatial distribution of MDMR results, all syndrome scales showed high probability of engagement by cognitive components associated with theory of mind, emotional processing, and declarative memory. These exploratory results suggest that despite differences in the specific brain areas identified through exploratory analysis, distinct patterns of behavioral dysfunction may be due to impairment in a common set of cognitive mechanisms, though follow-up studies are needed to confirm this result. This underscores the importance of considering cognition as it relates to activity and connectivity across the entire brain.

Disclosures: D.J. Lurie: None. **Z. Shehzad:** None. **M.A. Bertolero:** None. **B.T.T. Yeo:** None. **M. D'Esposito:** None. **M.P. Milham:** None.

Nanosymposium

656. Human Brain Networks

Location: N228

Time: Wednesday, October 21, 2015, 8:00 AM - 10:15 AM

Presentation Number: 656.08

Topic: F.01. Human Cognition and Behavior

Support: NUS Tier 1 Grant

SINAPSE seed funding

MOE Tier 2 Grant

NUS Strategic Research Grant

NIH/NIMH R01 MH074457

NIH P41EB015896

NIH 1S10RR023401

Title: Reverse inference revisited

Authors: *B. YEO[1], F. M. KRIENEN[2], S. B. EICKHOFF[3], P. T. FOX[4], M. D'ESPOSITO[5], M. A. BERTOLERO[5];
[1]Electrical and Computer Engin., Natl. Univ. of Singapore, Singapore, Singapore; [2]George Washington Univ., Washington, DC; [3]Inst. for Clin. Neurosci. and Med. Psychology, Heinrich-Heine Univ. Düsseldorf, Düsseldorf, Germany; [4]Res. Imaging Inst., Univ. of Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX; [5]Helen Wills Neurosci. Inst. and Dept. of Psychology, Univ. of California Berkeley, Berkeley, CA

Abstract: In a seminal 2006 article, Russ Poldrack outlined the limitations of reverse inference - the practice of inferring a cognitive function to be engaged based on observing an activated brain region previously evoked by tasks thought to probe that cognitive function. This inference is deductively valid only if the brain region is involved in only that cognitive function, and the task (contrast) engaged only that cognitive function. However, behavioral tasks engage common and distinct cognitive functions, which are in turn supported by multiple, possibly overlapping, brain regions (Walton and Paul, 1901; Mesulam 1990; Poldrack 2006). We recently instantiated a mathematical model that encoded this intuitive notion, allowing us to estimate a nested cognitive ontology based on the BrainMap database (Yeo et al., in press). The ontology consists of a collection of cognitive components, the probability that a task would recruit a component and the probability a component would activate a voxel. Here we consider how our mathematical framework and resulting ontology provide conceptual and computational advances over the original reverse inference framework, some of which are motivated by prescient arguments in the

original paper (Poldrack 2006). First, we argue that the original Bayesian framework (Poldrack 2006; Poldrack et al., 2011; Yarkoni et al., 2011) can produce inflated estimates of reverse inference probabilities due to each cognitive function being considered independently. Instead, we advocate a simple variation of Bayes' rule that considers all cognitive functions simultaneously. Second, complex behavior arises from interacting brain networks (Poldrack et al., 2006; Mesulam 1990). Therefore the original Bayesian framework might suffer lower sensitivity and specificity from considering each voxel/region independently (Poldrack 2006; Yarkoni et al., 2011). In contrast, our mathematical framework (Yeo et al., in press) explicitly models how interactions between cognitive functions give rise to brain activation. Therefore performing reverse inference for single voxels, single networks or even the entire brain is mathematically identical within our framework. Finally, we argue that the primary goal of cognitive neuroscience should be how the brain functions rather than where cognitive functions are localized. Indeed, given our mathematical model of how cognitive functions interact to give rise to observable data (e.g., brain activation), reverse inference is relatively straightforward. Conversely, reverse inference is (mathematically) ill-posed without a model of how cognitive functions interact to give rise to brain activation.

Disclosures: **B. Yeo:** None. **F.M. Krienen:** None. **S.B. Eickhoff:** None. **P.T. Fox:** None. **M. D'Esposito:** None. **M.A. Bertolero:** None.

Nanosymposium

656. Human Brain Networks

Location: N228

Time: Wednesday, October 21, 2015, 8:00 AM - 10:15 AM

Presentation Number: 656.09

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant K99MH102349

NIH Grant MH085328

NIH Grant MH078160

Kennedy Krieger Institute F. M. Kirby Research Center Grant EB015909

Title: Large-scale neural reconfiguration during response control in ADHD

Authors: *J. R. COHEN[1,2], A. D. BARBER[1,2], M. A. LINDQUIST[3], S. H. MOSTOFSKY[1,2]; [1]Kennedy Krieger Inst., Baltimore, MD; [2]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Johns Hopkins Bloomberg Sch. of Publ. Hlth., Baltimore, MD

Abstract: ADHD is theorized to result from dysfunctional connectivity patterns within and between brain networks. Extant literature focuses mainly on task-related connectivity of specific networks or pairs of brain regions, or on whole-brain connectivity during a resting state. This study's goal was to expand existing research by probing large-scale dynamics of functional network organization during response control and working memory (WM), two core cognitive deficits in ADHD. Whole-brain network reconfiguration was compared in children with ADHD and typically developing (TD) children. During an fMRI scan, participants were administered two Go/No-Go (GNG) tasks assessing response control: simple GNG (sGNG), which probed well-ingrained stimulus-response associations (Go stimuli were green; No-Go stimuli were red), and WM GNG (wmGNG), which varied stimulus-response associations so as to require WM to guide response selection. We applied graph theoretical tools to functional connectivity data to determine how network organization flexibly reconfigured across tasks. We quantified modularity (how much the brain separates into distinct networks, or modules); mutual information (the similarity of modular composition across two graphs); and participation coefficient (how integrated a brain region, or node, is with networks other than its own). As expected, across groups behavioral performance was worse during the more demanding wmGNG than sGNG. During sGNG, modularity was lower in children with ADHD than in TD children. During wmGNG, modularity was not different across groups. Previous work has shown that modularity decreases during cognitive control to allow for greater communication across networks. Thus, successful performance during sGNG may have required greater effort in children with ADHD, as reflected in increased global coordination. In support of that hypothesis, children with ADHD with lower mutual information, or more changes in network organization, between sGNG and wmGNG (similar to TD children) performed better on both tasks. Last, we found that the participation coefficient of key default mode network (DMN) nodes was higher in children with ADHD than in TD children during both tasks. This increased DMN inter-network communication is thought to contribute to attention lapses that may underlie poor response control in ADHD. These findings suggest that dysfunctional network dynamics during cognitive control, especially regarding network integration, may contribute to cognitive control impairments observed in ADHD. Future analyses will probe differences in network organization during successful and failed response control in ADHD.

Disclosures: J.R. Cohen: None. **A.D. Barber:** None. **M.A. Lindquist:** None. **S.H. Mostofsky:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.01

Topic: F.02. Animal Cognition and Behavior

Support: ISF Grant 225/11

MOST Grant 3-10373

EU Grant PCIG9-GA-2011-294001

Title: Intrinsic functional connectivity MRI of the hippocampal memory system in mice reveals coupling of sensory and association networks

Authors: *E. BERGMANN, G. ZUR, G. BERSHADSKY, A. KAVUSHANSKY, I. KAHN; The Ruth and Bruce Rappaport Fac. of Medicine, Dept. of Neurosci., Technion – Israel Inst. of Technol., Haifa, Israel

Abstract: While the hippocampal memory system has been relatively conserved across mammals, the cerebral cortex underwent radical changes. A central question in brain evolution is how the cortical development affected the nature of cortical inputs to the conserved hippocampus in primates relative to lower mammals. To address this question, we used high-resolution intrinsic functional connectivity MRI (fcMRI) in awake head-fixed mice as well as tract-tracing available from the Allen brain mouse connectivity atlas, examining cortico-hippocampal connectivity in the mouse brain as compared to human and non-human primates. Seed-based analysis showed that primary sensory areas of different modalities (auditory, somatosensory and visual) map to specific sub-regions of the parahippocampal region including the perirhinal and postrhinal cortices, revealing close agreement to anatomical connectivity. Further examination of the connectivity between the rhinal cortices and hippocampal subfields confirmed the known differential connectivity along the hippocampal longitudinal axis with the perirhinal and postrhinal cortices preferentially targeting the ventral and dorsal aspects, respectively. Finally, analysis of the connectivity of primary sensory areas with the hippocampus revealed functional coupling of the hippocampus to primary sensory regions expressed as a spatially localized topographic organization with limited overlap between sensory modalities. Taking into account the extensive representation of sensory networks relative to association networks in the mouse cortex, and the correlation patterns between primary sensory cortices and the hippocampal formation observed in the mouse but not in human and non-human primates, we propose that the cortico-hippocampal network in rodents represents a single hierarchy. The rodent hippocampus operates on inputs that are closely associated to the physical features of the external stimulus, rather than abstract information that emerges after several stages of processing. This qualitative difference indicates that in the primate brain non-canonical hierarchies emerged between canonical sensory hierarchies and the hippocampal memory system. Namely, cortical expansion and the emergence of new association areas in primates resulted in the fractionation, as observed

with fcMRI, of the primary and secondary sensory areas and the hippocampal memory system in the primate brain.

Disclosures: E. Bergmann: None. **G. Zur:** None. **G. Bershadsky:** None. **A. Kavushansky:** None. **I. Kahn:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.02

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant DA037255

NIH Grant AA020381

Title: A subtractive approach to learning: assessing activity in the hippocampus during acquisition versus performance

Authors: *T. G. WEYAND[1], M. KETCHUM[2], P. WINSAUER[2];
[2]Pharmacol. & Exptl. Therapeut., [1]LSU-Med Ctr., New Orleans, LA

Abstract: We compared neural activity in the CA1 region of the hippocampus during repeated acquisition and performance of response sequences. In this procedure, rats nose-poked response keys for food pellets. In one component ('performance'), the sequence was the same each session. In the other component ('acquisition'), the correct sequence changed each day. We concentrated on analyzing peri-response activity (+/- 0.8 sec preceding and following the poke), our hypothesis being that such activity would be different during initial acquisition than during execution of a well-known sequence. Because the responses were always the same (poking a key), differences in CA1 activity associated with acquisition versus performance components could potentially provide signatures of learning. Our initial results indicate most of the CA1 sites were modulated by the task, and for several sites, activity immediately preceding the response was clearly modulated by response key (left, center, right), or sequence order (e.g. 1^{st}, 2^{nd}, 8^{th}). The most significant change that we associate with learning was that CA1 activity immediately preceding the initial correct responses in acquisition were highly variable relative to activity preceding responses later in acquisition or in performance. During the 1^{st} ~60-90 correct responses in acquisition, activity shifted to conform to a response profile specific to that key. This profile basically matched in amplitude, direction (peak or trough) and timing (of peak or

trough). Once the sequence was acquired, the activity profile was indistinguishable from that which we observed in the performance blocks. We interpret this change in activity during acquisition from high variability to conformity to be associated with learning. We know the changes are unlikely related to kinematics because all key presses are basically the same, yet pressing at one key was preceded by an activity peak, whereas at that same CA1 site, pressing a different key was preceded by an activity trough. Our results are consistent with the idea that this hippocampal activity is encoding information regarding the sequencing of behavior; i.e., which key is pressed, and when. We are currently quantifying the predictive value of signals observed in initial acquisition in specifying error, key and order; and the degree to which correlations across sites can enhance prediction. (Supported by NIH: R01 DA037255 and F30-AA020381).

Disclosures: T.G. Weyand: None. **M. Ketchum:** None. **P. Winsauer:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.03

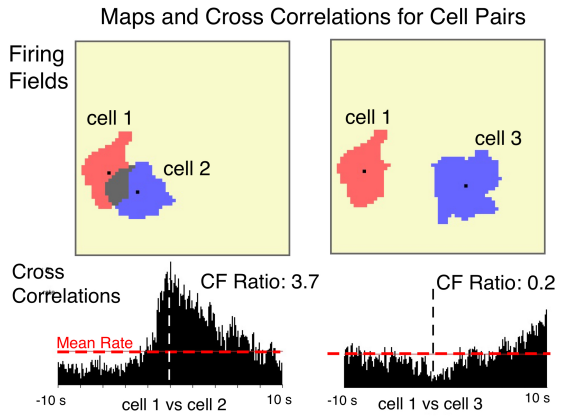
Topic: F.02. Animal Cognition and Behavior

Title: Mapping time onto space: spatial and temporal interactions among hippocampal place cells

Authors: *J. L. KUBIE[1], E. PASTALKOVA[2];
[1]Cell Biol., SUNY Downstate Med. Ctr., Brooklyn, NY; [2]Janelia Res. Campus, HHMI, Ashburn, VA

Abstract: Information processing between neurons is based on timing; as a result neuronal representations are based on time codes. It is not surprising that when temporal analysis is performed on hippocampal place cells, pairs with overlapping firing fields have correlated firing while pairs of with disjoint fields are anti-correlated. This has been shown on select cell pairs in several studies and is illustrated in the figure. We asked whether an analysis on a large dataset of place cells would yield clues about the time-to-space transform. An initial analysis was performed on a set of 33 single-field CA1 place cells recorded for one hour while the rat traversed an open field. Cross correlations between all place cell pairs (528) yielded interesting patterns. “Co-firing ratio” is the value at bin 0 divided by mean firing rate. This ratio sorts the data in useful ways. Values greater than 1.0 are above expectation. The median ratio for all pairs is low, 0.50. Only 24% have ratios above 1.0. Few pairs (3%) have ratios above 5.0. Temporal cross correlations match well with spatial patterns. Field overlap is number of pixels common to

the two fields divided by total field pixels. Cell pairs whose fields that do not overlap have ratios below 0.5. Pairs with fields that overlap at an edge have ratios about 1. Cell pairs whose field centroids are within the bounds of the second field have ratios of 5.0 or higher. There are rare exceptions to these patterns. The correlation between co-firing ratio and field overlap is 0.74. Correlation between co-firing ratio and distance between field centers is -0.48. These values are reliable for bins as narrow as 25 msecs, the estimated time range synaptic plasticity, suggesting mechanisms for stabilizing a hippocampal map. Future work will explore other features of the time-to-space transform. These include changes with remapping, using time-slice firing vectors to estimate location, and creating 2d maps from spike-time data. In brief, large-scale analysis of neuronal timing relationships holds promise for insights into the time-to-space transform in the hippocampus.



Disclosures: **J.L. Kubie:** None. **E. Pastalkova:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.04

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant NS078434

Title: Cell-type specific septal innervation of hippocampal formation

Authors: ***J. A. DELA CRUZ**, X. XU;
Anat. and Neurobio., Univ. of California, Irvine, Irvine, CA

Abstract: The circuit function and network activity of hippocampal formation is known to be significantly regulated by long-range inputs from the medial septum and the diagonal band of Broca complex (MS). Due to previous technical limitations, there is a lack of detailed understanding of cell type specific MS innervation of hippocampal formation. In this study, we used new advances in virology and genetic technology to map specific MS projections to hippocampal subregions. We examine the presence of diverse MS neuron types (excitatory vs. inhibitory) which may differentially innervate distinct hippocampal subregions. Cre-selective, preferentially anterograde adenoassociated virus (AAV) and herpes simplex virus (HSV, H129 strain) was applied in the MS of specific Cre mouse lines (ChAT-cre, GAD-cre and VGluT2-cre) to target cholinergic, GABAergic and glutamatergic projections. GFP-expressing, AAV-mediated axonal labeling from MS generally overlapped with tdTomato-expressing postsynaptic neuronal labeling by H129 in hippocampal regions, which supports the complementary and confirmatory nature of these two different viral tracing. Consistent with previous studies, septohippocampal cholinergic axons ramified extensively across hippocampal laminae, and there was heavy excitatory neuronal labeling by H129 in CA3 and the dentate gyrus. In comparison, GABAergic and glutamatergic septohippocampal projections were much less intense, with viral labeling mostly concentrated in the hippocampal oriens layer. While there was no clear difference of MS cholinergic innervation for the dorsal and ventral hippocampus, GABAergic and glutamatergic innervations were preferential in ventral hippocampus. All the three specific septohippocampal projections innervated deep layers of entorhinal cortex to a relatively weak degree. Together, this preliminary investigation indicates that AAV and H129 can be effectively used for mapping cell type specific septohippocampal circuit organization. Our ongoing study will provide new and important information on cell-type specific septohippocampal network interaction and will further our understanding of septal modulation of excitatory and inhibitory hippocampal neuronal function.

Disclosures: **J.A. Dela Cruz:** None. **X. Xu:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.05

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant NS078434

Title: Circuit connection mapping of the subicular neurons projecting to hippocampal CA1

Authors: *Y. SUN, X. XU;
Anat. & Neurobio., Univ. of California, Irvine, Irvine, CA

Abstract: Hippocampal circuit connections are generally believed to transfer information unidirectionally, such that the neurons in CA1 project to the subiculum which in turn projects to medial entorhinal cortex. However, our new viral mapping study has established non-canonical, backward subicular projections to hippocampal CA1, indicating that the subiculum does not act simply as a unidirectional relay for hippocampal output (Sun et al., 2014). This is supported by recent physiological studies showing that subicular network oscillations flow backward to actively modulate spike timing and local network activity in CA1 (Jackson et al., 2014, Craig and McBain, 2015). To further understand the Sub → CA1 pathway, we aim to investigate whether this projection shows a topographic relationship as seen in the CA1→ Sub projection, and examine whether CA1-projecting subicular neurons are a unique neuronal group that has distinct circuit connections. Subicular cells retrogradely labeled from the rabies tracing targeting excitatory pyramidal neurons in proximal versus distal CA1 *in vivo* were examined. We found that distal CA1 received much stronger subicular connections than proximal CA1 as determined by the measurement of the relative abundance of connected populations. The connection indices increased from 0.17 ± 0.06 to 1.15 ± 0.29 (N = 3) with targeting locations shifting from proximal to distal CA1. This indicates the subicular backward projections can have stronger influence on distal CA1 function. To target CA1-projecting subicular neurons for rabies tracing, we used canine adenovirus 2 (CAV2)-mediated retrograde Cre expression in these subicular neurons. The CAV2-Cre was injected into hippocampal CA1 to label the subicular neurons of interest. Cre-dependent rabies tracing was then applied to map their local and global circuit connections. We found that the CA1-projecting subicular neurons received strong inputs from hippocampal CA1. They were innervated by CA1 excitatory pyramidal neurons, and a considerable number of inhibitory interneurons. The subicular neurons also received some inputs from the neocortex such as visual cortex and auditory cortex, but little input from the entorhinal cortex and the medial septum. Thus, these non-canonical subicular neurons receive both excitatory and inhibitory inputs from CA1, and in turn they provide feedback regulation of CA1 activity. Our circuit mapping research supports a bidirectional functional interaction between the subiculum and intrahippocampal networks.

Disclosures: Y. Sun: None. **X. Xu:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.06

Topic: F.02. Animal Cognition and Behavior

Support: NIA RO1AG043688

Title: Is dentate gyrus pattern separation necessary for cognitive discrimination?

Authors: *M. T. VAN DIJK[1,2], A. A. FENTON[2,3];
[1]The Sackler Inst. of Grad. Biomed. Sci., New York Univ. Sch. of Med., New York, NY; [2]Ctr. for Neural Sci., New York Univ., New York, NY; [3]Robert F. Furchgott Ctr. for Neural and Behavioral Science, Dpt. of Physiol. and Pharmacol., SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: The dentate gyrus is crucial for distinguishing similar memories and events. Such cognitive discrimination is thought to rely on pattern separation, a computation that amplifies differences between similar situations. In foraging rats, dentate granule cell (DGC) place fields globally remap following small changes in environment shape; as such, low measures of firing rate map correlations have been taken as evidence of pattern separation. However, no direct evidence exists that this pattern separation underlies cognitive discrimination as demonstrated by subjects' awareness of the environmental changes. To learn whether pattern separation is necessary for cognitive discrimination, we recorded DGCs from mice under different conditions. First, neural pattern separation was assessed by making small changes to a familiar environment in a foraging task. Remapping of neuronal place fields occurred less when mice foraged in identical environments than in 'similar' environments in which visual cues were rotated. To assess whether this remapping underlies cognitive discrimination behavior we simultaneously assayed the neural and behavioral expressions of pattern separation. Cognitive discrimination was evaluated in an active place avoidance (APA) task in which mice learned to avoid a shock zone on a rotating arena. After two 30-min learning trials the shock zone location moved 180° for the conflict trial and mice quickly showed cognitive discrimination of the two shock locations. Most place fields did not remap; place field map correlations across APA trials were similar to correlations in identical environments, and significantly higher than correlations across foraging trials in cue rotated or physically distinct environments. Nonetheless, other measures of pattern separation were associated with cognitive discrimination. Rate remapping was significant between the prelearning and learning sessions. DGC firing rates increased during the first shock trial, returned to the prelearning rates in subsequent training trials, and decreased to below prelearning levels when the shock was subsequently turned off. Furthermore the overall similarity of 10 sec ensemble activity vectors was significantly higher within the prelearning trial than between the prelearning trial and conflict trial, when cognitive discrimination was explicit. These data suggest that DGC remapping does not underlie cognitive discrimination. Rather, rate remapping and changes in the temporal organization of ensemble activity better correlate with

the simultaneously observed ability to correctly distinguish between relevant situational changes in the same environment.

Disclosures: **M.T. Van Dijk:** None. **A.A. Fenton:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.07

Topic: F.02. Animal Cognition and Behavior

Support: NIMH Z01-MH-002498-24

Title: A distinct population of paraventricular nucleus vasopressin neurons excite the hippocampal CA2 area to promote social memory

Authors: ***A. S. SMITH**, S. K. WILLIAMS AVRAM, J. SONG, W. S. YOUNG;
Section on Neural Gene Expression, LCMR, Natl. Inst. of Mental Health, NIH, Bethesda, MD

Abstract: Peptide action in the brain propagates social living by influencing complex social behaviors. Vasopressin (Avp) is a neuropeptide that regulates a wide range of social behaviors from pair bonding to aggression. Two subtypes of Avp receptors are expressed in the brain (Avpr1a and Avpr1b); however, we are only beginning to learn about the role of Avpr1b in regulating social behavior. Previously, we noted Avpr1b is prominently expressed in the CA2 region of the hippocampus, afferent fibers from AVP-expressing neurons in the paraventricular nucleus of the hypothalamus (PVN) innervate this region, and unconditional deletion of the Avpr1b gene impairs social memory. Thus, it is reasonable to postulate that the $Avp^{PVN \rightarrow CA2}$ pathway may be involved in processing social memory. To test this, we virally targeted expression of the light-sensitive receptor channelrhodopsin-2 to Cre recombinase-expressing AVP neurons in the PVN of transgenic mice and assessed social memory in these mice. Social memory in mice is defined as a decrease in spontaneous investigation behaviors observed in a mouse reexposed to a conspecific, and memory from a brief encounter (5 minutes) does not extend beyond 1 h in mice. Thus, we exposed our transgenic mice to a conspecific over two 5-minute trials, optically stimulating only the AVP fibers within the CA2, and measured the amount of investigation behavior. Excitation of the $Avp^{PVN \rightarrow CA2}$ pathway dramatically prolonged social memory in mice from 30 minutes to at least 7 days. In addition, we observed a marked increase in neuronal activity in the PVN and CA2, as measured by enhanced immediate-early gene expression. No changes were observed in sociability or object memory. Interestingly, social

memory was only improved when the $Avp^{PVN \rightarrow CA2}$ pathway was optically stimulated during memory acquisition, not retrieval. Memory enhancement was lost by pharmacological antagonism of Avpr1b in the CA2 during the optical stimulation, confirming receptor-specific function of this pathway. Together, our data demonstrate that the strength or salience of social memories is enhanced by selectively targeting the excitation of the $Avp^{PVN \rightarrow CA2}$ pathway. The hippocampus is essential for encoding declarative memory; however, the CA2 region, which is selectively enriched with Avpr1b expression, has largely been ignored since it was first described over 80 years ago. Our work provides new knowledge about how the CA2 is integrated into a circuit regulating such memories.

Disclosures: **A.S. Smith:** None. **S.K. Williams Avram:** None. **J. Song:** None. **W.S. Young:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.08

Topic: F.02. Animal Cognition and Behavior

Support: NSF 1422438

Houston Bioinformatics Endowment

Title: Through synapses to spatial memory maps: a topological model

Authors: ***Y. A. DABAGHIAN**[1], A. BABICHEV[2], S. CHOWDHURY[3], F. MEMOLI[3]; [1]Neurol. and pediatrics, Jan and Dan Duncan Neurolog. Res. Institute, Baylor Col. of Med., Houston, TX; [2]Computat. and Applied Mathematics, Baylor Col. of Medicine, Rice Univ., Houston, TX; [3]Mathematics, Ohio State Univ., Columbus, OH

Abstract: It is widely accepted that the network of the hippocampal place cells provides a substrate of the "cognitive map" of the environment, although the mechanisms producing this map remain vague. Our approach to modeling hippocampal network's function is based on the hypothesis that spatial representations produced by place cell ensembles are fundamentally topological, i.e., more similar to a subway map than to a topographical city map, and hence are amenable to analysis by topological methods. Using Homology Theory based analyses, we have previously demonstrated that the information provided by the place cell spiking activity is sufficient to encode the topological features of the space in a biologically plausible timeframe.

However, in reality, the spike trains are not “analyzed” but processed through a complex network of unreliable and transient synaptic connections. Using the topological model of the hippocampal network, we studied how dynamic connections between cells influence the speed and reliability of spatial learning and found that despite transient connectivity, the place cell network may produce a stable representation of the topology of the environment. We also demonstrate that failures in synapses that detect coincident neuronal activity lead to spatial learning deficiencies similar to those observed in rodent models of neurodegenerative diseases. Moreover, we show that these learning deficiencies may be mitigated by increasing the number of active cells and/or by increasing their firing rate, suggesting the existence of a compensatory mechanism inherent to the cognitive map.

Disclosures: Y.A. Dabaghian: None. **A. Babichev:** None. **S. Chowdhury:** None. **F. Memoli:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.09

Topic: F.02. Animal Cognition and Behavior

Support: PSI2012-32093 from the Spanish Ministry of Economy and Competitiveness

Grant PI2012-15 from the Department of Education, University and Research from the Basque Government to P.M.P-A.

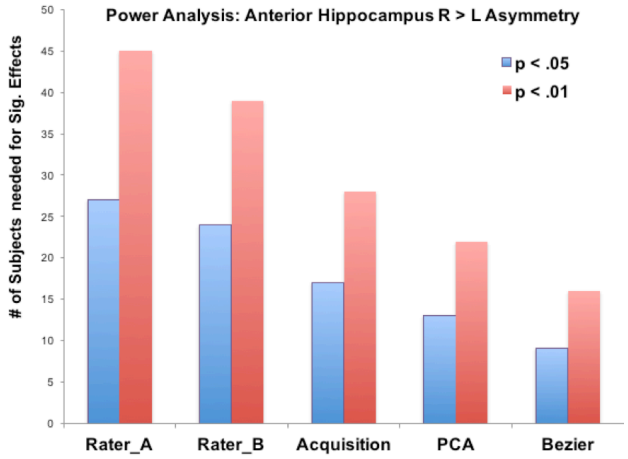
JEI was supported by the Gipuzkoako Foru Aldundia (Fellows Gipuzkoa Program)

Title: Hippocampal longitudinal axis segmentation: PCA-based automated segmentation tool

Authors: *G. LERMA-USABIAGA, E. IGLESIAS, P. M. PAZ-ALONSO;
BCBL, Basque Ctr. on Cognition, Brain and Language, San Sebastian, Spain

Abstract: The human hippocampal formation is a crucial brain structure for memory and cognitive function that is connected to other subcortical and cortical brain regions. Recent neuroimaging studies have found differences along the hippocampus longitudinal axis in terms of function, structure and connectivity, stressing the importance of improving the precision of the available segmentation methods that are typically used to divide it into anterior and posterior parts. In this regard, current segmentation conventions present two main sources of variability related to how separating planes along the longitudinal axis are chosen and how the in-scanner

head position is corrected and equated across subjects. These issues are typically addressed by manually aligning the brain for roll, pitch, and yaw rotations along the inter-hemispheric fissure, AC-PC line and orbits. Here, we propose an automated method based on estimating the hippocampal longitudinal axis with principal component analysis (PCA), as well as a variation curving this axis according to a Bezier curve, with the aim of following the shape of real human hippocampus more accurately. The estimated direction in either case is used to define the orientation of the separating planes, which removes the variability associated with the manual alignment of the in-scanner brain position. The output obtained with the PCA-based alignment was compared with the segmentations given by manual alignments provided by two trained and independent judges on a sample of 100 young adults. The results reveal that the automatized procedure minimizes the inconsistencies generated by the accumulation of manual operations, thus ensuring the reproducibility of the results between different sites. The automatic method also provides higher statistical power than the manual alignments when detecting well-known effects, such as the anterior hippocampus interhemispheric asymmetry (see figure). Matlab implementation source code of this automated method will be made publicly available for the research community.



Disclosures: **G. Lerma-Usabiaga:** None. **E. Iglesias:** None. **P.M. Paz-Alonso:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.10

Topic: F.02. Animal Cognition and Behavior

Support: NIMH Grant P50-MH0779720

Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: CCR5 is a suppressor for learning and memory

Authors: ***M. ZHOU**[1], S. GREENHILL[2], S. HUANG[1], T. SILVA[1], Y. SANO[1], S. WU[1], Y. CAI[1], Y. NAGAOKA[1], D. CAI[1], Y.-S. LEE[1], M. CHU[1], K. WONG[1], K. YAMAMOTO[1], K. FOX[2], A. J. SILVA[1];
[1]Neurobio., UCLA, Los Angeles, CA; [2]Cardiff Univ., Cardiff, United Kingdom

Abstract: Although the role of CCR5 in immunity and in HIV infection has been studied widely, its role in neuronal plasticity, learning and memory is not understood. In a reverse genetic screen, we found that a Ccr5 null mutation results in hippocampus-dependent memory enhancements. Molecular and cellular studies indicated that the memory enhancement is caused by increases in MAPK/CREB signaling and enhanced long-term potentiation. Ccr5 knockdown in the hippocampus of adult mice also led to enhancements in hippocampal memory, thus confirming a role for this receptor in adult plasticity and memory. These results suggest that besides its role as a co-receptor for HIV, CCR5 is a powerful suppressor for learning and memory, and that CCR5 over-activation may contribute to HIV-associated cognitive deficits. Consistent with this hypothesis, transgenic overexpression of CCR5 in neurons in the brain resulted in deficits in learning and memory. Accordingly, a single injection of an HIV coat peptide known to bind and activate CCR5 caused acute memory deficits, which were prevented by a Ccr5 knockout. Overall, our results demonstrate that CCR5 plays an important role in plasticity and memory. Since decreasing CCR5 function leads to robust increases in plasticity and memory, CCR5 may provide a novel target for cognitive enhancement, and brain permeable CCR5 antagonists could be useful to treat HIV-associated cognitive deficits.

Disclosures: **M. Zhou:** None. **S. Greenhill:** None. **S. Huang:** None. **T. Silva:** None. **Y. Sano:** None. **S. Wu:** None. **Y. Cai:** None. **Y. Nagaoka:** None. **D. Cai:** None. **Y. Lee:** None. **M. Chu:** None. **K. Wong:** None. **K. Yamamoto:** None. **K. Fox:** None. **A.J. Silva:** None.

Nanosymposium

657. Learning and Memory: Hippocampal Circuits

Location: N227

Time: Wednesday, October 21, 2015, 8:00 AM - 10:45 AM

Presentation Number: 657.11

Topic: F.02. Animal Cognition and Behavior

Title: Novel place field formation in hippocampal area CA1

Authors: *K. C. BITTNER, C. GRIENBERGER, J. C. MAGEE;
HHMI Janelia Farm, Ashburn, VA

Abstract: How neurons transform synaptic input into feature selective firing is a fundamental and yet unanswered question in neuroscience. Addressing this question experimentally is challenging given that neurons can receive tens of thousands of inputs each possibly with its own tuning. CA1 pyramidal cells receive external spatial information from EC3 grid cells onto their distal dendrites and internal information from CA3 place cells onto their apical and basal dendrites. These two pathways can be integrated nonlinearly when they are activated coincidently through the generation of a dendritic plateau potential. These plateau potentials have been shown to induce plasticity and therefore may play a role in place field formation. To investigate this possibility we recorded CA1 pyramidal neuron membrane potential (Vm) and local field potential (LFP) in mice running on a linear treadmill. Novel place fields were formed in silent cells either following the spontaneous appearance of a large and long lasting plateau potential or with current injections that produced plateau potentials at a single location on the track. Novel place fields had similar peak firing rates and subthreshold ramp amplitudes to non-induced place fields. Place fields could be induced at any location along the belt, indicating that these cells received proportional levels of position specific input. A Vm fluctuation analysis reveals the mechanism to be an increase in amplitude of position specific synaptic inputs. Finally, we also observed that the level of Vm depolarization and AP output produced during ripple activity was significantly increased following place field induction. These data demonstrate that a common mechanism, plateau potential induced plasticity, is sufficient to drive feature specific firing in CA1 pyramidal cells during both distinct hippocampal network states. Given that plateau potentials require coincident activation of EC3 and CA3, these data suggest that feature selectivity in CA1 may follow nonstandard learning rules that are able to generate context-dependent network representations.

Disclosures: K.C. Bittner: None. **C. Grienberger:** None. **J.C. Magee:** None.

Nanosymposium

742. Structural Plasticity

Location: N230

Time: Wednesday, October 21, 2015, 1:00 PM - 3:30 PM

Presentation Number: 742.01

Topic: B.08. Synaptic Plasticity

Support: MNIH Grant

Title: Stress-induced abnormality of dendritic spine dynamics in mouse cerebral cortex

Authors: *C.-C. CHEN, Y. ZUO;
Mol. Cell and Dev Biol, Univ. of California, Santa Cruz, Santa Cruz, CA

Abstract: It is widely accepted that significant experiences can rapidly cause long-lasting alterations of anatomical, physiological, and behavioral properties in the brain. Traumatically stressful experiences can have a profound and enduring influence on emotional and cognitive brain functioning, acting primarily through the dysregulation of synapses, which are the communication sites between neurons. Much is known about the deleterious effects of stress on the affective systems mediated through subcortical structures, but much less has been explored in cortical regions, which are the seats for sensation, perception, learning, memory, cognition, and consciousness. To address this question, we investigated how stress can alter synaptic structures in the cerebral cortex following acute, intermediate, and chronic stress. Using *in vivo* two-photon transcranial microscopy, we longitudinally followed the dynamics of postsynaptic dendritic spines of apical dendrites in layer V pyramidal cortical neurons. We found that stress induced significant changes of spine dynamics, and these changed dynamics of synaptic structures are strongly associated with specific functional and behavioral abnormalities. Comprehending how stress affects synaptic functions in the brain provides a foundation to the general understanding of how negative experiences may affect higher-order cognitive processes through the dysfunction of synaptic structures.

Disclosures: C. Chen: None. **Y. Zuo:** None.

Nanosymposium

742. Structural Plasticity

Location: N230

Time: Wednesday, October 21, 2015, 1:00 PM - 3:30 PM

Presentation Number: 742.02

Topic: B.08. Synaptic Plasticity

Title: Synaptic plasticity sets synaptic lifetime

Authors: *J. S. WIEGERT, T. G. OERTNER;
Ctr. for Mol. Neurobio., Inst. for Synaptic Physiol., Hamburg, Germany

Abstract: Long-term potentiation (LTP) and long-term depression (LTD) change synaptic transmission in an activity-dependent manner. On the level of entire pathways, averaging over many synapses, both LTP and LTD seem to be stable over days. It is less clear, however, how

plasticity affects individual synapses over time. We showed previously that LTD preferably leads to elimination of low release probability synapses, suggesting that weight adjustments affect the lifetime of synapses. Thus, reversible changes in the functional connectivity of neuronal networks induced by classical long-term plasticity (LTP/LTD) could be made permanent through synapse elimination and stabilization. During normal experience, synapses may be exposed to multiple plasticity-inducing events both increasing and decreasing synaptic weights. Thus, the persistence of synapses may depend directly on the precise sequence of potentiation and depression. We do not know, however, how potentiation and depression interact at individual synapses to regulate their persistence. We used hippocampal slice cultures to combine optogenetic stimulation of identified Schaffer collateral synapses with two-photon imaging of the genetically encoded calcium indicator GCaMP6s. All-optical induction of LTD and LTP allowed us to measure the strength of individual synapses and to follow their fate after depression or potentiation over 7 days. We found that LTP induction, using a presynaptic theta-frequency stimulation protocol, resulted in potentiation of postsynaptic calcium responses. Interestingly, successful potentiation was dependent on dendritic calcium spikes during the induction protocol. Synaptic stimulation after LTP induction often triggered dendritic calcium spikes invading neighboring, previously non-responding spines. Although concomitant spine volume increase was not sustained for > 24 h, spine survival was enhanced during the week following LTP induction. Thus, analogous to LTD, functional adjustments induced by LTP are stored in the network by stabilization of synapses. Interestingly, LTP induction 24 h after LTD induction completely reversed the reduction in synaptic lifetime, indicating that LTD did not trigger irreversible degradation of synapses. Our results indicate that individual synapses keep track of multiple potentiation and depression events distributed over many hours and that their probability of survival is adjusted accordingly.

Disclosures: J.S. Wiegert: None. **T.G. Oertner:** None.

Nanosymposium

742. Structural Plasticity

Location: N230

Time: Wednesday, October 21, 2015, 1:00 PM - 3:30 PM

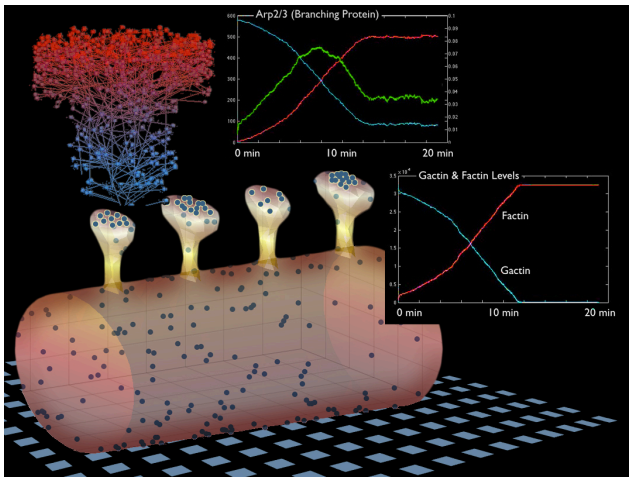
Presentation Number: 742.03

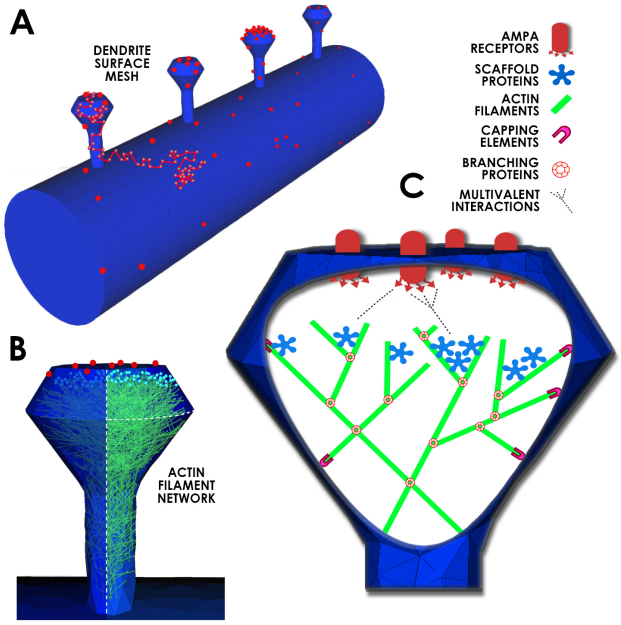
Topic: B.08. Synaptic Plasticity

Title: Simulating the spatial and temporal dynamics of synaptic plasticity

Authors: *B. R. MONK[1,2], R. MALINOW[3];
[1]UCSD, Tijuana, Mexico; [3]Neurosci., [2]UC San Diego, San Diego, CA

Abstract: The efficacy by which an upstream neuron evokes downstream responses via a particular synapse can be considered the ‘weight’ or 'strength' of that synaptic connection; with synaptic strengths being directly related to the postsynaptic levels of AMPA-type glutamate receptors (AMPARs). Memory formation is thought to involve dynamic changes to these otherwise stable synaptic weights. Indeed the ability of synaptic weights to remain stable over long time-periods and undergo evoked change is considered a fundamental feature of the brain’s information storage schema, and is currently the most compelling description of the neural analogs that underlie learning and memory. While synaptic regulation of AMPARs is considered fundamental to brain information storage, several basic questions remain unresolved; these include (a) how temporary signals induce metastable changes to synaptic strengths, and (b) how synaptic weights are maintained over long durations. This project explores these unknowns using MCMC modeling; a multiplex stochastic model was developed to simulate AMPAR trafficking in-and-around synapses. Primary model components included: (1) receptors that diffuse along a 3D dendritic surface, (2) a dynamic actin filament network, and (3) multivalent synaptic/scaffold-associated proteins (SAPs) that could interact with surface receptors, actin filaments, and other SAPs. This model unifies experimental data on structural and molecular dynamics, and simulates these processes in 3D space.





Disclosures: **B.R. Monk:** None. **R. Malinow:** None.

Nanosymposium

742. Structural Plasticity

Location: N230

Time: Wednesday, October 21, 2015, 1:00 PM - 3:30 PM

Presentation Number: 742.04

Topic: B.08. Synaptic Plasticity

Support: NIH Grant EY011261

Title: Experience-dependent bimodal plasticity of gabaergic neurons

Authors: ***H. HE**[1], W. SHEN[2,3], H. CLINE[2];
[1]Cell Bio, [2]The Scripps Res. Inst., La Jolla, CA; [3]Col. of Life and Envrn. Sci., Hangzhou Normal Univ., Hangzhou, China

Abstract: Maintaining a constant excitation/inhibition (E/I) ratio is thought to be critical for neural circuits function, however, it is not clear how excitatory and inhibitory neurons maintain E/I when challenged with changes in input activity, especially over development, when the neuronal circuit is actively making adjustment in synaptic connections to accommodate the environment. To tackle this question, we used *in vivo* time lapse structural and functional imaging to examine how excitatory and inhibitory neurons in the optic tectum of Xenopus laevis

tadpoles respond to different visual experience. We found that excitatory and inhibitory neurons display distinctive features in experience-dependent plasticity. Particularly, in response to short term visual enhancement (STVE), excitatory tectal neurons undergo typical Hebbian type plasticity, shown as significant growth of the dendritic arbor and increased visually-evoked calcium response. In contrast, the inhibitory neuron population displayed a bi-modal response to changes of the input activity. About half of the inhibitory neurons demonstrated changes similar as the excitatory neurons and the other half changed in the opposite direction, in which they decreased dendritic arbor growth and visually-evoked calcium responses with STVE. In addition, individual inhibitory neurons showed a tight inverse correlation of their plastic changes in response to opposing visual experience (dark vs STVE). To test if the E/I balance was maintained in the neural circuit, we recorded the visually evoked excitatory and inhibitory synaptic currents from tectal neurons and found no significant difference between the E/I ratios in control animals and animals subjected to STVE. These results provided experimental evidence of how excitatory and inhibitory neurons adjust to changes in sensory input and at the same time maintain circuit stability. What is especially intriguing is that the net increase in inhibitory synaptic inputs that occurred to maintain the E/I ratio was not the result of a homogenously increased response of the inhibitory neuronal population. These results suggest that different subpopulations of inhibitory neurons play diverse roles in experience-dependent plasticity and in stabilizing neuronal circuits in the face of a changing environment. Our study also draws attention to the unique and critical information provided by time-lapse imaging of individual neurons. With population sampling, the specific but distinct structural and functional plastic changes that occurred in individual inhibitory neurons would be completely lost.

Disclosures: H. He: None. **W. Shen:** None. **H. Cline:** None.

Nanosymposium

742. Structural Plasticity

Location: N230

Time: Wednesday, October 21, 2015, 1:00 PM - 3:30 PM

Presentation Number: 742.05

Topic: B.08. Synaptic Plasticity

Title: Spine clustering in a state-structured population model of activity dependent dendritic spines

Authors: *G. Y. TOUTAIN[1,2], S. CROOK[2,3], S. BAER[2];
[2]Sch. of Mathematical and Statistical Sci., [1]Arizona State Univ., Tempe, AZ; [3]Arizona State Univ., School of Life Sciences, AZ

Abstract: Over 90% of excitable synapses terminate on dendritic spines, which can change shape dynamically in response to synaptic input. This structural plasticity is thought to play a key role in learning and memory. Although spines display a continuum of shapes, in many studies they are classified as stubby (type-I), mushroom (type-II), or thin (type-III), where these anatomical categories are thought to be associated with the strength and maturity of the synapse (Harris and Jensen 1992). Recent imaging studies show that spines occur in localized groups, or clusters, and that spines cluster more often than would be expected if spine distribution were random, suggesting that clustering is driven by a biological process (Yadav et. al. 2012). Here, we formulate a model of a passive dendrite with excitable, activity-dependent spines using a continuum approach (Baer and Rinzel 1991, Verzi et al. 2005). In the model, isopotential spine heads are electrically connected to the dendritic shaft via a spine stem resistance that is dependent on the diameter, length, and intracellular resistance of the spine neck. This computational study models three dynamic populations of activity-dependent spine types, corresponding to the anatomical categories of stubby, mushroom, and thin spines. In this simplified "stage-population" model, spine types are characterized by the spine stem resistance, and transitions between spine types are driven by calcium levels that depend on local electrical activity. Consistent with empirical studies, new spines are created and old spines are pruned in response to local activity and synaptic input (Trachtenberg et. al. 2002). We use the model to examine the dynamics of spine cluster formation and how spine clustering affects the propagation of activity along the dendrite. These computational studies show that cluster formation strongly depends on the pattern of synaptic inputs and is shaped by spine transition dynamics. Like earlier modeling studies, simulations confirm that spine clustering provides for signal propagation that is more biologically efficient.

Disclosures: G.Y. Toutain: None. **S. Crook:** None. **S. Baer:** None.

Nanosymposium

742. Structural Plasticity

Location: N230

Time: Wednesday, October 21, 2015, 1:00 PM - 3:30 PM

Presentation Number: 742.06

Topic: B.08. Synaptic Plasticity

Support: HFSP fellowship LT000631/2013

Title: Measuring molecular dynamics in the brain using 2p-FLIM imaging

Authors: *T. LAVIV, R. YASUDA;
Max Planck Florida Institue For Neurosci., Jupiter, FL

Abstract: Neuronal circuits in the brain are constantly modified by external sensory experience. Detailed investigation of synaptic plasticity *in vitro* have yielded exquisite molecular mechanisms which are believed to underlie learning and memory in the brain. In addition, new *in vivo* imaging techniques have enabled high resolution exploration at the functional level of neuronal circuits, as well as structural and functional dynamics of single synapses. However, it is still unknown what molecular mechanisms the brain utilizes to encode experience-dependent plasticity. In order to address this question, we have established an imaging based approach to enable in-vivo 2-photon FLIM (Fluorescence lifetime imaging) measurements of fluorescently tagged protein activity in the mouse cerebral cortex. Currently, we are targeting molecular dynamics at different spatial and temporal scales. At the level of single cells, we have established and characterized a FLIM sensor for CREB, a well-known transcription factor which plays a vital role in long term memory and synaptic plasticity. At the level of single synapses, we are imaging the activity of CaMKII, a critical regulator of synaptic plasticity, in single dendritic spines during presentation of sensory stimulation. This approach may help to uncover the molecular mechanisms underlying experience dependent plasticity in the living brain.

Disclosures: **T. Laviv:** None. **R. Yasuda:** None.

Nanosymposium

742. Structural Plasticity

Location: N230

Time: Wednesday, October 21, 2015, 1:00 PM - 3:30 PM

Presentation Number: 742.07

Topic: B.08. Synaptic Plasticity

Support: USPHS grant DA000266 to SHS

Title: Inositol hexakisphosphate kinase-3 regulates cerebellar Purkinje cells via spectrin/adducin

Authors: ***C. FU**[1], J. XU[1], R.-J. LI[2], J. A. CRAWFORD[3], A. B. KHAN[1], T. M. MA[1], J. Y. CHA[1], A. M. SNOWMAN[1], M. V. PLETNIKOV[3], S. H. SNYDER[1];
[1]Neurosci., [2]Pharmacol. and Mol. Sci., [3]Psychiatry and Behavioral Sci., The Johns Hopkins Univ., Baltimore, MD

Abstract: The inositol hexakisphosphate kinases (IP6Ks) are the principal enzymes that generate inositol pyrophosphates. There are three IP6Ks (IP6K1, 2, 3). Functions of IP6K1 and IP6K2 have been substantially delineated, but little is known of IP6K3's role in normal physiology, especially in the brain. To elucidate functions of IP6K3, we generated mice with targeted deletion of IP6K3. We demonstrate that IP6K3 is highly concentrated in the brain in cerebellar

Purkinje cells. We find IP6K3 physiologically binds to adducin and spectrin, cytoskeletal proteins whose interactions are perturbed in IP6K3 null mutants. Consequently, IP6K3 knockout cerebella manifest abnormalities in Purkinje cell structure and reduced synapses. Accordingly, function with the mutant mice displaying deficits in motor learning and coordination. Thus, IP6K3 is a major determinant of cytoskeletal disposition and function of the cerebellar Purkinje cells.

Disclosures: **C. Fu:** None. **J. Xu:** None. **R. Li:** None. **J.A. Crawford:** None. **A.B. Khan:** None. **T.M. Ma:** None. **J.Y. Cha:** None. **A.M. Snowman:** None. **M.V. Pletnikov:** None. **S.H. Snyder:** None.

Nanosymposium

742. Structural Plasticity

Location: N230

Time: Wednesday, October 21, 2015, 1:00 PM - 3:30 PM

Presentation Number: 742.08

Topic: B.08. Synaptic Plasticity

Support: DFG Research fellowship SCHU 2701/1

Title: A role of late onset Alzheimer's disease risk factors in synaptic post-endosomal recycling exocytosis, as well as in structural and functional plasticity

Authors: B. SCHÜRMANN[1,2], K. J. KOPEIKINA[1], C. ASHFORD[1], M. MARTIN-DE-SAAVEDRA[1], M. FORREST[1], J. M. FAWCETT-PATEL[1], M. MARTINA[1], *P. PENZES[3]; [1]Northwestern Univ., Chicago, IL; [2]Univ. of Bonn, Bonn, Germany; [3]Dept Physio, Nothwestern Univ. Feinberg Sch. Med., Chicago, IL

Abstract: Post-endosomal recycling exocytosis, a process whereby cells return molecules from endosomes to the plasma membrane, is crucial for cellular signaling, motility, and growth, and in neurons, for synaptic transmission and plasticity. Glutamate receptors (GluAs) mediate fast excitatory neurotransmission. Their content in spines underlies synapse strength and is coordinated with spine morphology. Spine morphology and GluA content in spines are essential for synaptic function and cognition, and are altered in neurological disorders including Alzheimer's disease (AD). To investigate the roles of post-endosomal recycling exocytosis in spines, we performed quantitative structured illumination microscopy (SIM), a super resolution imaging method that allows the simultaneous imaging of multiple fluorophores relative to cellular architecture, combined with immuno-electron microscopy and molecular manipulations, in dissociated primary cortical neurons. These methods allowed us to investigate the relationship

between the architecture and molecular determinants of recycling exocytosis in dendritic spines. We focused on recently identified risk factors for late-onset AD, hypothesized to play a role in membrane traffic. Our results reveal key roles for one of these risk molecules in synaptic post-endosomal recycling exocytosis of GluA1 and in spine morphology that could be important for synaptic plasticity in AD.

Disclosures: B. Schürmann: None. **K.J. Kopeikina:** None. **C. Ashford:** None. **M. Martin-de-Saavedra:** None. **M. Forrest:** None. **J.M. Fawcett-Patel:** None. **M. Martina:** None. **P. Penzes:** None.

Nanosymposium

742. Structural Plasticity

Location: N230

Time: Wednesday, October 21, 2015, 1:00 PM - 3:30 PM

Presentation Number: 742.09

Topic: B.08. Synaptic Plasticity

Support: BMBF 13GW0028B

Title: Divergent phenotypes in a model for depression as compared to impaired trkB signaling

Authors: *H. VOLKMER[1], M. KRIEBEL[1], S. BEUTER[1], S. EDUT[2], O. HADAD[2], K. TRIPATHI[2], R. ANUNU[2], G. RICHTER-LEVIN[2];
[1]NMI, Reutlingen, Germany; [2]Sagol Dept. of Neurosci., Univ. of Haifa, Haifa, Israel

Abstract: Dysfunctional BDNF-trkB signaling is suspected to be implicated in depressive behaviour while the mechanistic relationship remains to be elucidated. For a comparison of impaired trkB signaling with depression-like phenotypes we developed lentiviral vectors for the knockdown of trkB *in vivo*. To this end, miRNA sequences targeting trkB were validated *in vitro* by qRT-PCR. Effective sequences were integrated into a lentiviral vector expressing miRNA under the control of a CAMKII promoter. Additionally, EGFP was expressed under the control of the synapsin promoter to allow for the identification of injection sites *in vivo*. mitrkB vectors were stereotactically injected into the dentate gyrus of adult rats. Immuno-histochemical analysis of gephyrin cluster densities, a marker for GABAergic postsynapses, revealed that trkB knockdown reduced GABAergic input on proximal dendritic and somatic compartments of granule cells while distal dendritic or axo-axonic synapses were spared. No impact on the density of excitatory postsynaptic marker PSD95 was observed. For comparison, rats were subjected to uncontrolled stress provoking consistent depression-like behavior. Immuno-histological analysis of these animals showed that GABAergic input of axo-axonic and distal dendritic synapses of

dentate gyrus granule cells were significantly reduced while proximal dendritic and somatic synapses remained unaffected. It is of note that Gabapentin application rescued the reduction of GABAergic synapses located at the distal dendrites. This finding is accompanied by a reduced freezing response of animals exposed to uncontrolled stress. Therefore, no evidence for a common mechanism of trkB signaling and depression-like behavior is shown by these experiments.

Disclosures: **H. Volkmer:** None. **M. Kriebel:** None. **S. Beuter:** None. **S. Edut:** None. **O. Hadad:** None. **K. Tripathi:** None. **R. Anunu:** None. **G. Richter-Levin:** None.

Nanosymposium

742. Structural Plasticity

Location: N230

Time: Wednesday, October 21, 2015, 1:00 PM - 3:30 PM

Presentation Number: 742.10

Topic: B.08. Synaptic Plasticity

Support: NIH grant EY02858 (CJS)

NIH grant MH07166 (CJS)

Mathers Charitable Foundation (CJS)

Rosenberg Family Foundation (CJS)

Regina Casper Stanford Graduate Fellowship (GSV)

NIH grant F31 EY023518 (GSV)

Title: Cell-autonomous regulation of dendritic spine density by PirB

Authors: ***G. S. VIDAL**[1], M. DJURISIC[2], C. J. SHATZ[2];
[1]Neurosciences, [2]Biol., Stanford Univ., Stanford, CA

Abstract: Experience-driven changes in synaptic strength and number are thought to be structural correlates of learning and memory in cerebral cortex. Paired Immunoglobulin-like Receptor B (PirB) has been shown to regulate experience-driven ocular dominance (OD) plasticity in visual cortex in excitatory cortical neurons (Bochner et al., 2014). PirB is also required for restricting dendritic spine density on layer 5 pyramidal neurons of mouse visual cortex, both during the critical period of OD plasticity and in adulthood (Djurisic et al., 2013). However, it is not known whether PirB is required on the pre- and/or postsynaptic side to exert

its function, nor is it known whether PirB initiates cell-autonomous signals that result in pruning of dendritic spines. To address these questions, We excised PirB from a small subset of layer 2/3 pyramidal neurons, so that only a very few neurons lacking PirB develop in a sea of WT neurons. Consequently, neurons lacking PirB receive the vast majority of input from WT neurons, permitting assessment of the contribution of PirB to spine density. Excision was accomplished by *in utero* electroporation of a GFP- and Cre-carrying vector into PirB flox/flox mouse embryos at E15.5; WT and germline PirB-/- embryos were used as controls. Spine density was assessed at P30. In PirB-/-, both apical and basolateral dendritic spine densities are elevated in GFP-labeled layer 2/3 cells by about 50% relative to WT. This finding is congruent with a previously measured increase in mEPSC frequency of layer 2/3 pyramidal neurons from PirB-/- brain slices (Djurisic et al., 2013). Sparse deletion of PirB in layer 2/3 cells in PirB flox/flox mice recapitulates the result seen in PirB-/-: apical and basolateral dendritic spine density of labeled cells was also elevated by about 50% over WT. Thus, deletion of PirB in only a small subset of layer 2/3 neurons is sufficient to change spine density. Together, results suggest that PirB regulates synaptic pruning in pyramidal cells in multiple layers of visual cortex, and that, specifically in layer 2/3 of the visual cortex, PirB regulates spine density in the neurons in which it is expressed; in other words, cell-autonomously.

Disclosures: **G.S. Vidal:** None. **M. Djurisic:** None. **C.J. Shatz:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.01

Topic: C.10. Trauma

Support: US Department of Veterans Affairs contract # RX001104-01 to Pamela VandeVord

Title: Blast induced neurotrauma causes overpressure dependent changes to the DNA methylation equilibrium

Authors: ***Z. S. BAILEY**[1], M. B. GRINTER[1], P. J. VANDEVORD[1,2];
[1]Biomed. Engin. and Mechanics, Virginia Tech., Blacksburg, VA; [2]Salem Veterans Affairs Med. Ctr., Salem, VA

Abstract: Traumatic brain injury (TBI) has a high prevalence in our society and often leads to morbidity and mortality. TBI also occurs frequently in a military setting where exposure to blast waves is common. Abnormal gene expression involved with oxidative stress, inflammation and

neuronal apoptosis has been well documented following blast induced neurotrauma (BINT). Altered epigenetic transcriptional regulation through DNA methylation has been implicated in the pathology of the injury as well. Imbalance between DNA methylation and DNA demethylation may lead to altered methylation patterns and subsequent changes in gene transcription. DNA methyltransferase enzymes (DNMT1, DNMT3a, and DNMT3b) are responsible for DNA methylation; the addition of methyl groups to DNA. Whereas the combined function of ten-eleven translocation enzymes (TET1, TET2, and TET3) and thymine-DNA glycosylase (TDG) facilitate the process of DNA demethylation; the removal of methyl groups from DNA. We used an established rodent model of BINT to assess changes in DNA methylation and demethylation enzymes following injury. Three different blast overpressures were investigated (10, 17 and 23 psi). Gene expression changes were investigated in the prefrontal cortex and hippocampus two weeks following injury. We observed overpressure dependent and regional dependent changes in expression of DNMT1, DNMT3b, TET2, TET3, and TDG. The hippocampus was more vulnerable to enzyme expression changes than the prefrontal cortex. The hippocampus showed increases in enzymes facilitating both DNA methylation and demethylation. The prefrontal cortex showed increases in TET2 and a decrease in DNMT3b following the 23 psi exposure. The enzyme expression changes of the hippocampus correlated with altered global DNA methylation levels. A significant negative correlation was found between global DNA methylation in the hippocampus and the magnitude of blast overpressure exposure ($p=0.0056$). Our results indicate altered mRNA expression of enzymes important to DNA methylation and demethylation processes in the BINT pathology. Through transcriptional regulation, an altered DNA methylation equilibrium drive some of the characteristic outcomes associated with the injury pathology including inflammation, oxidative stress and apoptosis. Chronic changes in the DNA methylation regulatory mechanisms in the hippocampus and prefrontal cortex may be important to the clinical manifestations including memory impairments. As such, these enzymes may be important targets to future therapeutic intervention strategies.

Disclosures: **Z.S. Bailey:** None. **M.B. Grinter:** None. **P.J. VandeVord:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.02

Topic: C.10. Trauma

Support: NIH Grant R01: R01NS091218

Title: cPLA2 mediated lysosomal damage leads to autophagy impairment after TBI

Authors: *C. SARKAR[1], Z. ZHAO[1], S. LIU[2], A. I. FADEN[1], M. M. LIPINSKI[1];
[1]Shock, Trauma and Anesthesiol. Res. (STAR) Ctr., [2]Dept. of Orthopaedics, Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Dysregulation of autophagy, a lysosome dependent major cellular degradative process, has been implicated in several neurodegenerative diseases. Recently we have demonstrated impairment of autophagy after controlled cortical impact (CCI) induced traumatic brain injury (TBI) in mice. We observed block of autophagosome degradation mainly within neuron at early time point after TBI. Our data also indicated that defect in autophagy flux may be a contributing factor in neuronal cell death following TBI. In the current study we investigated the underlying mechanisms causing the early impairment of autophagy after brain injury. Our data show that inhibition of autophagy flux is associated with lysosomal dysfunction, as evidenced by lower protein levels and enzymatic activity of the lysosomal enzyme, cathepsin D (CTSD) in injured cortex at day 1 after TBI. Interestingly, unlike the typical punctate structures observed in the sham mice, CTSD immunostaining in the injured cortex appeared diffused near the injury site. Furthermore we observed lower CTSD enzyme activity in the lysosomal fraction prepared from injured cortex as compared to that of sham animals. This suggests that lysosomal membrane damage following injury may have caused leakage of the lysosomal contents into the cytosol leading to lysosomal impairment and thus inhibiting autophagosome degradation. This could be at least in part mediated through the activation of cytosolic phospholipase A2 (cPLA2). Levels and phosphorylation of cPLA2 were elevated within neurons with accumulated autophagosomes following brain injury. Furthermore we observed partial co-localization of cPLA2 with lysosomes in the injured cortex indicating involvement of cPLA2 in lysosomal damage. *In vitro* activation of cPLA2 by ceramide-1-phosphate (C1P) in human neuroglioma H4 cells led to block of autophagosome degradation as compared to controls. This was mainly due to the lysosomal membrane damage caused by cPLA2 activation as evidenced by loss of lysotracker fluorescence in cells treated with C1P. Taken together these data indicate that cPLA2 mediated lysosomal membrane damage may be a contributing factor to autophagosome accumulation in the cortex after TBI. Blocking lysosomal damage by inhibiting cPLA2 activity early after TBI may restore autophagosome clearance and could provide an effective therapeutic strategy in restricting neuronal loss following TBI.

Disclosures: C. Sarkar: None. **Z. Zhao:** None. **S. Liu:** None. **A.I. Faden:** None. **M.M. Lipinski:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.03

Topic: C.10. Trauma

Title: Increased number of concussions is associated with higher levels of metabolic dysregulation

Authors: *Y. D. BRYANT, L. LEUNG, W. YANG, J. GILSDORF, F. TORTELLA, D. SHEAR;
Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: Clinical symptoms associated with mild concussion often resolve over time. However, recurring concussions can result in cumulative damage and increased risk for chronic neurological deficits. To date, no clinical prognosticators for concussion have been identified as objective endpoints that underlie the injury-associated neuropathologies. As such, the current study was designed to evaluate the cumulative effects of concussions on metabolic dysregulation in a rat model of projectile concussive injury (PCI) in order to identify biochemical signatures specific for concussive injury mechanisms. Adult male Sprague-Dawley rats received PCI for 1, 2 or 3 times with intervals set at 6 hours between concussions for the repeated PCI groups. Each concussed group was matched with respective sham controls (anesthesia only). Ipsilateral cerebral cortices were collected at 2 hours post-injury for each group (n=6-7/group). Mass spectrometry-based global metabolomics was performed to determine biochemical signatures, followed by statistical and pathways analysis to interpret the data. The results show significant alterations of biochemicals at 12.4%, 20.4% and 19.2% out of all biochemicals detected following 1×PCI, 2×PCI and 3×PCI ($p<0.05$ vs. sham) respectively, suggesting an increased risk of disrupted metabolic homeostasis associated with repeated concussion versus a single concussion. More specifically, repeated concussion, especially 3×PCI, resulted in increased level of glycogen degradation markers indicating disrupted glycolysis, as well as upregulated arginine metabolism for tissue remodeling and repair. Additionally, 3×PCI was accompanied by evidence of enhanced oxidative stress compared to 2×PCI, suggesting that higher incidence of concussion may be associated with an increased risk for redox imbalance. Most notably, markers of tissue injury and recovery were altered as indicated by the changes in polyamine levels, among which the putrescine level, in particular, was positively correlated with the number of concussions (i.e. higher numbers of concussion resulted in higher putrescine level; $R^2=0.6$). Overall, these findings demonstrate a differential metabolomic profile sensitive to the number of concussion as evidenced by the incremental increases in levels of biochemical alterations. Further analysis will focus on the specificity of selected biochemical signatures that warrant analysis for their potential as concussion biomarkers.

Disclosures: Y.D. Bryant: None. **L. Leung:** None. **W. Yang:** None. **J. Gilsdorf:** None. **F. Tortella:** None. **D. Shear:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.04

Topic: C.10. Trauma

Support: Department of Veterans Affairs (Veterans Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development and Rehabilitation Research and Development)

Bay Pines Foundation

Florida Department of Health James and Esther King Biomedical Research Program

Title: Mild and repetitive traumatic brain injuries and pathogenic proteins

Authors: J. N. CHANG[1,2], K. L. SALIGA[1,2], C. G. PICK[4], S. BHASKAR[5], *R. F. MERVIS[5,3], B. A. CITRON[1,2];
[1]Lab. of Mol. Biol., Bay Pines VA Healthcare Syst., Bay Pines, FL; [2]Mol. Med., [3]Ctr. for Aging and Brain Repair, Dept. of Neurosurg., Univ. of South Florida Morsani Col. of Med., Tampa, FL; [4]Anat. and Anthrop., Sackler Sch. of Med., Tel Aviv, Israel; [5]Neurostructural Res. Labs, Temple Terrace, FL

Abstract: Recent data suggests that mild head injuries can cause significant proteinopathies resulting in a progressive decline of cognition and memory where patients display dementia similar to that of Alzheimer's patients. We do not fully understand the molecular underpinnings and protein processing that occurs following a single traumatic brain injury moreover the neuropathology that occurs following multiple traumatic events. Brain trauma is a multifactorial disease and more insight into the changes that occur following a head injuries and is necessary to develop effective treatments for Veterans. A closed head model of traumatic brain injury is used to induce a mild injury. Mice are exposed to either one or five injuries with successive injuries occurring 24 hours apart. Cortex and hippocampus were collected at 30 and 60 days following the final injury and protein expression was analyzed by western blot. To date we have found 12 days following a single injury we observe an increase in both phosphorylated Tau and TDP-43 expression compared to sham controls. Similarly, following 5x injuries we observe an increase in phosphorylated Tau and TDP-43 increased 60 days post injury in injured vs. sham controls. Sholl analysis of the granule cells of the dentate gyrus indicated greater dendritic branching after repetitive injury. Pathogenic proteins are increased following both a single mild closed head injury as well as multiple injuries. Further characterization of both the short and long term time

course of pathogenic protein expression following single and multiple head injuries is still necessary.

Disclosures: **J.N. Chang:** None. **K.L. Saliga:** None. **C.G. Pick:** None. **S. Bhaskar:** None. **R.F. Mervis:** None. **B.A. Citron:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.05

Topic: C.10. Trauma

Support: NIH Grant NS077675

Title: The effect of mild traumatic brain injury (mTBI) on the structural plasticity of the axon initial segment (AIS)

Authors: ***M. VASCAK**, M. L. BAER, J. T. POVLISHOCK;
Dept. of Anat. and Neurobio., Virginia Commonwealth University, MCV Campus, Richmond, VA

Abstract: The AIS is the site of action potential (AP) initiation and a crucial regulator of neural activity. Homeostatic fine-tuning of AIS structure has been associated with neuronal information processing. In sensory circuits, altered presynaptic input induces AIS plasticity that modifies neuronal excitability. Ankyrin-G (ankG) is the structural protein regulating neuron excitability via clustering voltage-gated sodium channels (NaV). In pyramidal neurons (PN), NaV1.6 density at the distal AIS sets the threshold for AP initiation. Recently, in mTBI-mice we demonstrated substantial electrophysiological changes in non-axotomized/structurally intact neocortical PN, consistent with AIS-specific alterations, and mTBI related circuit disruption. Since altered neural activity modifies AIS architecture and neuronal excitability, the current study sought to determine if mTBI induces AIS structural plasticity within a specific, well-defined subset of intact neocortical PN. Thy1-YFP mice exposed to either sham injury or mTBI were perfused 2-days postinjury. Antibodies to ankG and NaV1.6 were used to fluorescently label the AIS. Confocal microscopy was employed to identify YFP^+ intact PN in Layer 5 (L5) of S1 barrel field, whose axons were continuous from the soma of origin to the subcortical white matter (SCWM). Immunofluorescent profiles of ankG were then superimposed on YFP^+ axonal traces to determine the proximal (start) and distal (end) positions of ankG, from which overall AIS length was computed. We found that while mTBI had no effect on ankG start position, the end

position and length were decreased significantly. AIS shortening from the distal end corresponded to the peak NaV1.6 immunofluorescent signal, consistent with the site of AP initiation. This change in AIS structure most likely explains some of the electrophysiological abnormalities seen within intact PN after mTBI. Because AIS position and length vary even within a neuronal subtype, we also probed for L5 PN subsets by measuring distance from SCWM, somatic area, and apical dendrite width. We found that PN distance from SCWM was a covariate of ankG end position and length, suggesting L5 sublayer differences, but did not interact with group affects. We also observed a trend toward smaller somatic area concomitant with a significant decrease of apical dendrite width. These morphological metrics may reflect the presence of L5 PN subsets that are vulnerable to mTBI-induced changes. Since spatial and morphological features of PN correlate to subsets that project to different brain regions, these results also indicate specific neuronal substrates of mTBI-induced circuit disruption.

Disclosures: **M. Vascak:** None. **M.L. Baer:** None. **J.T. Povlishock:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.06

Topic: C.10. Trauma

Support: Department of Veterans Affairs (Veterans Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development and Rehabilitation Research and Development)

Bay Pines Foundation

Florida Department of Health James and Esther King Biomedical Research Program

Title: Neuroprotective transcription factor modulation after blast-induced TBI

Authors: *B. A. CITRON[1,2], L. RACHMANY[3], V. RUBOVITCH[3], K. L. SALIGA[1,2], C. G. PICK[3], J. N. CHANG[1,2];
[1]Lab. of Mol. Biol., Bay Pines VA Healthcare Syst., Bay Pines, FL; [2]Mol. Med., Univ. of South Florida Morsani Col. of Med., Tampa, FL; [3]Anat. and Anthrop., Sackler Sch. of Med., Tel Aviv, Israel

Abstract: Traumatic brain injury has a prevalence of approximately 0.5% per year worldwide and there is a 30 fold higher rate among deployed service personnel. Mild injuries are the most

common yet they do result in significant deficits in brain function and cognitive performance. We have identified transcription factor pathways involved in inflammatory responses that impact on neuronal damage. Most of our previous work focused on a closed head impact injury model. With an explosive blast injury of model system, mice exposed to a sharp pressure wave from a TNT detonation suffer memory deficits. The injury is accomplished by a calibrated explosion in a controlled field environment and distance from the blast serves to titrate the degree of injury. The advantages of the explosion model are that it most accurately reproduces the battlefield environment and the microsecond pressure wave. The blast injury resulted in dysregulation of regulators of plasticity and transcription factor pathways, e.g., Inhibitor of DNA binding 2, Id2. Protein and mRNA levels for the transcription factor, Nrf2 were measured after mild TBI exposures at different distances and times from the blast and we found that the injury exposure itself induced an upregulation in Nrf2 levels. This indicated that Nrf2 may be able to partially respond to this form of TBI insult. Post-injury treatment tested mice receiving tert-butylhydroquinone, an activator of the transcription factor Nrf2. We have also surveyed several protein changes that could affect neuronal health, focused on the hippocampus as a sensitive region in this brain injury model. In summary, the examination of altered expression levels in regulatory pathways should help advance the identification of therapeutic targets that will benefit Veterans and other individuals suffering TBI.

Disclosures: B.A. Citron: None. **L. Rachmany:** None. **V. Rubovitch:** None. **K.L. Saliga:** None. **C.G. Pick:** None. **J.N. Chang:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.07

Topic: C.10. Trauma

Title: Posttraumatic propofol neurotoxicity is mediated via the ProBDNF-p75NTR pathway

Authors: *A. S. SEBASTIANI[1], M. GRANOLD[2], C. GÖLZ[3], B. POETTKER[3], C. WERNER[3], M. K. E. SCHAEFER[4], K. ENGELHARD[4], B. MOOSMANN[2], S. C. THAL[3];
[1]Univ. Med. Ctr. of the Johannes Gutenberg-University, Mainz, Germany; [2]Inst. for Pathobiochemistry, [3]Dept. of Anesthesiol., [4]Dept. of Anesthesiology; Focus Program Translational Neurosciences (FTN), Univ. Med. Ctr. of the Johannes Gutenberg Univ., Mainz, Germany

Abstract: The $GABA_A$ modulator propofol induces neuronal cell death in healthy immature brains by unbalancing neurotrophin homeostasis via p75 neurotrophin receptor (p75NTR) signaling[1]. In adulthood, p75NTR expression becomes depressed, and propofol loses its neurotoxic effect. However, acute brain lesions like traumatic brain injury (TBI) reactivate developmental-like programs and increase p75NTR expression[2], probably to foster reparative processes which in turn could render the brain sensitive to propofol-mediated neurotoxicity. The present study investigated the influence of single-bolus propofol application at the peak of the p75NTR expression, 24 hours after experimental TBI (controlled cortical impact; CCI) in adult C57/BL6 mice. Propofol sedation at 24 hours after CCI increased the lesion volume by 30% (Nissl staining), enhanced calpain-induced αII-spectrin cleavage (Western blotting), and increased cell death in peri-lesional tissue (TUNEL staining). 30-Day post injury, motor function determined by CatWalk® gait analysis was significantly impaired in propofol-sedated animals compared to the control group. Propofol enhanced the ProBDNF/BDNF ratio (quantified by Western blotting), which might aggravate p75NTR-mediated cell death. Propofol toxicity was abolished by pharmacological inhibition of the cell death domain of the p75NTR pathway, and in mice lacking exon III of the p75NTR extracellular domain ($NGFR^{-/-}$). The present study provides first evidence that propofol sedation after TBI may have a deleterious impact and implicates a role for the ProBDNF-p75NTR pathway therein. This observation is important as sedation by propofol is frequently used in patients with acute brain pathologies to facilitate surgical and interventional procedures. 1. Lu LX, 2006, Apoptosis 2. Shulga A, 2013, Neuroscience

Disclosures: **A.S. Sebastiani:** None. **M. Granold:** None. **C. Gölz:** None. **B. Poettker:** None. **C. Werner:** None. **M.K.E. Schaefer:** None. **K. Engelhard:** None. **B. Moosmann:** None. **S.C. Thal:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.08

Topic: C.10. Trauma

Support: UPMC Rehabilitation Institute

Title: Controlled cortical impact (CCI) produces regiospecific dysfunction of striatal dopamine (DA) neurotransmission

Authors: R. HARUN[1], M. MUNOZ[3], M. E. BROUGH[1], *A. K. WAGNER[2];
[1]Phys Med. & Rehab, Safar Ctr., [2]Phys Med. & Rehab, Psych, Safar Ctr., Univ. of Pittsburgh, Pittsburgh, PA; [3]Dept. of Biol. Sci., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Dysfunction in the dopaminergic (DAergic) system is common following traumatic brain injury (TBI), which may underlie many aspects of cognitive and behavioral impairments following TBI. Although the DAergic system has widespread projections throughout the cortex and basal ganglia to modulate diverse functions throughout the brain, little is known about the regiosepcificity of DAergic dysfunction following brain injury. Using fast-scan cyclic voltammetry (FSCV), our group has previously demonstrated that there are impairments in electrically stimulated DA response amplitudes in the dorsomedial striatum 2 weeks following the controlled cortical impact (CCI) model of moderate TBI in young-adult male Sprague Dawley rats. Moreover, CCI rats exhibit a differential pharmacological response to the DA transporter inhibitor methylphenidate. In this study, we used FSCV to examine the effects of CCI on electrically stimulated DA responses in the dorsolateral striatum (DL-STR) and nucleus accumbens (NAc), which are two regions that differ in functional connectivity and neurochemistry, including sensitivity to D2 DA receptor antagonists like raclopride (RAC). By performing simultaneous recordings in both regions, a majority of naïve animals exhibited responses in both regions with only 1/9 rats exhibiting non-responses in the DL-STR. In contrast, 7/8 CCI rats exhibited non-responses in the DL-STR, indicative of severe dysfunction of DA neurotransmission in the DL-STR after injury. Using our recently developed quantitative theoretical framework to disentangle release and reuptake dynamics from FSCV stimulated DA responses, we demonstrated that there was a 47.5±7% decrease in the amount of stimulated DA released by 60Hz,5s stimulation in the NAc of CCI rats ($p<0.05$). Moreover, Vmax, which reflects that maximal reuptake capacity tended to be lower in CCI rats as well (18.2±9% lower than naïve rats, $p=0.118$). This work suggests that there are widespread striatal impairments of DA neurotransmission after CCI, while certain regions like the DL-STR appear to be more susceptible to injury-induced deficits. Notably, this work has important relevance to the associations between TBI and Parkinson's disease, for which the DL-STR is known to be particularly susceptible to degeneration.

Disclosures: R. Harun: None. **M. Munoz:** None. **M.E. Brough:** None. **A.K. Wagner:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.09

Topic: C.10. Trauma

Title: Structural and functional alterations in mouse visual cortex following mild traumatic brain injury

Authors: *E. WITKOWSKI, G. DEWALT, A. FOSTER, W. ELDRED, I. DAVISON;
Biol., Boston Univ., Boston, MA

Abstract: Despite dramatic increases in the prevalence of mild traumatic brain injury (TBI) in recent years, the underlying neurobiological mechanisms remain poorly understood. To examine the extent and time course of fine-scale structural and functional changes in cortical networks, we perform high-resolution chronic *in vivo* imaging and ex vivo whole-cell electrophysiology in a rodent blast model of TBI. Imaging of dendritic spines on layer V pyramidal cells in the visual cortex reveals a transient phase of elevated turnover lasting approximately 2-4 days after injury. In contrast, both spine density and the underlying dendritic arbor remain stable, indicating that mild TBI induces reorganization of the existing cortical network rather than large-scale changes in dendritic anatomy or number of excitatory synapses. Furthermore, whole-cell recordings from this same cell type show a higher frequency of excitatory synaptic events 2 days after injury, pointing to changes in release properties of excitatory synapses while inhibitory synapses are unaltered. Thus, cortical networks undergo both functional as well as structural alterations after TBI, in agreement with the increased excitation observed both clinically and in studies using non-blast models of TBI. Together, the combination of chronic imaging and whole-cell recording allows us to investigate neurobiological changes, such as synaptic reorganization, over different phases of injury and recovery, the first critical step in understanding and developing treatment strategies.

Disclosures: E. Witkowski: None. **G. DeWalt:** None. **A. Foster:** None. **W. Eldred:** None. **I. Davison:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.10

Topic: C.10. Trauma

Support: Martha Entenmann Tinnitus Research Center

Grant-in-aid of Research, Sigma Xi, The Scientific Research Society

The Institute for Basic Research in Developmental Disabilities

Title: The effect of the novel calpain inhibitor ala-1.0 on traumatic brain injury

Authors: *R. DUGUE[1], S. BRAREN[4], G. W. HASSEN[2], P. SERRANO[4], H. MICHELSON[1], A. SHULMAN[3], J. GOODMAN[5], D. S. F. LING[1];
[1]Physiol. & Pharmacol., [2]Emergency Med., [3]Otolaryngology, SUNY Downstate Med. Ctr., Brooklyn, NY; [4]Hunter Col., New York, NY; [5]The Inst. for Basic Res. in Developmental Disabilities, Staten Island, NY

Abstract: Traumatic brain injury (TBI) is a leading cause of chronic disability; it afflicts people of all ages with over 1.7 million traumatic brain injuries occurring per year. A successful treatment for TBI has not yet been determined. Calpain over-activation is a major contributor to cell dysfunction and neurodegeneration in secondary injury following TBI. Therefore, calpain inhibition is a viable therapeutic strategy to halt neurodegeneration and preserve neurological function post-TBI. The aim of this study seeks to evaluate ALA-1.0, a blood-brain barrier permeable calpain-inhibitor, as a potential TBI therapeutic. ALA-1.0 is a novel calpain-inhibitor composed of the inhibitor end of the calpain protease inhibitor, leupeptin (leucyl-argininal), linked to the FDA-approved anti-epileptic drug, pregabalin, as a carrier molecule. This formulation allows the entire compound to cross the blood-brain barrier and target the site of neural injury after peripheral administration. We hypothesize that the administration of ALA-1.0 after injury can halt detrimental calpain over-activation and reduce consequent neurological and functional deficits post-TBI. A single 80 mg/kg of ALA-1.0 was administered i.p. immediately following severe injury induced by the controlled cortical impact (CCI) rodent model of TBI (2.0 mm depth, 4.0 m/s). Control rats were subjected to the same severe CCI injury, but received only saline vehicle i.p. immediately following injury. At 48 hours after injury, rats were euthanized and tissue from the injury site was collected. In comparison to control rats, rats given ALA-1.0 immediately following severe TBI displayed a significant reduction in the number of degenerating cortical neurons, as shown by Fluoro-Jade B staining ($p<0.05$). Western blot analysis showed a decrease in the amount of calpain-cleaved αII-spectrin breakdown products in injured rats given ALA-1.0 ($p<0.05$). Microglia and astrocyte activation were analyzed via immunohistochemistry for ionized calcium-binding adapter molecule 1 (Iba-1) and glial fibrillary acidic protein (GFAP), respectively. The results of these studies suggest that a single dose of ALA-1.0 administered peripherally after CCI injury is able to reach the site of injury and prevent TBI-induced neurodegeneration through the inhibition of calpain. Future studies will clarify the role of ALA-1.0's pregabalin carrier molecule and will determine the efficacy of ALA-1.0 administration at later, clinically relevant time-points post-injury through the evaluation of histological, biochemical, and behavioral outcome measures.

Disclosures: R. Dugue: None. **S. Braren:** None. **G.W. Hassen:** None. **P. Serrano:** None. **H. Michelson:** None. **A. Shulman:** None. **J. Goodman:** None. **D.S.F. Ling:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.11

Topic: C.10. Trauma

Support: P30 Cobre Pilot Award

Child Health Signature Program

NIH NS060765

Title: Serum and diffusion tensor imaging biomarkers in a preclinical model of infant traumatic brain injury

Authors: L. L. JANTZIE[1], J. L. DENSON[1], J. L. WINER[2], J. R. MAXWELL[1], L. A. S. CHAN[2], *S. ROBINSON[2];
[1]Pediatrics, Univ. of New Mexico, Albuquerque, NM; [2]Neurosurg., Boston Children's Hosp., Boston, MA

Abstract: Infants suffer traumatic brain injury (TBI) from multiple types of impact including falls, collisions and abusive head trauma. To guide the diagnosis and management of infant TBI, we developed a rat model to mimic impact injury in infants 2-3 months old, and investigated acute and chronic serum and imaging biomarkers. On postnatal day 12 (P12) rats underwent anesthesia, left craniotomy, and controlled-cortical impact (CCI). Sham animals underwent anesthesia and incision only. Half of CCI rats were randomized to receive erythropoietin (EPO, 3000U/kg/dose, 6 doses ip over 8 days) or saline (veh). Brain and serum were evaluated with multi-array electrochemiluminescence detection, diffusion tensor (DTI) and susceptibility weighted imaging (SWI) ex vivo. Mortality was 5% for CCI and zero for sham. Most CCI rats experienced loss of consciousness and brief seizures. At 3 days post-injury (dpi), serum tumor necrosis factor-α was elevated in CCI rats compared to shams (n=4-6, $p<0.01$). DTI and SWI scans at 20dpi revealed hemorrhage and a significant reduction white matter fractional anisotropy in CCI animals compared to sham (0.39±0.01 vs. 0.17±0.01, n=3, $p<0.001$). Additionally, CCI-veh white matter showed increased axial (4.9±0.5 x10-4 vs.9.8±1.2 x10-4 mm2/s) and radial diffusivity (2.5±0.3 x10-4 vs. 8.8±0.2 x10-4 mm2/s), indicative of poor axon and myelin integrity, respectively. Abnormalities were less prominent in CCI-EPO white matter. These pilot results demonstrate the feasibility of mimicking impact TBI in young infants using a preclinical rat model. Serum and DTI biomarkers are sensitive to detection of injury and may inform dosing regimens for emerging interventions.

Disclosures: **L.L. Jantzie:** None. **J.L. Denson:** None. **J.L. Winer:** None. **J.R. Maxwell:** None. **L.A.S. Chan:** None. **S. Robinson:** None.

Nanosymposium

743. Traumatic Brain Injury: Cellular and Mechanisms

Location: S403

Time: Wednesday, October 21, 2015, 1:00 PM - 4:00 PM

Presentation Number: 743.12

Topic: C.10. Trauma

Support: The Roskamp Foundation

Title: Influence of a Western Diet on pathological and biochemical outcomes in a mouse model of mild repetitive TBI

Authors: *F. C. CRAWFORD[1,2,3,4], C. BACHMEIER[1,3,4], B. MOUZON[1,3,4,2], J. OJO[1,3,4,2], C. LYNCH[1,4], S. FERGUSON[1,3,2], M. MULLAN[1];
[1]Roskamp Inst., Sarasota, FL; [2]James A. Haley Veteran's Hosp., Tampa, FL; [3]Chronic Effects of Neurotrauma Consortium, Sarasota, FL; [4]The Open University,, Buckinghamshire, United Kingdom

Abstract: Traumatic brain injury (TBI) carries serious neurological consequences stemming from both the initial trauma and from the secondary damage that occurs hours and days to years after the injury. Apoliporotein E (apoE) is recognized for its importance in the transport and metabolism of lipoproteins and cholesterol, and is a known risk factor for outcome after TBI. Environmental factors influencing outcome after TBI, in particular mild TBI (mTBI) are poorly understood at this time. Given the high incidence of TBI in the US military and athletes we were interested in the influence that may be conferred by the "Western Diet" and whether animals raised on such a diet (high fat, high carbohydrate) might be predisposed to worse outcome after mTBI. We further hypothesized that the influence of APOE genotype might be more pronounced in mice on the Western diet as compared to normal mouse chow. We explored the effects of different diets administered to young APOE3 or APOE4 TR mice from weaning: control diet (19% Protein; 47% Carbohydrate; 6% Fat) or Western diet (17% Protein; 49% Carbohydrate; 21% Fat) both from Harlan Laboratories. Mice were aged 10-12 weeks at the time of injury and we investigated the effects of our previously published mTBI administered as a closed head injury on the midline, using the myNeuroLab controller at a strike velocity of 5m/s, strike depth of 1.0mm, and dwell time of 200ms. Two repetitive injury paradigms were explored: one with 5 mTBI administered with a 48hr inter-injury interval, the other with 2 mTBI/week for three months. At euthanasia mouse brains and plasma were harvested for neuropathological and

biochemical analyses. Immunohistochemical analyses of mouse brains is ongoing, using inflammatory markers, vascular markers and markers for tau and amyloid pathology. Previous work in our laboratories with both of these r-mTBI models has revealed a prominent neuroinflammatory response to the injury, and the new data will be compared against existing data in wild type and hTau mice on control diet to determine the influence of APOE genotype and Western diet.

Disclosures: F.C. Crawford: None. **C. Bachmeier:** None. **B. Mouzon:** None. **J. Ojo:** None. **C. Lynch:** None. **S. Ferguson:** None. **M. Mullan:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.01

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Mortality differences between C57BL/6 mice from Jackson and Charles River Laboratories due to exposure to isoflurane

Authors: *C. G. WARD[1], T. DEYOUNG[1], R. ECKENHOFF[3], M. ECKENHOFF[3], G. BARR[2]; [1]Dept. of Anesthesia and Critical Care, [2]Anesthesia and Critical Care, Children's Hosp. of Philadelphia, Philadelphia, PA; [3]Anesthesiol. and Critical Care Med., Perelman Sch. of Med., Philadelphia, PA

Abstract: **Introduction**: Anesthesia is used to facilitate surgical and radiological procedures in millions of children every year, but has repeatedly been shown to cause extensive apoptotic cell death in developing and more recently mature animals. Studies examining the clinical consequences of this anesthetic induced neurotoxicity in rodents have given conflicting results with regard to any short term or long lasting learning and behavioral differences. Genetic drift is a known phenomenon occurring in different animal laboratories housing inbred strains of laboratory mice. In order to examine the possible influence of this genetic drift within the C57BL/6 strain on the difference in clinical outcomes reported in the literature, we exposed C57BL/6 postnatal day (PND) 7 mouse pups procured from Charles River (CR) and Jackson (J) Laboratories to the same anesthetic regimen. **Methods**: On PND 7, 60 CR and 39 J were exposed to 1.5% isoflurane anesthesia in 30% oxygen for 6 hours. The anesthetic and control chambers were kept partially submerged in a 44 degree C water bath to maintain normothermia and continuous chamber concentrations of isoflurane, oxygen and carbon dioxide were measured. **Results**: Using t-test analyses, there was a statistical difference between the increased mortality

observed for J C57BL/6 versus CR C57BL/6 (38% vs. 26%). There was no statistical difference between body weights at time of exposure between the two groups. **Discussion**: Retrospective human studies looking at the possible consequences of anesthetic exposure and long term learning and behavior outcomes in children have given inconclusive results and are unable to separate surgical and anesthesia related outcomes. Numerous previous studies in animals have repeatedly demonstrated that exposure to anesthesia causes apoptotic neuronal cell death but have shown conflicting results about what clinical effects this damage may or may not cause. The difference in mortality observed between the same C57BL/6 inbred strains from two different laboratories is possibly due to genetic drift over the years. This finding is important in that it provides a possible explanation for the striking differences in mortality from the same anesthetic exposure in this study as well as different learning and behavior deficits from similar anesthetic exposures from different labs using the 'same' strain of rodent. Further studies utilizing the known genetic differences between C57BL/6 strains could aid in developing an increased understanding of the mechanism of anesthetic induced neurotoxicity as well as better define the genetic subset of the population that may be susceptible to this phenomenon.

Disclosures: C.G. Ward: None. **T. DeYoung:** None. **R. Eckenhoff:** None. **M. Eckenhoff:** None. **G. Barr:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.02

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: HHMI to JHZ

NIH R01 GM088801 to ZX

NIH R01 AG041274 to ZX

Title: Sevoflurane causes long-lasting dendritic spine head enlargement in mouse hippocampal neurons associated with decreased RhoA Immunolocalization to spine head

Authors: J. H. ZIMERING[1,2], Y. DONG[1], F. FANG[1], *Y. ZHANG[1], Z. XIE[1];
[1]Dept. of Anesthesia & Critical Care and Pain Med., Massachusetts Gen. Hosp., Charlestown, MA; [2]Univ. of Rochester Sch. of Med. and Dent., Rochester, NY

Abstract: Early postnatal anesthesia causes long-lasting learning and memory impairment in rodents (1), however, the underlying mechanisms remain largely unknown. We tested a hypothesis that clinically relevant concentrations of the volatile anesthetic sevoflurane alters morphology and synaptic activity in developing mouse hippocampal neurons. Mouse fetal day 16 hippocampal neurons were cultured in Neurobasal medium for 7 days *in vitro* (DIV) prior to a single (4 hour) exposure to 3% sevoflurane in 95% air/5% CO2 or control condition (95% air/5% CO2). Neurons were either immediately fixed in 4% paraformaldehyde or maintained for 14 additional days prior to staining for filamentous (F)-actin using Alexa Fluor555-Phalloidin, or actin-binding drebrin. Proximal and distal dendritic segments were randomly selected for analysis. Sevoflurane caused acute significant enlargement in a subset of dendritic spines which persisted in DIV14 sevoflurane- treated vs. control neurons (0.83 μm vs 0.61 μm, P = 0.0001, n= 52). At DIV21, sevoflurane-treated neurons still demonstrated a higher proportion of unusually large spines (> 8 μm diameter) (18% vs 10%; P = 0.053) compared to control neurons. The spine head enlargement (DIV 14) was associated with significantly (P = 0.047) increased filamentous F-actin concentration. It was mimicked by exposure in control neurons to Y27632 (10 uM), a selective Rho kinase inhibitor. Active RhoA - GTP immunoreactivity was absent in spine heads in sevoflurane compared to control DIV14 neurons consistent with the known (RhoA) translocation defect (from cytosol to apical membrane) induced by sevoflurane (2). Taken together, these novel findings suggest that sevoflurane induces a translocation-dependent defect in local RhoA/Rho kinase signaling activity in the spine head F-actin pool leading to persistent head enlargement. More study is needed to determine the functional consequences (if any) of spine enlargement on learning and memory. 1. PLoS One 9(8):e105340; 2014. 2. Anesthesiology 99(3):646-51; 2003.

Disclosures: **J.H. Zimering:** None. **Y. Dong:** None. **F. Fang:** None. **Y. Zhang:** None. **Z. Xie:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.03

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01 HD044517 (NIH/NICHD) (to VJT)

R01 HD044517S (NIH/NICHD) (to VJT)

R21 HD 080281 (NIH/NICHD) (to VJT)

March of Dimes National Award (to VJT)

Harold Carron Endowment (to VJT)

R01 GM102525 (to SMT)

Title: Isoflurane impairs dendritic branching of the immature human and rat neurons *in vitro*

Authors: A. OKLOPCIC[1], C. DEFREITAS[1], D. MILANOVIC[2], *V. JEVTOVIC-TODOROVIC[1];
[1]Anesthesiol., Univ. Virginia, Charlottesville, VA; [2]Neurobio., Univ. of Belgrade, Belgrade, Serbia

Abstract: OBJECTIVE: Rodent studies show that volatile anesthetic, isoflurane (ISO) causes damage to the developing neurons. Since the importance of this finding in humans remains unclear we set to examine the effects of ISO on cultured primary human neurons vis-à-vis cultured rat primary neurons. We focus on the neuronal viability and the complexity of the branching of neuronal processes since the formation of neuronal circuitries during early stages of brain development relies on proper development of dendritic trees. METHODS: Human fetal brain tissue, (17-21 g.w.) was obtained from the Human Fetal Tissue Repository at the Albert Einstein College of Medicine after legal abortion and with proper consent. Rat hippocampal cells were co-cultured with astroglia. Both human and rat neurons were exposed to 1.5% ISO on day *in vitro* 3 for 6 hours using tightly closed gas chamber in a 37oC humidified atmosphere containing 21% oxygen. The sham controls were exposed to 21% oxygen under the same conditions. For the studies of neuronal viability we used LDH assay. For the morphological analysis the neurons were stained with MAP2 (neuronal marker), DAPI (nucleus marker) and GFAP (astroglia marker) at 0h, 24h, 48h and 7 days post-ISO anesthesia. We quantified the complexity of process branching in each neuron by analyzing the primary, secondary and tertiary branches. RESULTS: Six hours of ISO exposure impairs human neuronal viability shown as a 50% decrease in cell lysate LDH 24 h post-exposure when compared to sham controls. In addition, human neurons tend to release LDH into the culture medium after exposure to ISO suggested by a significant (about 40%; $p<0.001$) increase in LDH compared to sham controls. Morphological analysis shows that ISO-treated neurons exhibit a trend towards lesser complexity of branching compared to sham controls. Specifically, primary, secondary and, in particular tertiary branching of human neuronal processes is decreased at 24 and 48h with seeming recovery noted at 7 days suggesting that ISO might impair the fine tuning of neuronal branching. Interestingly, morphological development of rat neurons was affected at 24 h post-exposure with seeming recovery thereafter (at 48 h and 7 days). Interestingly, the tertiary branching of rat neuronal processes was not as severely impaired as the human ones. CONCLUSION: ISO impairs human neuronal viability *in vitro* and delays proper process development in human and rat neurons. Fine branching of human neurons compared to rats' is more vulnerable to an early

exposure to ISO. We propose that lesser complexity of branching could be the morphological correlate of previously reported impairment of synaptic communication.

Disclosures: A. Oklopcic: None. **C. DeFreitas:** None. **D. Milanovic:** None. **V. Jevtovic-Todorovic:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.04

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: IARS Mentored Research Award (to NL)

School of Medicine Research and Career Development Award, University of Virginia (to NL)

R01 HD044517 (NIH/NICHD) (to VJT)

R01 HD044517S (NIH/NICHD) (to VJT)

R21 HD 080281 (NIH/NICHD) (to VJT)

March of Dimes National Award (to VJT)

Harold Carron Endowment (to VJT)

Title: Exposure to general anesthesia during critical stages of brain development has long lasting effects on the function of surviving synapses

Authors: *N. LUNARDI[1], M. PRILLAMAN[2], A. OKLOPCIC[1], H. OSURU[1], A. ERISIR[3], S. TODOROVIC[1], V. JEVTOVIC-TODOROVIC[1];
[1]Anesthesiol., Univ. of Virginia Hlth. Syst., Charlottesville, VA; [2]Anesthesiol., Univ. of Virginia, Undergraduate Program, Charlottesville, VA; [3]Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: Objectives: Although numerous studies have focused on the morphological fate of neurons dying acutely by general anesthesia (GA)-induced developmental apoptosis, the long lasting effects of an early exposure to GA on the synaptic transmission of surviving neurons remain unclear. Thus, we set out to study 1) Whether an early exposure to GA causes functional

impairment of surviving synapses by disrupting synaptic transmission and/or short-term plasticity 2) Whether exposure to GA impairs the fine regulation of the dynamic spatial organization and trafficking of synaptic vesicles in developing pre-synaptic terminals. Methods: We exposed post-natal day 7 (PND7) rat pups, at the peak of their brain development, to a clinically relevant anesthetic combination of midazolam, nitrous oxide and isoflurane. In the rat subiculum, an area of the hippocampal complex that is crucial for learning and short-term memory, we performed 1) Whole cell patch clamp recordings of evoked excitatory postsynaptic currents (eEPSCs) and paired-pulse depression from PND8 to PND15 and 2) Detailed ultrastructural analysis of the synaptic vesicle architecture of pre-synaptic terminals at PND12. Results: I. Early GA impairs excitatory synaptic transmission and short term plasticity in the developing subiculum. GA-treated rats show a trend towards smaller amplitudes of EPSCs in response to increasing stimulus strengths compared to sham control animals and a significant decrease in paired-pulse ratio ($p<0.05$). II. Early GA disrupts the trafficking of synaptic vesicles in pre-synaptic terminals of the developing subiculum. In addition to a significant decrease in the density of pre-synaptic vesicles ($p<0.05$), we observe a reduction of docked vesicles ($p<0.01$), as well as a reduction of vesicles located within 100 nm from the active zone ($p<0.05$), in animals five days after an initial exposure to GA. We also find that the synaptic vesicles of animals exposed to GA are located more distally with respect to the plasma membrane than those of sham-control animals ($p<0.05$), and that the distance between pre-synaptic vesicles is increased in GA-exposed animals compared to sham-controls ($p<0.01$). Conclusions: We conclude that GA-induced long lasting effects on the synaptic transmission of surviving neurons are marked by significant morphological disturbances of the spatial organization and trafficking of synaptic vesicles, as well as impairment of excitatory synaptic transmission and short-term plasticity. This may contribute to the learning and memory deficits that occur after exposure of the immature brain to anesthesia.

Disclosures: **N. Lunardi:** None. **M. Prillaman:** None. **A. Oklopcic:** None. **H. Osuru:** None. **A. Erisir:** None. **S. Todorovic:** None. **V. Jevtovic-Todorovic:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.05

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NICHD R01-HD068388

Icahn School of Medicine at Mount Sinai Department of Anesthesiology

Title: Motivation to work for food two years following neonatal sevoflurane administration in rhesus monkeys

Authors: *J. C. DE BIASIO[1,2], P. G. BROWNING[1], S. W. BROOKSHIRE[1], M. C. ALVARADO[3], M. G. BAXTER[1,2];
[1]Neurosci., [2]Anesthesiol., Icahn Sch. of Med. At Mount Sinai, New York, NY; [3]Yerkes Natl. Primate Res. Ctr., Atlanta, GA

Abstract: Anesthesia delivered early in life has been shown to have long-term effects on cognition and memory in rodents and has been correlated with increased risk of learning disabilities in humans. One study in rhesus monkeys that received a 24-hour ketamine anesthetic on postnatal days 5 or 6 found that these monkeys had less motivation to work for food later in development (Paule et al., Neurotoxicol Teratol 2011), potentially confounding other results within the study that were dependent on food reward. In our long-term study of cognitive and socioemotional development in rhesus monkeys exposed to sevoflurane as infants, we sought to determine motivation to work for food at approximately 30 months of age, in advance of testing these monkeys on cognitive tasks in which food rewards are delivered. The present study was a randomized controlled trial conducted across two cohorts each of 10 rhesus monkeys randomized to an experimental group of 10 monkeys (5 male, 5 female) that were anesthetized with sevoflurane three times for four hours each on postnatal day 6-10 and again 14 and 28 days later, and a control group of 10 (5 male, 5 female) that were briefly separated from their mothers at matching time points. At approximately 30 months of age, the first cohort of monkeys was trained to use a touchscreen apparatus and touch objects (alphanumeric characters) presented on the screen with a fixed ratio of one accurate response required per food reward given. Their motivation to work for a food reward was subsequently assessed using a progressive ratio task in which the required number of accurate responses required for a reward doubled every eight rewards given, beginning with one response required. The session was completed when no response was given for two minutes. Preliminary results for the first cohort of five sevoflurane-treated monkeys and five control monkeys demonstrated no group differences in motivation to work for a food reward on any measure. Thus, sevoflurane anesthesia early in life does not appear to have a long-term effect on motivation to work for food reward in rhesus monkeys. Subsequent cognitive tests with these monkeys may be interpreted with less concern for motivational confounds. Moreover, deficits in primary motivation do not appear to be a consistent part of the phenotype of long-term neurocognitive impairments after early-life anesthesia.

Disclosures: J.C. De Biasio: None. **P.G. Browning:** None. **S.W. Brookshire:** None. **M.C. Alvarado:** None. **M.G. Baxter:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.06

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NICHD Grant R01-HD068388

ORIP P51OD11132 (formerly funded by NCRR P51RR000165) to Yerkes NPRC

Title: Memory assessment in juvenile rhesus macaques following multiple sevoflurane exposures in infancy

Authors: *M. C. ALVARADO[1], K. L. MURPHY[2], M. G. BAXTER[3];
[1]Yerkes NPRC/Emory Univ., Atlanta, GA; [2]Dept. Biomed. Serv., Univ. of Oxford, Oxford, United Kingdom; [3]Neurosci., Anesthesiol.,, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Children who received more than one general anesthetic before the age of 4 are at a greater risk of learning disability directly related to the number of anesthetic exposures. We recently reported that infant rhesus macaques show similar vulnerability to multiple sevoflurane exposures during the first month of life. Specifically, we have shown changes in socioemotional behavior and stress hormone regulation (see Raper et al., this session) as well as evidence of a mild memory impairment evident during the first year of life (Alvarado et al., Soc. Neurosci. 846.19.2014). The present report assessed the permanence and magnitude of that early cognitive impairment in the now juvenile monkeys at 2 years of age. Subjects were two cohorts of infants (n=20, 10 males) who received either 3, 4-hour exposures to 2.5% sevoflurane at 1, 3, and 5 weeks of age (Anesthesia Group), or a brief maternal separation at the same ages (Control Group). The infants were returned to their dams following each procedure and were reared in large social groups at the Yerkes National Primate Research Center. Beginning at six months of age, and over their first 24 months of life, they were tested on the visual paired comparison task (VPC) using color images of everyday objects and delays of 10, 30, 60 & 120 s. We previously reported that at 6 and 12 months, subjects in the Anesthesia group performed at chance at the 120 s delay. Preliminary results from all subjects show similar results, namely a trend towards chance performance for the Anesthesia group at the 60 and 120 s delays. These findings suggest a persistent impairment in medial temporal lobe-dependent memory following multiple postnatal exposures to anesthesia, lasting at least to an age (2 years) in monkeys equivalent to the beginning of formal schooling in children (6 years).

Disclosures: M.C. Alvarado: None. **K.L. Murphy:** None. **M.G. Baxter:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.07

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH GM098308

Title: A Critical role of matrix metallopeptidase 9 in postoperative neuroinflammation and cognitive dysfunction

Authors: *Z. ZUO[1], J. BI[2];
[1]Dept of Anesthesiol, Unvi of VA, Charlottesvle, VA; [2]Univ. of Virginia, Charlottesville, VA

Abstract: Postoperative cognitive dysfunction (POCD) is an established clinical syndrome. Neuroinflammation is an important pathological process for POCD. However, the molecular mechanism for the transmission of surgery-induced inflammation in the peripheral tissues to the brain is not clear. Matrix metallopeptidase 9 (MMP9) is a collagenase that can affect blood-brain barrier. Our previous study suggests that surgery may activate MMP9. We hypothesize that MMP9 plays a critical role in allowing the transmission of inflammation in peripheral tissues to the brain. To test this hypothesis, 8 week old C57 male mice were subjected to carotid artery exposure under isoflurane anesthesia. This surgery induced neuroinflammation and impairment of learning and memory. The permeation of blood-brain barrier was increased. These effects did not appear in the mice with MMP9 knockout. These results suggest that MMP9 plays a critical role in allowing transmission of inflammation in the peripheral tissues to the brain and the development of POCD.

Disclosures: Z. Zuo: None. **J. Bi:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.08

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01 HD044517 (NIH/NICHD) (to VJT)

R01 HD044517S (NIH/NICHD) (to VJT)

R21 HD 080281 (NIH/NICHD) (to VJT)

March of Dimes National Award (to VJT)

Harold Carron Endowment (to VJT);

R01 GM102525 (to SMT).

Title: General anesthesia causes epigenetic histone modulation of target genes important for neuronal development in the immature rat hippocampus

Authors: *H. OSURU[1], L. DALLA MASSARA[1,2], D. MILANOVIC[1,3], A. OKLOPCIC[1], V. JEVTOVIC-TODOROVIC[1];
[1]Anesthesiol., Univ. of Virginia Hlth. Systems, Charlottesville, VA; [2]Dept. of anesthesia and intensive care Univ. of Padua, Padua, Italy; [3]Dept of neurobiology,Institute for Bioligical research,University of Belgrade, Belgrade, Serbia

Abstract: Objective: Early postnatal exposure to general anesthesia (GA) causes impairment of an early brain development. Numerous studies have shown an association between neuronal impairments caused by GA exposure during critical stages of synaptogenesis and long-term cognitive impairments later in life. Of particular interest for this study is an older finding which suggests that *in utero* exposure of rodents to GA causes cognitive impairments in the first- as well as the second-generation offspring never exposed to GA. This begs the possibility that transient exposure to GA during critical stages of synaptogenesis causes epigenetic changes in chromatin that could be damaging to transcription of target genes crucial for proper synapse formation and ultimately for cognitive development. We focus on the effects of GA on histone acetylase (HAT) activity of cAMP-responsive element binding protein (CREB) Binding Protein (CBP) and the histone (H) 3 acetylation status in the promoters of target genes, BDNF and c-fos known to regulate the development of neuronal morphology and function. Methods: Our *in vivo* method used 7 day-old rat pups exposed to our routine protocol containing sedative dose of midazolam (9 mg/kg, sc) followed by a combined nitrous oxide (70-vol%) and isoflurane (0.75-vol%) anesthesia for 6 hours. Our *in vitro* method used cultured hippocampal neurons and organotypic hippocampal slice culture that were exposed to midazolam, isoflurane and nitrous oxide for 24 hours. Results: GA causes epigenetic modulations manifested as H3 hypoacetylation and the fragmentation of CBP with the impairment of its HAT activity. Importantly, in addition to global H3 hypoacetylation, GA promotes the hypoacetylated status of H3 in CREB binding sites of the promoter regions of two target genes of interest, c-fos and BDNF as shown with individual loci-specific ChIP assays. H3 hypoacetylation results in more condensed chromatin structure leading to downregulated transcription of the important target

genes, BDNF and c-fos. Reversal of histone hypoacetylation with global histone deacetylase (HDAC) inhibitor, sodium butyrate, reversed GA-induced morphological and functional impairments of neuronal development and synaptic communication. Conclusions: We suggest that the long-term impairments of neuronal development and synaptic communication we and others have been reporting for over a decade could be caused by GA-induced post-translational modification of H3 acetylation status. It is highly likely that histone hypoacetylation is not the only one that could explain a myriad of changes in neuronal development and communication that occur post-GA exposure.

Disclosures: H. Osuru: None. **L. Dalla Massara:** None. **D. Milanovic:** None. **A. Oklopcic:** None. **V. Jevtovic-Todorovic:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.09

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01 GM107469

Title: Ampakine CX546 rescues anesthesia-induced learning and synaptic deficits by promoting post-anesthesia neuronal activity

Authors: *G. YANG, L. HUANG, J. CICHON;
New York Univ. Sch. of Med., New York, NY

Abstract: General anesthesia is commonly used for surgical operations in infants and young children. Recent studies have indicated that repeated and prolonged anesthetic exposure, during the period of extensive synaptogenesis, leads to neuronal and behavioral deficits later in life. It is therefore important to develop strategies to mitigate the neurotoxic effects of anesthesia on brain development. By performing *in vivo* two-photon calcium imaging, we have found that ketamine anesthesia causes a prolonged and significant reduction in neuronal activity of layer 5 pyramidal neurons in the mouse motor cortex. Administration of an ampakine drug, CX546, during the period of post-anesthesia recovery restores neuronal activity and prevents neonatal anesthesia-induced long-term motor learning deficits. Additionally, we found mice repeatedly exposed to ketamine display multiple defects in the motor cortex, including decreased synaptic expression of NMDA and AMPA receptor subunits, reduced running-evoked neuronal activity and decreased dendritic spine remodeling associated with motor learning. Administration of CX546

after ketamine anesthesia ameliorated these synaptic structural and functional deficits. Together, our results indicate that pharmacologically enhancing neuronal activity during the post-anesthesia recovery period could be an important strategy for reducing the adverse effects of childhood anesthesia.

Disclosures: **G. Yang:** None. **L. Huang:** None. **J. Cichon:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.10

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant GM088801

NIH Grant AG041274

Title: Anesthetic isoflurane induces apoptosis by separating the binding of CypD, ANT and VDAC in Caenorhabditis elegans

Authors: C. LI, Y. DONG, Y. ZHANG, *Z. Z. XIE;
Massachusetts Gen. Hosp. and Harvard Med. Sch., Charlestown, MA

Abstract: Anesthetic isoflurane has been reported to promote Alzheimer's disease neuropathogenesis by inducing apoptosis, which may then lead to the accumulation of β-amyloid *in vitro* and *in vivo* 1-4. However, the mechanism by which isoflurane induces apoptosis remains largely to be determined. Therefore, we extended the isoflurane studies to Caenorhabditis elegans (*C. elegans*), an established model to study apoptosis and toxicity. Specifically, we determined whether isoflurane could induce apoptosis via the interaction with Cyclophilin D (CypD), adenine nucleotide translocase (ANT) and Voltage-dependent anion channel (VDAC), the components of mitochondrial permeability transition pore (mPTP) 5, in the *C. elegans*. 7% Isoflurane (100% EC50) for 2 or 4 hours was delivered to the wild type *C. elegans* with pretreatment of control condition, mPTP inhibitor cyclosporine A, or RNA interference of CypD, ANT or VDAC, as well as in the *C. elegans* with the ced-9 (n1950) mutation. We found that isoflurane induced apoptosis and decreased survival rate, lifespan, egg laying, body movement, and body size in the *C. elegans* with treatment time dependent manner. Moreover, co-immunoprecipitation technology showed that the treatment with isoflurane for 4, but not 2, hours separated the binding of CypD, ANT and VDAC to each other. These isoflurane-induced

changes were inhibited by the treatment of cyclosporine A and RNA interference of CypD, ANT or VDAC, as well as ced-9 (n1950) mutation. These data suggested that isoflurane could induce apoptosis via opening mPTP by separating the components of mPTP. The isoflurane-induced apoptosis might cause toxic effects in *C. elegans*, leading to reduction in survival rate. The on-going studies include the investigation of the mechanism by which isoflurane interacts with CypD, ANT or VDAC in the *C. elegans*. References 1.Eckenhoff RG, Johansson JS, Wei H, et al. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. Anesthesiology. 2004;101(3):703-709. 2.Xie Z, Dong Y, Maeda U, et al. The inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid beta-protein accumulation. J Neurosci. 2007;27(6):1247-1254. 3.Xie Z, Culley DJ, Dong Y, et al. The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid beta-protein level *in vivo*. Ann Neurol. 2008;64(6):618-627. 4.Zhang Y, Xu Z, Wang H, et al. Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. Ann Neurol. 2012;71(5):687-698. 5.Fulda S, Galluzzi L, Kroemer G. Targeting mitochondria for cancer therapy. Nat Rev Drug Discov. 2010;9(6):447-464.

Disclosures: **C. Li:** None. **Y. Dong:** None. **Y. Zhang:** None. **Z.Z. Xie:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.11

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant K08-GM073224

NIH Grant R01-GM084979

NIH Grant 3R01GM084979-02S1

NIH Grant 2R01GM084979-06A1

Title: Propofol regulates autophagy and cell survival by its effects on intracellular calcium homeostasis

Authors: Y. ZHOU[1,2], G. REN[1], Y. LI[1], S. LI[2], *H. WEI[1];
[1]Dept Anethesiol & Critical Care, Univ. Pennsylvania, Philadelphia, PA; [2]Anesthesiol., Shanghai First People's Hospital,Jiaotong Univ., Shanghai, China

Abstract: Our previous studies have demonstrated that inhalational anesthetics may cause cell death via over activation of the $InsP_3R$ calcium channel on the membrane of the endoplasmic reticulum (ER). We investigated effect of propofol on cell survival through activation of type 1 $InsP_3R$ ($InsP_3R$-1), and its association with regulation on autophagy. Chicken B lymphocytes with all three $InsP_3R$ isoforms knocked out (DT40-TKO) or TKO expressed with rat recombined $InsP_3R$-1 were treated with propofol at various concentrations for 24 hrs in the presence or absence of regulators on intracellular Ca^{2+} homeostasis and autophagy. MTT reduction assay was measured to determine cell viability. Western blot was used to determine the expression of LC_3-II, a biomarker reflecting the autophagy activity. Two-way ANOVA was used to analyze the data. Propofol dose-dependently reduced cell viability in both type of cells with R1 cells slightly more vulnerable to propofol toxicity at high concentrations. BAPTA-AM, an inhibitor of cytosolic Ca^{2+} ($[Ca^{2+}]_c$) elevation, dose-dependently decreased cell viability in R1 but not in TKO cells, suggesting a baseline level of $[Ca^{2+}]_c$ supported by activation of $InsP_3R$-1 is required to maintain cell survival, which may be altered in TKO cells. BAPTA-AM dose-dependently potentiated propofol-induced cell death in both types of cells, but more remarkably in TKO than in R1 cells, suggesting elevation of $[Ca^{2+}]_c$ via $InsP_3R$-1 activation play important role in propofol induced cell damage. The autophagy stimulator rapamycin dose- and time-dependently decreased cell viability in both cells, but more remarkably in R1 cells. Autophagy inhibitor 3-MA significantly potentiated propofol induced toxicity in TKO but not R1 cells. Propofol dose-dependently increased autophagy biomarker LC_3-II more in R1 than in TKO cells, which was augmented by impairment of autophagy flux with bafilomycin, suggesting that propofol treatment for short time (2.5 hours) induced the activation of autophagy. Overall, these results suggest that autophagy activity play an important role in propofol induced cytotoxicity, which may be associated with activation of $InsP_3R$-1.

Disclosures: **Y. Zhou:** None. **G. Ren:** None. **Y. Li:** None. **S. Li:** None. **H. Wei:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.12

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NICHD Grant R01-HD068388

NIH Grant P51-OD011132

Title: Basal rhythm and stress reactive cortisol responses in infant rhesus monkeys after multiple anesthetic exposures

Authors: *J. RAPER[1,2], K. L. MURPHY[3], J. M. JOHNSON[1], M. G. BAXTER[4], M. C. ALVARADO[1];
[1]Emory Univ., Yerkes Natl. Primate Res. Ctr., Atlanta, GA; [2]Psychology, Emory Univ., Atlanta, GA; [3]Exptl. Psychology, Oxford Univ., Oxford, United Kingdom; [4]Neurosci. and Friedman Brain Inst., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Between 50-80% of children exhibit immediate negative behavior changes after exposure to general anesthetics (GA), and nearly 16% of children exhibit increased anxiety for up to 6 months after GA exposure (Stipic et al, 2014, Eur J Anaesthesiol). Evidence from animal studies suggest that early life exposure to GA causes neurotoxic damage to the developing brain and impairs cognition in adulthood (Jevtovic-Todorovic et al, 2003, J Neurosci; Satomoto et al, 2009, Anesthesiol). Although neurotoxic damage is widespread, medial temporal lobe structures, such as the amygdala and hippocampus, are particularly sensitive to GA exposure. We have previously shown that rhesus monkeys exposed to 4-hours of sevoflurane (Sevo) anesthesia at postnatal day 6-10 and repeated 14 and 28 days later, exhibit increased anxiety-like behaviors on the Human Intruder (HI) paradigm at 6 months of age. The current study shows that although Sevo exposed monkeys exhibit increased anxiety, they have a lower cortisol response to the HI paradigm as compared to controls. Interestingly, multiple Sevo exposures only impacted cortisol stress reactivity and did not impact the basal cortisol rhythm. These data are similar to findings of a blunted cortisol reactivity, but increased anxiety, in patients with hippocampal damage (Buchanan et al, 2009, Horm Beh). Thus, the current data suggest that multiple Sevo exposures may have directly impacted hippocampal development, resulting in altered emotional and hormonal responses to an acute stressor.

Disclosures: J. Raper: None. **K.L. Murphy:** None. **J.M. Johnson:** None. **M.G. Baxter:** None. **M.C. Alvarado:** None.

Nanosymposium

744. Perioperative Neurotoxicty

Location: S404

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 744.13

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01 HD044517 (NIH/NICHD) (to VJT)

R01 HD044517S (NIH/NICHD) (to VJT)

R21 HD 080281 (NIH/NICHD) (to VJT)

March of Dimes National Award (to VJT)

Harold Carron Endowment (to VJT)

R01 GM102525 (to SMT)

Title: Long-lasting impulsivity, novelty seeking and hyperactivity with anxiety-like behavior in rats after early exposure to anesthesia

Authors: *P. DIANA[1,2], A. OKLOPCIC[2], S. JOKSIMOVIC[2], H. OSURU[2], C. ORI[1], V. JEVTOVIC-TODOROVIC[2];
[1]Anestesiologia e Terapia Intensiva, Univ. degli Studi di Padova, Padova, Italy; [2]Anesthesiol., Univ. of Virginia Hlth. Syst., Charlottesville, VA

Abstract: OBJECTIVES General anesthesia (GA) is toxic to the developing brain of several mammalian species. Although the impairment of social interaction has been described, many behavioral consequences of an early exposure to anesthesia remain unclear. Thus, we sat out to explore the behavioral consequences of an early exposure to GA, specifically with regard to its impact on animals' interaction with the environment. METHODS Rat pups were randomly assigned to two treatment groups at post-natal day 7 (the peak of brain development). The GA group received a well-established neurotoxic anesthesia protocol (Midazolam 9mg/kg i.p. + 6 hr of Isoflurane 0.75%, Nitrous Oxide 70% and Oxygen 30%). The Sham control group was exposed to a mock treatment (vehicle i.p. + 6 hr of room air + separation from the mother). Animals were subjected to the Open Field, Elevated Plus Maze and Social Novelty tests at 5 and 9 weeks, 4 and 11 weeks and 12 weeks of age, respectively. Test sessions were recorded and analyzed using Anymaze software. RESULTS Open Field Test. GA-exposed animals did not show any difference in the total distance travelled during the Open Field Test vs control rats, indicating no impairment in motor function. In the Open Field Test at 9 weeks of age, GA-exposed female animals unlike males, showed a significant increase in the time spent in the middle area of the arena ($p<0.05$), as well as a significantly decreased latency to first enter into that area ($p<0.05$), compared to age-matched controls, suggesting increased impulsivity in females. Elevated Plus Maze Test. GA-exposed female animals but not males exhibited a decrease in the time spent in the open arms of the Elevated Plus Maze when tested at 11 weeks of age compared to controls ($p<0.05$), suggesting an increased level of anxiety. Social Novelty Test. During the first part of the experiment (unknown animal vs empty cage), GA-exposed female but not male rats exhibited an increased number of crossings between the three chambers of the apparatus compared to same sex controls ($p<0.05$), suggesting hyperactive behavior. During the second part (known animal vs novel animal), female but not male GA rats showed a significantly increased number of explorations of the novel-animal ($p<0.05$), suggesting novelty

seeking behavior. The Social Novelty Index also confirmed a trend towards an increased exploration of the novel-animal by both female and male rats exposed to GA. CONCLUSIONS A single exposure to GA during critical stages of brain development induces sex-and age-dependent changes in rats behavior relative to their interaction with the environment, indicating increased impulsivity, novelty seeking and hyperactivity with anxiety.

Disclosures: P. Diana: None. **A. Oklopcic:** None. **S. Joksimovic:** None. **H. Osuru:** None. **C. Ori:** None. **V. Jevtovic-Todorovic:** None.

Nanosymposium

745. New Findings in Neural Mechanism of Addiction

Location: S401

Time: Wednesday, October 21, 2015, 1:00 PM - 3:15 PM

Presentation Number: 745.01

Topic: C.17. Drugs of Abuse and Addiction

Support: DA025785

DA004398

MH91427

Title: 5-HT_{1A} autoreceptors in the dorsal raphe nucleus convey vulnerability to compulsive cocaine seeking

Authors: *I.-J. YOU[1], R. ZHAO-SHEA[1], G. F. KOOB[2,3], D. E. LEONARDO[4,5], L. M. BOHN[6], S. WEE[6], A. R. TAPPER[1], P. D. GARDNER[1];
[1]Brudnick Neuropsychiatric Res. Institute, Dept. of Psychiatry, Univ. of Massachusetts Med. Sch., Worcester, MA; [2]Committee on the Neurobio. of Addictive Disorders, The Scripps Res. Inst., La Jolla, CA; [3]Natl. Inst. on Alcohol Abuse and Alcoholism, Rockville, MD; [4]Dept. of Psychiatry, Columbia Univ., New York, NY; [5]New York State Psychiatric Inst., New York, NY; [6]Dept. of Mol. Therapeut., The Scripps Res. Institute-Florida, Jupiter, FL

Cocaine addiction and depression are comorbid disorders. While it is well recognized that 5-Hydroxytryptamine (5-HT; serotonin) plays a central role in depression, our understanding of its role in addiction is notably lacking. The 5-HT system in the brain is carefully controlled by a combined process of regulating 5-HT neuron firing through 5-HT autoreceptors, neurotransmitter release, enzymatic degradation, and reuptake by transporters. The present study tests the hypothesis that activation of 5-HT_{1A} autoreceptors, which would lessen 5-HT neuron firing, contributes to cocaine seeking behaviors. Using 5-HT neuron-specific reduction of 5-

HT_{1A} autoreceptor gene expression in mice, we demonstrate that 5-HT_{1A} autoreceptors are necessary for cocaine conditioned place preference. Additionally, using designer receptors exclusively activated by designer drugs (DREADDs) technology, we found that stimulation of the serotonergic dorsal raphe nucleus (DRN) afferents to the nucleus accumbens (NAc) abolishes cocaine reward and promotes anti-depressive-like behaviors. Lastly, using a rat model of compulsive-like cocaine self-administration, we found that inhibition of dorsal raphe 5-HT_{1A} autoreceptors attenuates cocaine self-administration in rats with 6 hour extended access, but not 1 hour access to the drug. Therefore, our findings suggest an important role for 5-HT_{1A} autoreceptors, and thus DRN→NAc 5-HT neuronal activity, in the etiology and vulnerability to cocaine reward and addiction. Moreover, our findings support a strategy for antagonizing 5-HT_{1A} autoreceptors for treating cocaine addiction.

Disclosures: I. You: None. **R. Zhao-Shea:** None. **G.F. Koob:** None. **D.E. Leonardo:** None. **L.M. Bohn:** None. **S. Wee:** None. **A.R. Tapper:** None. **P.D. Gardner:** None.

Nanosymposium

745. New Findings in Neural Mechanism of Addiction

Location: S401

Time: Wednesday, October 21, 2015, 1:00 PM - 3:15 PM

Presentation Number: 745.02

Topic: C.17. Drugs of Abuse and Addiction

Support: K08 DA036657

Leon Levy Fellowship

R01MH054671

1U01NS090526-01

1U01NS090583-01

R01MH102840

Title: Selective plasticity of connections between hippocampus and nucleus accumbens is a neural substrate of cocaine conditioned place preference

Authors: *L. L. SJULSON, D. CASSATARO, V. WOO, A. CUMPELIK, G. BUZSAKI; NYU Sch. of Med., New York, NY

Abstract: Cocaine conditioned place preference (CPP) has been used extensively to demonstrate the rewarding properties of cocaine and as a preclinical assay to evaluate the potential therapeutic effects of various drugs or interventions. However, the actual neural mechanisms underlying CPP have never been established conclusively. Based on silicon probe recordings and optogenetic manipulation of synaptic plasticity in awake behaving mice, our results suggest that a key substrate of CPP is the selective strengthening of specific synapses between the hippocampus, which encodes spatial location, and the nucleus accumbens, a brain region implicated in reward processing. Results from this study are likely to yield insight not only into CPP itself, but also into the more general role of selective corticostriatal plasticity in cocaine addiction.

Disclosures: L.L. Sjulson: None. **D. Cassataro:** None. **V. Woo:** None. **A. Cumpelik:** None. **G. Buzsaki:** None.

Nanosymposium

745. New Findings in Neural Mechanism of Addiction

Location: S401

Time: Wednesday, October 21, 2015, 1:00 PM - 3:15 PM

Presentation Number: 745.03

Topic: C.17. Drugs of Abuse and Addiction

Support: Grants-in-Aid for Scientific Research (15K19164)

Title: Persistent reduction of MHC-I in dopamine neurons underlies enduring potentiation of its synaptic inputs in cocaine-seeking behavior

Authors: *G. MURAKAMI[1], M. EDAMURA[1], T. FURUKAWA[2], A. FUKUDA[2], T. IWASHITA[3], D. NAKAHARA[4];
[2]Neurophysiol., [3]Regenerat. Infect. Patho, [4]Psychiatry, [1]Hamamatsu Univ. Sch. Med., Shizuoka, Japan

Abstract: MHC class I (MHCI), an important immune protein, is expressed in the brain that has long been designated as an immune privilege region. This protein plays an important role in the modulation of synaptic plasticity such as elimination of long-term depression and enhanced long-term potentiation, resulting in the enhanced synaptic connections. Dysfunction of MHCI leads to exaggerated synaptic connections in various brain regions, resulting in abnormal brain functions. However, the contribution of MHCI to brain reward functions remains unknown. By employing our novel drug self-administration system, we found that MHCI is important for the regulation of synaptic transmission in dopamine neurons and its deficiency underlies robust cocaine-seeking

behavior. In wild-type mice, cocaine intakes lead to persistent reduction of MHCI expression specifically in dopamine neurons. This reduction is accompanied with enhancement of its synaptic inputs, as represented by AMPA/NMDA receptors ratio as well as the expression of dopamine-related genes, both of which are major pathogenesis of robust cocaine-seeking behavior. MHCI deficiency further potentiated these increases, resulting in exaggerated cocaine-seeking behavior. In the analysis of the mechanism behind this potentiation, MHCI deficiency amplified cocaine-induced increase of AMPA receptor-associated functions such as mEPSC amplitude and spine head diameter. In addition, deficiency of MHCI cocaine-independently enhanced NMDA-induced current, mEPSC frequency and spine density, which are associated with NMDA receptor function. In contrast to knockout mice, cocaine-seeking behavior was suppressed by over-expressing a gene of MHCI through recombinant AAV-2 specifically in dopamine neurons of wild-type mice. These results suggest that MHCI regulates synaptic transmission in dopamine neurons and its deficiency underlies robust cocaine-seeking behavior.

Disclosures: **G. Murakami:** None. **M. Edamura:** None. **T. Furukawa:** None. **A. Fukuda:** None. **T. Iwashita:** None. **D. Nakahara:** None.

Nanosymposium

745. New Findings in Neural Mechanism of Addiction

Location: S401

Time: Wednesday, October 21, 2015, 1:00 PM - 3:15 PM

Presentation Number: 745.04

Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant DA006214

NIH Grant DA015369

NHMRC Grant 1072706

Title: A role for anterior cingulate cortex in mediating economic demand for cocaine

Authors: ***M. H. JAMES**, G. ASTON-JONES;
Rutgers Univ., Brain Hlth. Insitute, Piscataway, NJ

Abstract: Introduction: Anterior cingulate cortex (ACC) has been proposed to play a role in performance monitoring and guiding decisions about which actions are worth making (Shenhav et al., 2013). Neural activity in ACC differentiates between high and low reward sizes (Jung et al., 1998), and rats with ACC lesions consistently select actions that require less effort and result in smaller reward (Walton et al., 2002). Economic demand analysis in behavioral economics

offers a sensitive measure of how demand (motivation) for cocaine reward is affected by changes in 'price' (effort). Here, we assessed whether demand for cocaine reward is affected by manipulation of ACC activity. We also carried out single unit recordings in ACC during the behavioral economics paradigm to examine whether changes in cocaine 'price' are associated with changes in neural activity in this region. Methods: Rats were prepared with ACC-directed bilateral cannula or received bilateral ACC injections of the AAV-hSyn-HA-hM4D(Gi)-IRES-mCitrine inhibitory DREADD. Rats were trained to self-administer cocaine on the within-session behavioral economics demand curve paradigm (Bentzley et al., 2013). Once stable demand was achieved, rats received either intra-ACC infusions of baclofen/muscimol (B/M; 125µg/0.5µl/side), systemic injections of clozapine-N-oxide (CNO) or vehicle, and were again assessed for cocaine economic demand. A second group of rats were implanted bilaterally with recording wires in ACC and underwent training as above. Single unit recordings were conducted during behavioral economics demand analyses. Results: Inactivation of ACC by microinjections of B/M or systemic CNO treatment significantly reduced economic demand for cocaine (increased demand elasticity) as well as decreased the maximal effort animals were willing to expend to defend desired brain cocaine concentrations (Pmax). In contrast, ACC inactivation had no effect on free cocaine consumption or the desired brain level of cocaine (Qo). A subset of ACC cells showed increased phasic responses when higher effort was required to obtain cocaine reward. Further, ACC tonic activity declined rapidly following Pmax. Conclusions: Inactivation of ACC increased demand elasticity (reduced motivation) for cocaine reward but had no effect on free cocaine consumption (self-administration under low effort conditions). Neural activity of ACC appears to reflect changes in cocaine 'price', consistent with the view that this structure plays a role in performance and reward monitoring. Ongoing studies utilizing DREADDs are characterizing the pathways through which ACC regulates motivational responding for cocaine.

Disclosures: **M.H. James:** None. **G. Aston-Jones:** None.

Nanosymposium

745. New Findings in Neural Mechanism of Addiction

Location: S401

Time: Wednesday, October 21, 2015, 1:00 PM - 3:15 PM

Presentation Number: 745.05

Topic: C.17. Drugs of Abuse and Addiction

Support: NIDA R01

Title: Determining the contribution of nucleus accumbens glutamatergic afferents during addiction-related behaviors using Gi/o-coupled DREADDs

Authors: *A. M. WUNSCH[1,3], E. A. DONCKELS[3], L. M. YAGER[3], J. F. NEUMAIER[2], S. M. FERGUSON[2,3];
[1]Seattle Childrens Res. Inst., [2]Univ. of Washington, Seattle, WA; [3]Seattle Children's Res. Inst., Seattle, WA

Abstract: Repeated exposure to psychostimulant drugs produces dysfunction in corticostriatal circuits thought to underlie addiction. Alterations in glutamatergic signaling within the nucleus accumbens (NAc) may be particularly important in the development of addiction and also accompany psychomotor sensitization and self-administration behaviors. One predominant source of glutamate within the NAc arises from the prefrontal cortex (PFC). While the PFC has been implicated in the regulation of addiction, lesion studies have yielded conflicting results regarding its role. Incongruous findings may be due to PFC neurons projecting to several other brain regions that also regulate addiction behaviors as well as lack of temporal control of the manipulations, thus making it difficult to define the precise role of PFC afferents to NAc in addiction-related behaviors. In order to address these issues, we utilized a combinatorial chemogenetic approach to selectively modulate the activity of defined sets of glutamatergic afferents during the development of amphetamine sensitization. Rats received bilateral injections of a retrogradely transported canine adenovirus expressing cre-recombinase (cre) into NAc and an adeno-associated virus expressing cre-dependent, Gi/o-coupled hM4Di-DREADD (Designer Receptors Exclusively Activated by Designer Drugs) into PFC. Because hM4Di expression is restricted to PFC neurons projecting to NAc, we can selectively examine the role of Gi/o-signaling cascades in these neurons in the development of addiction behavior. We found that this manipulation attenuated the development of amphetamine sensitization and enhanced conditioned responses to the drug-taking environment following 2 weeks of abstinence. These results suggest that a dampening of cortical control over striatal circuitry may underlie the development of drug-induced behavioral plasticity and regulate responses to cues related to drug-taking. Follow-up studies will address the role of PFC neurons in cue-induced reinstatement following cocaine self-administration. In addition, because projection neurons originating in the thalamus provide the second largest source of glutamate into the NAc and their role in addiction-related behavior is unclear, we are currently examining the effect of increasing Gi/o-signaling cascades in thalamic afferents to NAc during psychomotor sensitization and cue-induced reinstatement of drug-seeking.

Disclosures: A.M. Wunsch: None. **E.A. Donckels:** None. **L.M. Yager:** None. **J.F. Neumaier:** None. **S.M. Ferguson:** None.

Nanosymposium

745. New Findings in Neural Mechanism of Addiction

Location: S401

Time: Wednesday, October 21, 2015, 1:00 PM - 3:15 PM

Presentation Number: 745.06

Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant K01DA031745

NIH Grant T32NS007433

NIH Grant T32DA031111

Title: Investigating a novel role for CaMKII signaling in the control of cocaine-associated memory

Authors: *M. T. RICH[1], M. M. TORREGROSSA[2];
[2]Psychiatry, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Disrupting cue-induced memories may reduce the risk of relapse and can be accomplished either by preventing reconsolidation of a reactivated memory or by extinction of the memory. Although extinction and reconsolidation involve similar neurobiological processes, there may be components of the two pathways that diverge, allowing the development of a single medication that simultaneously enhances extinction and inhibits reconsolidation. This treatment strategy would prevent unintentional strengthening of the drug-associated memory by reconsolidation, which is a common limitation to many previously tested medications. Using a discovery-based phosphoproteomics approach, we have previously identified a small number of candidate proteins in the BLA, including a phosphorylation site (serine 331) on calcium-calmodulin dependent kinase II alpha (CaMKIIα), that are differentially regulated by reconsolidation vs. extinction of a cue-evoked memory associated with self-administered cocaine. In the current studies, we have created site-specific phospho-deficient (S331A) and phospho-mimetic (S331E) CaMKIIα mutants and show that phosphorylation at this site regulates kinase activity. Furthermore, in rodents trained to self-administer cocaine, we reactivated the drug-cue memory via brief presentation of cues or extinguished the memory via multiple presentations of cues. We then infused KN-93 directly into the BLA to immediately inhibit CaMKII following the memory manipulations and show that CaMKII inhibition in the BLA enhances the extinction and inhibits the reconsolidation of cocaine-cue memories. Ongoing studies will seek to determine the structural effect of intra-BLA CaMKII inhibition by examining the time course of dendritic spine changes during cocaine-cue memory manipulations.

Disclosures: M.T. Rich: None. **M.M. Torregrossa:** None.

Nanosymposium

745. New Findings in Neural Mechanism of Addiction

Location: S401

Time: Wednesday, October 21, 2015, 1:00 PM - 3:15 PM

Presentation Number: 745.07

Topic: C.17. Drugs of Abuse and Addiction

Support: This work was supported by NIDA/NIH.

Title: Effect of the novel positive allosteric modulator of mGluR2 AZD8529 on incubation of methamphetamine craving after prolonged voluntary abstinence in a rat model

Authors: *D. CAPRIOLI, M. VENNIRO, T. ZERIC, L. XUAN, S. ADHIKARY, R. MADANGOPAL, N. J. MARCHANT, F. LUCANTONIO, G. SCHOENBAUM, J. M. BOSSERT, Y. SHAHAM;
Behavioral Neurosci., Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Background: Cue-induced methamphetamine craving increases after prolonged forced (experimenter-imposed) abstinence from the drug (incubation of methamphetamine craving). Here, we determined whether this incubation phenomenon would occur under conditions that promote voluntary (self-imposed) abstinence. We also determined the effect of the novel mGluR2 positive allosteric modulator, AZD8529, on incubation of methamphetamine craving after forced or voluntary abstinence. Methods: We trained rats to self-administer palatable food (6 sessions) and then to self-administer methamphetamine under two conditions: 12 sessions (9-hr/day) or 50 sessions (3-hr/day). We then assessed cue-induced methamphetamine seeking in extinctions test after 1 or 21 abstinence days. Between tests, the rats underwent either forced abstinence (no access to the food- or drug-paired levers) or voluntary abstinence for 19 days (achieved via a discrete choice procedure between methamphetamine and palatable food; 20 trials per day). We also determined the effect of subcutaneous injections of AZD8529 (20 and 40 mg/kg) on cue-induced methamphetamine seeking 1 or 21 days after forced or voluntary abstinence. Results: Under both training and abstinence conditions, cue-induced methamphetamine seeking in the extinction tests was higher after 21 abstinence days than after 1 day (incubation of methamphetamine craving). AZD8529 decreased cue-induced methamphetamine seeking on day 21 but not day 1 of forced or voluntary abstinence. Conclusions: We introduce a novel animal model to study incubation of drug craving and cue-induced drug seeking after prolonged voluntary abstinence, mimicking the human condition of relapse after successful contingency management treatment. Our data suggest that PAMs of mGluR2 should be considered for relapse prevention.

Disclosures: D. Caprioli: None. **M. Venniro:** None. **T. Zeric:** None. **L. Xuan:** None. **S. Adhikary:** None. **R. Madangopal:** None. **N.J. Marchant:** None. **F. Lucantonio:** None. **G. Schoenbaum:** None. **J.M. Bossert:** None. **Y. Shaham:** None.

Nanosymposium

745. New Findings in Neural Mechanism of Addiction

Location: S401

Time: Wednesday, October 21, 2015, 1:00 PM - 3:15 PM

Presentation Number: 745.08

Topic: C.17. Drugs of Abuse and Addiction

Support: R21DA032718

Title: Reinstatement of 3,4-methylenedioxypyrovalerone-seeking (mdpv) following intravenous self-administration and associated 50-khz ultrasonic vocalizations (usvs)

Authors: *L. R. WATTERSON[1], R. GREGG[2], S. J. SIMMONS[3], T. GENTILE[2], D. BARKER[4], J. W. MUSCHAMP[2], S. M. RAWLS[2];
[2]Ctr. for Substance Abuse Res., [1]Temple Univ. Sch. of Med., Philadelphia, PA; [3]Temple Univ. Sch. of Med., Center for Substance Abuse Research, PA; [4]Integrative Neurosci. Br., Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: 3, 4- methylenedioxypyrovalerone (MDPV) is an illicit synthetic cathinone that is widely abused in the United States and elsewhere. MDPV induces euphorogenesis and is readily self-administered in rodent models of substance abuse. Additionally, MDPV has been shown to reduce brain reward thresholds in intracranially self-stimulating animals. Together, these findings corroborate the extensive literature with other abused psychostimulants such as cocaine and amphetamine in demonstrating potent alterations in reward processing and, consequently, addiction liability. Accordingly, the abuse potential of MDPV has been attributed in part to its ability to inhibit the uptake of dopamine and norepinephrine. The present study was designed to further characterize the abuse liability of MDPV by assessing its effects on affective processing and reinstatement behaviors. Adult male Sprague-Dawley rats were trained to self-administer MDPV (0.056 mg/kg/inf) under a fixed-ratio 1 schedule of reinforcement in 2-hr daily sessions for 14 days. Active lever presses elicited a 2-sec infusion paired with a 2-sec stimulus tone + light complex conditioned stimulus (CS+). Following training, animals underwent daily context extinction trials until operant responding dropped to <25% of the mean of the final two days of self-administration sessions. Following extinction, animals were given reinstatement probe trials consisting first of CS+-only priming and then of combined CS+/drug priming. In addition to operant responses, ultrasonic vocalizations (USVs) were recorded and analyzed to assess changes in affective state during acquisition, extinction and reinstatement phases of MDPV self-administration. Results from the present study confirm that MDPV is robustly self-administered and also show that MDPV-seeking can be reinstated by both CS+ and CS+/drug priming. Further, acquisition of MDPV self-administration is associated with a relative predominance of

50-kHz positive affective USVs. This study adds to a growing body of evidence characterizing the abuse liability of MDPV and demonstrates reinstatement and affective processing changes in MDPV self-administering rats.

Disclosures: L.R. Watterson: None. **R. Gregg:** None. **S.J. Simmons:** None. **T. Gentile:** None. **D. Barker:** None. **J.W. Muschamp:** None. **S.M. Rawls:** None.

Nanosymposium

745. New Findings in Neural Mechanism of Addiction

Location: S401

Time: Wednesday, October 21, 2015, 1:00 PM - 3:15 PM

Presentation Number: 745.09

Topic: C.17. Drugs of Abuse and Addiction

Support: NIDA

Title: Cocaine-induced chromatin modifications are associated with increased expression and DNA looping of Auts2

Authors: *O. ENGMANN[1], B. LABONTE[1], A. MITCHELL[2], E. CALIPARI[3], D. BUREK[3], J. RABKIN[3], Y. L. HURD[4], S. AKBARIAN[2], E. J. NESTLER[1];
[1]Dept. of Neurosci. and Friedman Brain Inst., [2]Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Dept. of Neurosci. and Friedman Brain Inst., Sch. of Med. at Mount Sinai, New York, NY; [4]Icahn Sch. of Med. at Mount Sinai, Fishberg Dept. of Neurosci. and Friedman Brain Inst., New York, NY

Abstract: Exposure to drugs of abuse alters the epigenetic landscape of the brain's reward regions. We investigated how a combination of chromatin modifications (as previously measured by ChIP-sequencing) affects genes that are relevant for cocaine responses. Autism-candidate 2 (*Auts2*), a gene linked to human evolution and autism, is among the genes with the largest number of cocaine-induced chromatin modifications in the mouse nucleus accumbens (NAc). We observed by FACS sorting that *Auts2* mRNA expression is increased specifically in the NAc within D2-type medium spiny neurons of cocaine-injected mice. *Auts2* mRNA is also up-regulated postmortem in the NAc of human cocaine addicts. Additionally, by using chromatin conformation capture (3 and 4C) approaches, we obtained evidence that the *Auts2* gene forms a cocaine-inducible DNA-loop which enables *Auts2* to bind to and potentially regulate the expression of distal genes. We are currently characterizing the character and function of these genes after cocaine exposure. Our results may help to identify how a given gene can mediate a drug-induced phenotype at the mRNA as well as DNA level.

Disclosures: **O. Engmann:** None. **B. Labonte:** None. **A. Mitchell:** None. **E. Calipari:** None. **D. Burek:** None. **J. Rabkin:** None. **Y.L. Hurd:** None. **S. Akbarian:** None. **E.J. Nestler:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.01

Topic: D.04. Vision

Support: NN401 557640 from the Polish Ministry of Science and Higher Education

Title: Plasticity of the motion pathway in adult cats after central retinal lesions

Authors: ***K. BURNAT**[1], T.-T. HU[2], M. KOSSUT[1], U. T. EYSEL[3], L. ARCKENS[2]; [1]Nencki Inst., Warsaw, Poland; [2]Lab. of Neuroplasticity and Neuroproteomics, Univ. of Leuven, Leuven, Belgium; [3]Dept. of Neurophysiol., Ruhr Univ., Bochum, Germany

Abstract: Induction of focal central retinal lesions in both eyes leads to cortical map reorganization in the primary visual cortex of adult animals. Following the instant deactivation of the cortical lesion projection zone (LPZ), visual activity can be restored during the months following the lesion. The restoration of cortical activity depends on the distance from the LPZ, with far peripheral area 17, after an initial mild but significant activity reduction, achieving again normal signals by 3 months post-lesion (Hu et al., 2009). In accordance, injury to the central retina leads to the well-described acuity deficits, while the behavioral outcome for motion perception has not yet been examined. Here we verified the motion perception performance upon induction of binocular circular lesions (diameter ≈ 10 deg) centered over the area centralis in cats behaviorally naive prior to lesioning. In all motion tasks the S+ was composed of a circular random dot pattern consisting of dots moving coherently on a black background, or else in more difficult tasks composed of random dots, S- differed only in the motion domain (direction of movement or velocity). A previously described set of five global motion tasks was used, which progressively introduce perceptual difficulty (Zapasnik and Burnat, 2013). Overall, naive lesioned cats outperformed normal animals in all tested motion tasks. In particular, they were significantly faster in learning the easiest, global motion detection task as compared to normal not lesioned animals. Naive lesioned cats were also more sensitive to higher velocities of the stimuli and in tasks based on velocity discrimination. These behavioral findings corroborate with our preliminary data on molecular activity levels measured by means of real-time PCR for the immediate early gene zif268 in cat motion area PMLS, which exhibited an activity peak at 3

months post-lesion in naive lesioned animals. Thus, central retinal lesions may enhance the peripheral retina to better recruit the parts of the visual system devoted to fast analysis of motion stimuli.

Disclosures: K. Burnat: None. **T. Hu:** None. **M. Kossut:** None. **U.T. Eysel:** None. **L. Arckens:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.02

Topic: D.04. Vision

Support: NSF Grant 1157121

Title: Encodings of implied motion and object category in the two visual pathways

Authors: *Z. LU, M. MENG;
Dartmouth Col., Hanover, NH

Abstract: Motion perception is not isolated from object categorization and scene understanding. For example, although no direct motion signal is contained in still pictures, based on object recognition and knowledge about how things move, a sense of motion can be implied from a picture of running athlete or an object dropping off a shelf. Such implied motion is sufficient to activate the middle temporal cortex (Kourtzi & Kanwisher, 2000; Senior et al., 2000), where neurons are prototypically tuned to motion direction and speed. Moreover, animacy appears to be a major attribute that the visual system uses to represent object categories in the inferior temporal cortex (e.g., Chao, Haxby & Martin, 1999). These studies suggest a relationship between the dorsal "where" pathway and the ventral "what" pathway. However, to understand this relationship, this present study examines how implied motion and object category information are encoded, either similarly or differentially along the two visual pathways. FMRI was used to measure the neural activity corresponding to different animate and inanimate categories of still pictures (humans, animals, objects, and natural scenes) with different levels of perceived speediness (e.g., a sleeping baby, a walking man, and a running athlete). In both pathways, activity induced by pictures of humans and animals was only weakly modulated by the perceived speediness, as rated by human observers. In contrast, activity in these areas correlated with the rated levels of speediness for pictures of inanimate objects and scenes. Moreover, multivariate pattern analysis of activity in both pathways revealed significant effects of stimulus category but

not perceived speediness, although the effect of stimulus category decreased as the perceived speediness of implied motion increased. These results reveal a common organizing principle of object categorization corresponding to animacy in the dorsal pathway as well as in the ventral pathway, challenging the notion that information of object and scene categorization is only represented in the ventral pathway. Although averaged BOLD activity, rather than the activation patterns, was found to be correlated with the perceived speediness in implied motion, still pictures of fast moving inanimate objects/scenes evoked activation patterns that are difficult to differentiate from humans/animals, suggesting an important functional role of motion related information in encoding object categories. Together, these results provide insights to understand how motion and objects are represented conjunctively along the two visual pathways.

Disclosures: Z. Lu: None. **M. Meng:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.03

Topic: D.04. Vision

Support: NSF CRCNS Grant IIS-1309725

Title: Binocular models of 3D motion tuning in area MT built from direction and disparity selective V1 circuits

Authors: *P. M. BAKER, W. BAIR;
Dept. of Biol. Structure, Univ. of Washington, Seattle, WA

Abstract: Cortical area MT is a critical stage in the pathway underlying the perception of visual motion. Not only is MT known for the emergence of sensitivity to pattern motion, which is based on the integration of V1 inputs that represent motion of local oriented components, but recent studies have revealed that many MT neurons also respond well to 3D motion, or motion-in-depth (MID; Czuba et al., 2014; Sanada and DeAngelis, 2014). There are primarily two binocular cues for MID, interocular velocity differences (IOVD) and changing disparity (CD), but how these cues are combined to generate MID perception is unknown. While many models of MT have been proposed to explain how pattern motion sensitivity arises, these models are not binocular, and thus cannot address the origin of MID sensitivity. We have built binocular MT models that incorporate motion selectivity and binocular integration, including a binocular disparity computation. The models are image-computable to allow testing with diverse experimental

protocols, and have spiking output so that the relevant data analyses can be performed. We first built binocular MT models that were either component- or pattern-direction selective (CDS or PDS) in a framework without a disparity computation and found that the characteristic reduction in pattern sensitivity with dichoptic presentation of plaids can be explained by including monocular motion-opponent suppression in the circuit. The models predict that there must be motion-opponent suppression prior to binocular integration, with stronger opponency in PDS cells. Testing these models with the MID protocol of Czuba et al. exposed differences in the ability of CDS and PDS models to fit responses of the frontoparallel and 3D motion-tuned MT cells, predicting a link between pattern motion and MID sensitivity. We found that a motion-only model could also produce responses to the motion and disparity cue-isolating stimuli of Sanada and DeAngelis that are consistent with their results, with model units producing MID sensitivity from IOVD motion cues. We next included disparity computation at the stage of binocular integration. In models where motion and disparity tuning in MT are inherited jointly from V1 inputs, we found that direction tuning in CDS and PDS cells for motion may vary with disparity, with preferred direction reversing at non-preferred disparities. The binocular models have generated testable predictions concerning the ordering of motion and disparity computations that are necessary to satisfy constraints from diverse stimulus protocols, resulting in a more complete framework for building and testing MT circuits.

Disclosures: P.M. Baker: None. **W. Bair:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.04

Topic: D.04. Vision

Support: Hilldale Award for Undergraduate Research

Title: Optimal combination of the binocular cues to 3D motion

Authors: *B. ALLEN, A. M. HAUN, T. HANLEY, C. S. GREEN, B. ROKERS;
Psychology, Univ. of Wisconsin - Madison, Madison, WI

Abstract: Introduction The perception of stereoscopic 3D motion is based in two binocular cues: changes in binocular disparity over time (CD) and inter-ocular velocity differences (IOVD). Since these cues co-occur naturally, there is considerable debate regarding the extent to which observers rely on each cue. In 81 observers we tested sensitivity to either cue in isolation. This

allowed us to investigate sensitivity to these cues across the normal population and determine the degree of independence of CD and IOVD sensitivities. We also compared sensitivity to isolated versus combined-cue stimuli to investigate if and how observers combine the CD and IOVD cues under natural conditions. Methods In all conditions, participants fixated the center of a display, while we presented two dot arrays (above/below fixation), which moved in opposite directions in depth on each trial. The combined-cue stimulus consisted of dots matched for contrast and position in both eyes; the CD-cue stimulus randomly repositioned the dots on each screen refresh; the IOVD-cue stimulus used anti-correlated dots in the two eyes. Participants indicated which panel of dots appeared to move towards them. We estimated sensitivity by computing d′. Results Our results show considerable variation in sensitivity to the CD and IOVD cues across observers. Moreover, the sensitivity to these cues is largely independent. We further found that when the CD and IOVD cues are presented together, observers perform better than would be predicted based on their sensitivity to either cue alone. A model that assumed that the cues are processed independently and are optimally combined according to their reliability provided a good fit to the data. Discussion We assessed the extent to which the perception of stereoscopic 3D motion in depth is driven by binocular disparity and interocular velocity cues. Our results indicate that the perception of stereoscopic 3D motion relies on two relatively independent mechanisms. Observers can vary considerably in sensitivity to each cue, and ultimately combine the two cues in a statistically optimal fashion. While the neural basis for such variability in the normal population is currently unknown, these results help clarify the sometimes inconsistent findings across previous studies and laboratories. Those results may have been due to natural variability in the population, and the small sample sizes typical of intensive psychophysics.

Disclosures: **B. Allen:** None. **A.M. Haun:** None. **T. Hanley:** None. **C.S. Green:** None. **B. Rokers:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.05

Topic: D.04. Vision

Title: The neural correlates of 3D motion perception

Authors: *J. M. FULVIO[1], B. ROKERS[2];
[2]Psychology, [1]Univ. of Wisconsin - Madison, Madison, WI

Abstract: Introduction Recent work has established that in addition to processing 2D motion, neurons in area MT and its human analogue hMT+ occupy a central role in the signaling of specific 3D motion directions (Rokers et al., 2009, Czuba et al., 2014, Sanada & DeAngelis, 2014). It is currently unclear however, to what extent activity in hMT+ reflects either the presented or the reported direction of 3D motion. We used a motion adaptation paradigm similar to Rokers et al. (2009) to disentangle contributions of presented and reported 3D motion to the BOLD fMRI response. Methods Observers adapted to an array of dots continuously approaching or receding at 100% coherence for 90s. Then on each 7.5s trial they viewed the dots moving in the same adaptor direction for 4s, followed by a 1s probe in which the dots moved in the 'same' or 'opposite' direction as the adapter at 25% coherence. Observers judged the motion direction of the probe on each trial. We extracted the BOLD response to the probe stimuli in regions of interest (ROIs) including extrastriate area hMT+. We compared the average response between trials in which the probe moved in the opposite or same direction as the adaptor. Separately, in trials where the probe moved in the same direction as the adaptor, we compared the BOLD response based on the motion direction reported by the observer. Results Behavioral results: On ~66% of trials observers reported 3D motion consistent with the presented direction (and on ~44% of trials reports were inconsistent). Imaging results: In area hMT+, and to a lesser extent in earlier visual areas, activation was attenuated when the probe moved in the same direction as the adaptor compared to when the probe moved in the opposite direction. Importantly however, when considering only probe trials that moved in the same direction as the adapter, attenuation seemed to predominantly occur in those trials in which the observer reported that the probe moved in the same direction as the adaptor. Discussion These results indicate that the BOLD response in hMT+ and to some extent earlier visual areas depends in part on the perceived direction of 3D motion, rather than the presented direction. These results mirror the role of hMT+ in 2D motion perception (Kamitani & Tong, 2006; Serences & Boynton, 2007), with the exception that reported 3D motion direction seems to affect activity in earlier visual areas. These results therefore refine the role of hMT+ in motion perception and suggest that the resolution of ambiguity in 3D motion signals begins in early stages of visual processing.

Disclosures: **J.M. Fulvio:** None. **B. Rokers:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.06

Topic: D.04. Vision

Support: NIH Grant EY022443

Univ. of Wisconsin-Madison School of Medicine and Public Health

Wisconsin Alumni Research Foundation

Title: Encoding of multiple component directions of transparently moving stimuli by a subpopulation of neurons in macaque extrastriate area MT provides a plausible neural basis for perceptual direction repulsion

Authors: *X. HUANG[1], J. XIAO[2];
[1]Dept. of Neurosci., [2]Physiol. Grad. Training Program, Univ. of Wisconsin - Madison, Madison, WI

Abstract: Motion transparency refers to the perception of overlapping motion vectors in the same spatial region. The perceived angular separation (AS) between two component directions of transparently moving stimuli appears wider than the veridical AS when the veridical AS is ≤ 90° (Marshak & Sekuler 1979, Science 205:1399-1401). The neural mechanism underlying perceptual direction repulsion remains unclear. We investigated whether direction repulsion may result from how multiple motion directions are encoded in the direction tuning curves of neurons in extrastriate area MT of macaque. Visual stimuli were two overlapping random-dot patches moving in two directions separated by 60°. We recorded from ~200 neurons in area MT of two monkeys as they performed a fixation task. We varied the vector-averaged (VA) direction of the bi-directional stimuli to characterize the tuning curve. At the AS of 60°, the average of MT responses elicited by individual component directions typically contained a single response peak, located when the VA direction was at the neuron's preferred direction (PD). However, we found ~20% of the neurons showed two response-peaks in the tuning curves. The response peaks were reached when one component direction was near the PD. For this group of neurons, the mean AS between the two response peaks was 68° (std = 16°), significantly greater than the veridical AS of 60°. We also found that the separation between the two response peaks developed over time. The initial response tuning only contained a single peak, reached when the VA direction was at the PD. The two response-peaks emerged after 30-40 ms following the response onset. It took another 40-50 ms for the two peaks to separate farthest to ~80° and then the separation reduced to and remained at ~70°. To determine whether the whole tuning curve also supports direction repulsion, we fitted the tuning curve elicited by the bi-directional stimuli as a linear weighted summation of the neuronal responses elicited by the two unidirectional components, plus a multiplicative interaction term of the component responses. As a free parameter θ of the model, we allowed the AS between the two component response tuning curves elicited by unidirectional stimuli to vary from 0 to 180°. We found that, when θ was on average 71° (std = 22°), significantly greater than 60°, the model provided the best fit of the bi-directional responses. In conclusion, we found that the response tuning curves of a subpopulation of MT neurons are dynamically shaped and encode bi-directional stimuli in a way as if the component directions

were separated more than the actual AS. These results reveal a plausible neural basis for perceptual direction repulsion.

Disclosures: X. Huang: None. **J. Xiao:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.07

Topic: D.04. Vision

Support: Alfred P Sloan Foundation

Whitehall Foundation

Brain Research Foundation

NEI EY023371

Title: Rapid gain rescaling maximizes information about motion fluctuations in MT neurons and pursuit eye movements

Authors: *B. LIU, M. MACELLAIO, L. OSBORNE;
Neurobio. Dept., Univ. of Chicago, Chicago, IL

Abstract: In a rapidly changing world, the statistics of sensory stimuli can fluctuate across a wide range. Theoretically, in order to maximize the information sensory neurons can transmit, they should rescale their sensitivity dynamically, allocating their limited response bandwidth to the current range of inputs. Such adaptive coding has been observed in a variety of systems, but the theory that adaptation optimizes behavior has not been tested. Here we show that adaptive rescaling maximizes information about visual motion in cortical MT neurons and in pursuit eye movements guided by that cortical activity. We use time-varying motion signals that transition between different levels of variance as stimuli for extracellular recording of isolated, extrastriate cortical area MT neurons and as targets for pursuit tracking in monkeys. We find that adaptation drives a rapid (<100ms) recovery of motion information after steps in variance because the neurons and behavior rescale their sensitivity to motion fluctuations. At the cortical level we show that MT neurons adapt to a response gain that maximizes information about motion. At the level of behavior, we find that pursuit adapts to a gain that maximizes the mutual information between eye and target movements and that, very nearly, minimizes tracking errors. Thus

efficient sensory coding is not simply an ideal standard but rather a compact description of real sensory computation that manifests in improved behavioral performance.

Disclosures: **B. Liu:** None. **M. Macellaio:** None. **L. Osborne:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.08

Topic: D.04. Vision

Support: ARC Grant DE1411505

ARC Grant CE140100007

NHMRC Grant 1020839

NHMRC Grant 1083152

Title: Context-dependent robust coding of stimulus speed in primate extrastriate cortex

Authors: ***A. J. DAVIES**, M. G. P. ROSA, H.-H. YU;
Physiol., Monash Univ., Clayton, Australia

Abstract: The ability to estimate the speed of a moving object irrespective of its size, shape or texture is a crucial function of the visual system. However, in the middle temporal area (MT) - an area considered central to the analysis of motion signals in the primate visual cortex, neurons that show unambiguous tuning to motion speed appear to be rare. Instead, it has been reported that the vast majority of MT neurons are tuned to the temporal frequency of the stimulus. It follows that the speeds for eliciting maximal responses are dependent on the spatial frequency of the stimulus. Using single-unit electrophysiological recordings in anesthetized marmosets, we show that the ability for MT neurons to encode speed has been underestimated. Responses of MT neurons were compared in two situations: one in which sinusoidal patterns moved across the receptive field in predictable trajectories (moving grating), versus the traditional stimulus, in which sinusoidal patterns, stationed over the receptive field, modulates their spatial phases in time (drifting gratings). We found that approximately half the neurons showed spatial-frequency-invariant speed tuning when tested with moving gratings, but not drifting gratings. The ecologically more realistic motion signal, therefore, can reduce the ambiguity in the coding of motion speed. This context dependency was not evident in the primary visual area, suggesting

that speed-tuning emerges from computations performed in MT. These results support the notion that neuronal activity in MT provides accurate coding of speed in natural situations, and that nonlinear operations enable the history and context of visual stimuli to alter how motion information is processed in the brain.

Disclosures: **A.J. Davies:** None. **M.G.P. Rosa:** None. **H. Yu:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.09

Topic: D.04. Vision

Title: The visual motion stream: a speeded route distinct from the dorsal stream that serves a diversity of visual functions and supports continuous perception by motion binding

Authors: *S. GILAIE-DOTAN;
UCL, London, United Kingdom

Abstract: The visual system is known to be segregated into two main processing streams: the dorsal “where”/”how”/”action” stream associated with aspects related to attention, spatial navigation, and preparation for action, and the ventral “what”/”perception” stream associated with aspects leading to form and shape perception such as edges, textures, surfaces, and colors. Visual motion perception, which is multifaceted and diverse in the real world is involved in almost all our visual functions (e.g. visuo-vestibular body balancing, attentional capture, space perception, movements and action perception, facial expression and social interactions perception, and even reading and shape perception). But despite its multifaceted nature, visual motion processing and perception have been consistently considered to be under the purview of the dorsal stream. However, our studies and others show that some types of visual motion perception critically depend on the integrity of regions outside the dorsal stream. Furthermore, some dorsal functions are preserved when very basic aspects of motion perception are significantly impaired. And in addition, different types of motion perception have been shown to dissociate, indicating that they rely on segregated neuronal mechanisms. Combining these and a manifold of additional findings in primates and in humans into account, I now propose that visual motion is processed by a third visual motion stream that is distinct from the dorsal stream. Visual motion information feeds rapidly into MT/V5 via parallel subcortical and cortical routes to bypass the dorsal/ventral slower information flow, and from MSTl and MSTd reaches a multiplicity of brain areas. Critically, while the motion stream is critical for all visual motion

perception, it is insufficient on its own, and the transfer of information to these additional brain areas is crucial to allow the different motion perception tasks.

Disclosures: S. Gilaie-Dotan: None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.10

Topic: D.04. Vision

Support: Challenge Grant from Research to Prevent Blindness Inc. to the Department of Ophthalmology at SUNY Downstate

Empire Innovation Program (Awards to SLM and SMC)

Barrow Neurological Foundation (Awards to SLM and SMC)

National Science Foundation (Awards 0643306, 0852636, and 113786 to SMC and Award 0726113 to SLM)

XGT was a Fellow of the Caja Madrid Foundation

JOM was a Fellow of the Pedro Barrié de la Maza Foundation

Title: V1 neurons respond differently to motion in the world and to self-generated motion due to eye movements

Authors: S. MARTINEZ-CONDE[1,2], X. G. TRONCOSO[2,3], M. B. MCCAMY[2], A. NAJAFIAN JAZI[2,4], J. CUI[2], J. OTERO-MILLAN[2,5], *S. L. MACKNIK[1,2], F. M. COSTELA[2,4]; [1]SUNY Downstate Med. Ctr., Brooklyn, NY; [2]Barrow Neurolog. Inst., Phoenix, AZ; [3]UNIC-CNRS, Paris, France; [4]Arizona State Univ., Tempe, AZ; [5]Johns Hopkins Univ., Baltimore, MD

Abstract: How does the visual system differentiate self-generated motion from motion in the world? We can discern world motion from identical retinal image displacements due to eye movements, but the brain mechanisms underlying this ability are unknown. Here we exploit the frequent production of microsaccades during attempted ocular fixation in the primate, to compare area V1 responses to self-generated motion (real microsaccades) versus motion in the world (stimulus motions mimicking microsaccades). Real and simulated microsaccades were randomly interleaved in the same viewing condition, thereby producing equivalent oculomotor

and behavioral engagement. Here we show that real microsaccades generate biphasic neural responses, consisting of quick spike rate increases followed by slower and smaller decreases that drop below baseline. Simulated microsaccades generate solely excitatory responses. These results indicate that V1 neurons can respond differently to internally and externally generated motion, and expand V1's potential role in information processing and visual stability during eye movements.

Disclosures: **S. Martinez-Conde:** None. **X.G. Troncoso:** None. **M.B. McCamy:** None. **A. Najafian Jazi:** None. **J. Cui:** None. **J. Otero-Millan:** None. **S.L. Macknik:** None. **F.M. Costela:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.11

Topic: D.04. Vision

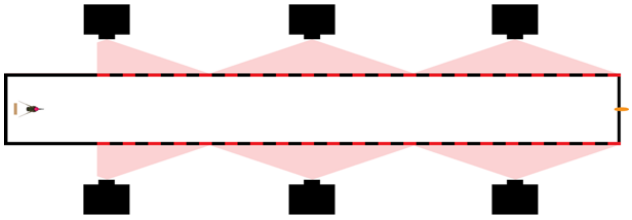
Support: Human Frontier Science Program

Title: Visual guidance of forward flight in birds

Authors: ***D. L. ALTSHULER**, R. DAKIN, T. FELLOWS;
Zoology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Flying birds use diverse sensory information to guide their flight, and the available evidence suggests that visual information plays a prominent role in flight control. Although there is considerable information available about the neural circuitry for sensing and processing visual motion in birds, there is a major gap in our understanding of how motion perception is used during flight. Numerous studies with bees and flies indicate that insects use image pattern velocity, the ratio of temporal to spatial frequency, to guide forward flight, including velocity, distance estimation, and centering in confined corridors. A recent study with budgerigars suggests that birds also use pattern velocity to guide forward flight. We tested this hypothesis further by working with hummingbirds in a virtual reality flight tunnel. Because hummingbirds will frequently fly between a perch and feeder located on opposite sides of the tunnel, we were able to obtain a large data set of flight trajectories with diverse visual stimulus patterns. We confirmed the main results of the budgerigar study, namely that hummingbirds will also increase speed when both sides of the tunnel have horizontal stripes (zero pattern velocity) as opposed to vertical stripes (high pattern velocity), and that hummingbirds will fly closer to horizontal stripes

when these are paired with vertical stripes. However, we show that large horizontal stripes inhibit these effects, and furthermore, that direct manipulation of pattern velocity along the tunnel axis does not affect forward flight speed or trajectory as proposed. Moving stripe patterns up and down has a strong effect on birds' altitude during forward flight, suggesting that pattern velocity can influence flying birds, just not in the manner we hypothesized based on insect studies. Moreover, these results indicate that forward flight control in birds relies on visual cues other than pattern velocity.



Disclosures: D.L. Altshuler: None. **R. Dakin:** None. **T. Fellows:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.12

Topic: D.04. Vision

Support: Human Frontier Science Program

Title: Response properties of global motion sensitive neurons in the hummingbird and zebra finch midbrain

Authors: *A. H. GAEDE, J. P. M. LAM, D. L. ALTSHULER;
Zoology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Visual guidance is a key feature of avian flight that has been relatively unexplored. It was recently demonstrated that hovering hummingbirds stabilize their position by minimizing perceived motion in their visual field. A flying bird perceives large-field visual motion, or global optic flow, when it is moving through its environment and this strong visual signal is processed in the avian accessory optic system (AOS). One of the two major midbrain nuclei in this pathway is the pretectal nucleus lentiformis mesencephali (LM), which is hypertrophied in hovering hummingbirds, and to a lesser extent in transiently hovering bird species. In recent years, tract tracing and behavioral studies have further implicated the AOS in gaze stabilization and flight

control. However, many of the studies examining motion processing in the avian visual system have been carried out in pigeons, where LM cells are classed into two categories: 'fast' cells (prefer speeds > 6°/s) and 'slow' cells (prefer speeds < 6°/s). We hypothesized that the hypertrophied LM of hummingbirds contains a higher proportion of slow cells, which would explain the strong response to slow moving visual stimuli that has been demonstrated behaviorally. Furthermore, we expected hummingbird LM cells to have narrower speed-tuning curves, possibly allowing for finely tuned motor control during both hovering and high-speed flight. Using standard electrophysiological techniques and computer-generated stimuli (a single plane of random dots), we characterized the response properties of these motion-sensitive cells in the LM of Anna's hummingbirds (Calypte anna) and zebra finches (Taeniopygia guttata), which are small birds that do not hover and do not have a hypertrophied LM. As for pigeons, we found that LM cells in both species have large receptive fields and are directionally selective, as demonstrated by increased firing in response to motion in their preferred direction and suppression of spontaneous firing in their anti-preferred direction. In this study, we examine the distribution of direction preferences within the LM, as well as the distribution of 'slow' versus 'fast' cells in zebra finches and hummingbirds. In zebra finches, we saw cells with both broad and narrow speed-tuning curves, as well as a preference for moderately slower speeds than reported for pigeon LM cells. Surprisingly, in hummingbirds, we found a number of LM cells that prefer very high speeds and are narrowly tuned. The role of these neurons in hummingbird flight is currently unknown.

Disclosures: **A.H. Gaede:** None. **J.P.M. Lam:** None. **D.L. Altshuler:** None.

Nanosymposium

746. Visual Motion

Location: S102

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 746.13

Topic: D.04. Vision

Title: Spatial and temporal frequency tuning to visual motion in human mt+ measured with ecog

Authors: A. GAGLIANESE[1,2], B. HARVEY[3], M. J. VANSTEENSEL[1], S. O. DUMOULIN[3], *N. PETRIDOU[2], N. F. RAMSEY[1];
[1]Dept. of Neurosurg. and Neurology, Brain Ctr. Rudolf Magnus, Univ. Med. Ctr. Utrecht, Utrecht, Netherlands; [2]UMC Utrecht, Utrecht, Netherlands; [3]Exptl. Psychology, Helmholtz Inst., Univ. of Utrecht, Utrecht, Netherlands

Abstract: Detection of motion is an important component in our daily life, and plays a key role in the recognition of the dynamic aspects of the environment. Perception of the direction and speed of an object allows us to understand and to promptly react to sudden events. The core region involved in detecting and processing motion in the visual scene is the middle temporal cortex MT/V5. Although MT/V5 has been extensively investigated in monkeys in terms of its retinotopic properties and selectivity for direction of the moving stimuli it is still unclear how it encodes the speed of motion. Non-human primate studies have shown that the majority of MT neurons are separably tuned for spatial and temporal frequencies, implying that their response to speed, given by the ratio of spatial and temporal frequency of visual stimuli, is dependent on one of these stimulus properties. However, some neurons encode the stimulus speed, with a tuning profile selective to particular combinations of spatiotemporal frequency. Here, we characterize the neuronal response to stimuli moving at different spatial and temporal frequencies in human MT+ using intracranial electrocorticography (ECoG). We ask whether the response preferences of the underlying neural populations depend on stimulus speed, or on independent spatial and temporal frequency components. Four subjects underwent implantation of ECoG grids for epilepsy monitoring (128 channel recording system, 512 Hz sampling rate). Visual stimuli consisted of three high-contrast black-and-white dartboards with spatial frequencies of 0.2, 0.33 and 1 deg/cycle expanding for 1s from the fixation point at three temporal frequencies (1, 3 and 5 Hz, randomly interleaved), alternating with stationary periods between 3 and 4.5s. For electrodes located in the proximity of hMT+ we extracted high frequency broadband (HFB: 65-95 Hz) responses for all combinations of spatial and temporal frequencies and we fitted them to two variant 2D Gaussian functions allowing optimal tuning for speed or for separable spatial and temporal frequency properties. Our results show that HFB responses were characterized by the spatiotemporal frequency properties of the dartboard presented. Thus the underlying hMT+ neuronal populations exhibited separable selectivity for spatial and temporal frequencies rather than speed tuning. Moreover, HFB responses exhibited the largest responses at a particular spatial frequency (0.33 deg/cycle), suggesting that the hMT+ neuronal populations we examined may be described as spatial frequency filters for motion detection. Tuning for speed may still occur in a subset of neurons, but was not encountered with our coverage of cortex.

Disclosures: **A. Gaglianese:** None. **B. Harvey:** None. **M.J. Vansteensel:** None. **S.O. Dumoulin:** None. **N. Petridou:** None. **N.F. Ramsey:** None.

Nanosymposium

747. Spatial and Feature Based Attention

Location: S402

Time: Wednesday, October 21, 2015, 1:00 PM - 3:00 PM

Presentation Number: 747.01

Topic: D.04. Vision

Support: National Eye Institute Intramural Research Program at the National Institutes of Health

Title: Modeling the effects of superior colliculus inactivation on performance in a spatial attention task

Authors: *J. P. HERMAN[1], R. J. KRAUZLIS[2];
[1]Lab. of Sensorimotor Res., Natl. Eye Institute/NIH, National Institute Of Health, MD; [2]Lab. of Sensorimotor Res., NEI / NIH, Bethesda, MD

Abstract: The primate superior colliculus (SC) participates in the control of spatial attention. Neuronal activity in the SC is modulated by spatial cueing, and damping SC activity with chemical inactivation impairs performance in attention tasks. Can a reduction of SC neural activity account for the behavioral deficits resulting from inactivation? To test this, we developed a model relating single unit electrophysiology data to the behavioral effects of SC inactivation. Data were collected from a monkey performing an attention task using color stimuli. The animal was required to report color changes at a cued location by releasing a joystick and to ignore changes at an opposing foil location by maintaining his hold; in each trial, either cued or foil stimulus might change, not both. The monkey maintained central fixation for the duration of the trial. As we previously reported, SC neurons exhibited robust increases in activity immediately after the near-threshold stimulus changes, and the magnitude of these increases were greater if the monkey responded to the change. The goal of the model was to test whether this change-related activity could account for the animal's performance both before and during SC inactivation. The model was designed to predict behavioral responses for individual cued or foil changes based on the single-unit activity recorded in the SC during performance of the task. The model had three main components: (1) change-evoked responses from units in each colliculus were pooled, (2) pooled responses from the two colliculi were normalized, and (3) normalized activity was compared to a fixed threshold to predict whether or not a response to the change would occur. The effect of chemical inactivation was simulated by multiplicative scaling of single-unit activity in one colliculus prior to pooling. We found that this simple normalization model could replicate the observed hit and false alarm rates in the absence of SC inactivation. Moreover, by scaling activity in a simulated pool of ~75 neurons by 80%, we could reproduce the distinctive effects of SC inactivation: a large reduction in correct responses to cued changes inside the inactivation area, and a similarly large increase in erroneous responses to foil changes outside. These results illustrate how the dramatic effects on attention performance caused by SC inactivation in our task can be explained by simply combining a normalized read-out stage with a modest unilateral reduction in SC neuronal activity.

Disclosures: J.P. Herman: None. **R.J. Krauzlis:** None.

Nanosymposium

747. Spatial and Feature Based Attention

Location: S402

Time: Wednesday, October 21, 2015, 1:00 PM - 3:00 PM

Presentation Number: 747.02

Topic: D.04. Vision

Support: National Eye Institute Intramural Research Program at the National Institutes of Health

Title: Sensorimotor encoding in Caudate Nucleus during a covert attention task

Authors: *F. ARCIZET, R. J. KRAUZLIS;
LSR-NIH, Bethesda, MD

Abstract: The complete circuit linking the Superior Colliculus (SC) to the control of covert attention remains unknown; one possibility is a pathway through the basal ganglia. Last year, we showed that neurons in the caudate nucleus, a major input structure of the basal ganglia, exhibit correlates of attention - their activity is related to factors such as cue location and response choice. Here, we present results from a complementary analysis on response choice activity and demonstrate that caudate neurons do not simply report sensory or motor events but instead establish a link between sensory signals and action selection. A rhesus macaque started the motion-change detection task by fixating a central spot and pressing down a joystick. After 250 ms of fixation, a spatial cue was flashed for 200 ms at a peripheral location (~12 deg eccentric), indicating the spatial location he should monitor. Next, two motion patches were presented. In some trials, the cued motion patch changed direction slightly, and the animal had to release the joystick within 1000 ms to get rewarded. In other trials, the motion change occurred at the non-cued location, and the animal was rewarded for not releasing the joystick. The animal performed the task well, achieving hit and false alarm rates of 62% and 5% respectively. We focused our analysis on 60 phasically active neurons (PANs) recorded in the head and body of the caudate nucleus that showed a phasic response after the motion change. We computed how well caudate PANs 1) discriminated the location of the cued change and 2) predicted whether or not the monkey would release the joystick. First, based on ROC analysis comparing activity when the cued stimulus was ipsilateral versus contralateral, 56% of caudate PANs showed significant preference for stimulus location, showing that caudate PANs encoded stimulus location even within the phasic activity related to the response choice. Second, comparing activity when the animal correctly released the joystick (hits) versus when he mistakenly failed to release (misses), 70% of caudate PANs showed significant choice probability predicting whether or not the monkey would release the joystick. Notably, many caudate PANs (42%) showed significant effects for both stimulus location and response choice. Together, these results illustrate how caudate nucleus may contribute to the performance of visual attention tasks: by linking sensory

selectivity to particular motor actions, caudate activity could be used to select the action appropriate for the sensory context. Signals from the SC related to spatial priority could bias the outcome of this selection in favor of particular sensorimotor contingencies.

Disclosures: F. Arcizet: None. **R.J. Krauzlis:** None.

Nanosymposium

747. Spatial and Feature Based Attention

Location: S402

Time: Wednesday, October 21, 2015, 1:00 PM - 3:00 PM

Presentation Number: 747.03

Topic: D.04. Vision

Support: National Eye Institute Intramural Research Program at the National Institutes of Health

Title: Attention-related BOLD modulation with and without superior colliculus inactivation

Authors: *A. R. BOGADHI[1], A. BOLLIMUNTA[1], D. A. LEOPOLD[2], R. J. KRAUZLIS[1]; [1]Lab. of Sensorimotor Res., Natl. Eye Inst. - NIH, Bethesda, MD; [2]Lab. of Neuropsychology, Natl. Inst. of Mental Health, NIH, Bethesda, MD

Abstract: We recently showed that inactivation of the superior colliculus (SC) leads to attention deficits in a behavioral task despite normal attention-related signal modulation in the visual cortex (Zenon & Krauzlis, 2012). This finding suggests that SC inactivation might affect brain regions downstream to visual cortex, leading to the observed spatial attention deficits. To identify these potential brain regions, we employed fMRI with and without SC inactivation in a monkey trained to perform a spatial attention task in a vertical scanner. The stimulus sequence on a single imaging run (~480s) consisted of three different blocks: Baseline (B), Foveal Attention (FA) and Peripheral Attention (PA) blocks. B blocks (~10s long) were interleaved between FA and PA blocks, each 20s long. In B block trials, the relevant stimulus was a central fixation point that dimmed at randomized times. FA block trials were similar to B block trials but added a peripheral motion-change stimulus as an irrelevant distracter. In PA block trials, the fixation point did not dim and the peripheral motion-change was the relevant stimulus. The task of the monkey was to maintain central fixation and to report the relevant stimulus change (fixation dimming in B & FA blocks, peripheral motion change in PA blocks) by releasing a lever to get a juice reward. A total of 56 runs from 4 control sessions and 44 runs from 4 inactivation sessions were included. Eye movements were recorded during each imaging run. For our preliminary analysis, we defined several cortical and sub-cortical anatomical ROIs on high-resolution anatomical images using stereotaxic atlas coordinates (Saleem & Logothetis, 2007). In

each ROI, voxels with significant differences between PA and B blocks (t-scores > 2) were included for analysis of attention modulation, in which we calculated % change in BOLD for PA versus the FA blocks. Based on this difference, we assigned an attention modulation index to each voxel (AMIs). Following SC inactivation, the monkey's behavioral performance was significantly impaired for stimulus changes in the contralateral hemifield. However, during the same trials, the AMIs for many attention-related cortical areas (V1, MT/MST, LIP and FEF) remained normal. At the same time, AMIs for several sub-cortical areas (pulvinar, caudate and putamen) showed a dramatic reduction in attentional modulation on the side of the injection. These results confirm and extend our previous findings that activity in visual cortex is unaffected by SC inactivation, and suggest instead that the basis of the observed behavioral changes lies in an interaction between the SC, pulvinar, and striatum.

Disclosures: **A.R. Bogadhi:** None. **A. Bollimunta:** None. **D.A. Leopold:** None. **R.J. Krauzlis:** None.

Nanosymposium

747. Spatial and Feature Based Attention

Location: S402

Time: Wednesday, October 21, 2015, 1:00 PM - 3:00 PM

Presentation Number: 747.04

Topic: D.04. Vision

Support: Wellcome Trust grant 099757

Wellcome Trust grant 093104

Title: Layer dependent attentional modulation of neuronal activity in macaque V1 and V4

Authors: ***M. BOYD**[1], M. A. SAVAGE[1], C. BRANDT[1], M. DASILVA[1,2], A. THIELE[1]; [1]Newcastle Univ., Newcastle Upon Tyne, United Kingdom; [2]Current Address: The Univ. of Manchester, Manchester, United Kingdom

Abstract: Attention enhances task performance and affects various signatures of neuronal activity. It increases firing rates of neurons representing attended locations, features or objects. It additionally reduces firing rate variance, noise correlations of neurons and affects coherence between neuronal groups. Attentional signals have been studied in many different areas, but we currently have little understanding how attention affects neurons in different cortical layers, how it affects the flow of information between layers, and how it affects interactions between different areas in different layers. To address these questions we trained two male rhesus

macaque monkeys to perform a covert visuospatial attention task where the location to attend to was cued by a central stimulus. Cue onset occurred after stimulus onset, which allowed dissociation of bottom up (sensory stimulation) and top down (spatial attention) signals entering the cortical areas and layers. Recordings were taken simultaneously from V1 and V4 whilst the animal performed this task. Multichannel laminar electrodes (16 contact, 150um intercontact distance) were positioned to record from infragranular, granular and supragranular layers within single cortical microcolumns. We simultaneously recorded in area V1 and V4 in 31 sessions in monkey 1 and in 11 sessions in monkey 2. Simultaneous recordings were done when V1 and V4 channels had overlapping receptive fields. We used the current source density profile to align our recording contacts relative to the granular input layer. Connectivity between and within areas was measured through field, spike-field and spike-spike coherence. We report how interareal and interlaminar connectivity between these two cortical areas is modulated by visual attention at the spiking and the LFP/CSD signal level. Supported by the Wellcome Trust

Disclosures: **M. Boyd:** None. **M.A. Savage:** None. **C. Brandt:** A. Employment/Salary (full or part-time); Newcastle University. **M. Dasilva:** A. Employment/Salary (full or part-time); The University of Manchester. **A. Thiele:** A. Employment/Salary (full or part-time); Newcastle University.

Nanosymposium

747. Spatial and Feature Based Attention

Location: S402

Time: Wednesday, October 21, 2015, 1:00 PM - 3:00 PM

Presentation Number: 747.05

Topic: D.04. Vision

Support: The Center for Brains, Minds and Machines, funded by National Science Foundation (NSF) STC award CCF-1231216

NIH grant EY017077

Tab Williams Family Endowment fund

Title: How PFC and LIP process single and multiple-object ‘pop-out’ displays

Authors: *E. M. MEYERS[1], A. LIANG[2], F. KATSUKI[3], C. CONSTANTINIDIS[4];
[1]Brain & Cognitive Sci., Hampshire Col., Amherst, MA; [2]MIT, Cambridge, MA; [3]Harvard Med. Sch., Brockton, MA; [4]Wake Forest Univ., Winston-Salem, NC

Abstract: Images in which one object is more salient than its surroundings lead to a 'pop-out' effect where subjects show very efficient behavioral responses to the salient object. This pop-out effect is present for displays in which: 1) a single object is on a blank background, and 2) a single object is highly distinct from other surrounding objects. Thus it is generally assumed that this pop-out effect arise from the same neural computations for both of these types of displays, and it is thought that this effect is mediated by "bottom-up" attentional mechanisms. To directly examine whether these two types of displays are indeed processed the same way, we recorded neural activity in LIP and PFC which are two brain regions implicated in attentional processing. Using population decoding methods, in a population of 280 LIP and PFC neurons recorded from two monkeys we observed that when a single isolated object is displayed, information about the object's location appeared ~10 ms earlier in LIP than in PFC, which is consistent with a feed-forward account for processing isolated objects. However, when a salient object is presented among multiple distractor objects, information about the location of the salient object was delayed by 60-90 ms in both brain regions, and information now first appeared in PFC. Despite the differences in the latency of information between the two display types, the latency of population firing rate activity was similar for both types of displays. Additionally, we see that pattern of neural activity is very similar for both types of displays (and across different color transformations of the stimuli) indicating that information about the object's location is being coded in the same way regardless of display type. These results indicate that there is 'top-down' neural component for processing pop-out displays, and that firing rate latencies can be quite distinct from the latency of when information first appear in a brain region.

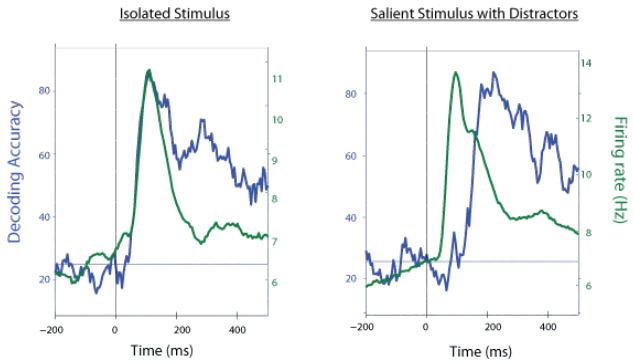


Figure showing that firing rate latencies and information latencies can be different in PFC (similar results were obtained from LIP).

Disclosures: E.M. Meyers: None. **A. Liang:** None. **F. Katsuki:** None. **C. Constantinidis:** None.

Nanosymposium

747. Spatial and Feature Based Attention

Location: S402

Time: Wednesday, October 21, 2015, 1:00 PM - 3:00 PM

Presentation Number: 747.06

Topic: D.04. Vision

Support: NIH Grant EY014924

Title: Effects of reversible inactivation of parietal cortex on the processing of visual salience in the frontal eye field

Authors: *M. ZIRNSAK[1,2], X. CHEN[1,2], S. G. LOMBER[3], T. MOORE[1,2];
[1]Dept. of Neurobio., Stanford Univ., Stanford, CA; [2]Howard Hughes Med. Institute, Stanford Univ. Sch. of Med., Stanford, CA; [3]Brain and Mind Institute, The Univ. of Western Ontario, London, ON, Canada

Abstract: The seemingly effortless detection of salient stimuli is a key capacity of the primate visual system. It is widely believed that areas within the frontoparietal network contribute significantly to the computation of visual salience. For example, representations of salience have been demonstrated for neurons within the lateral intraparietal area of the parietal cortex and the frontal eye field (FEF) within prefrontal cortex. However, clear causal links between those representations and the emergence of salience are lacking. In this study, we investigate the effect of reversible inactivation of parietal cortex on the processing of salience by FEF neurons. We implanted two stainless steel cryoloops within the intraparietal sulcus of a macaque monkey. Chilled methanol was pumped through the loops to induce localized hypothermia in the surrounding cortical tissue, thus silencing nearby neuronal activity. Simultaneously, we recorded from FEF neurons using linear, multi-electrode arrays and measured the visual responses to single stimuli, homogenous stimulus arrays, and "pop-out" arrays (i.e., a single, unique stimulus among homogenous flankers). Confirming the effectiveness of the cooling, we observed strong behavioral biases consistent with deficits in human patients with parietal brain damage and deficits observed in previous lesion and inactivation studies in monkeys. Specifically, eye movements were biased away from the contralateral hemifield. We observed this bias during a free-viewing task and during a two-target, free-choice saccade task in which the monkey is selecting one out of two targets presented in opposite hemifields with varying onset asynchronies. For the free-viewing task we observed a shift of the median number of fixations by up to 6 dva into the ipsilateral hemifield and an increase in the duration of fixations within the same of up to 43 % as compared to control trials. In the free-choice task, we observed that following inactivation, the onset of the contralateral target needed to lead the ipsilateral target by up to 180 ms more than during control trials in order to be selected with equal probability by the monkey. In addition to these behavioral effects, we observed clear modulations of visual responses of FEF neurons in our preliminary recordings. Following inactivation, responses to visual stimuli were reduced compared to control trials. However, in addition to the reduction in visual responses, the selectivity to pop-out arrays was also reduced; that is, the reduction in pop-

out responses was more profound than responses to other stimuli. These results suggest a dependence of visual salience signals in the FEF on parietal cortex.

Disclosures: **M. Zirnsak:** None. **X. Chen:** None. **S.G. Lomber:** None. **T. Moore:** None.

Nanosymposium

747. Spatial and Feature Based Attention

Location: S402

Time: Wednesday, October 21, 2015, 1:00 PM - 3:00 PM

Presentation Number: 747.07

Topic: D.04. Vision

Support: Wellcome Trust 093104

Title: Cholinergic control of attentional signals in broad and narrow spiking cells in macaque frontal eye-field

Authors: ***A. THIELE**, C. BRANDT, S. GOTTHARDT;
Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: Attention improves perception by affecting different aspects of the neuronal code. It enhances firing rates, it reduces firing rate variability and noise correlations of neurons, and it alters the strength of oscillatory activity. In striate cortex, attention induced rate enhancement requires cholinergic mechanisms (1), while attention induced variance and noise correlation reduction are supported by (glutamatergic) NMDA receptor availability (2). Here we investigate how acetylcholine affects attentional signals in the frontal eye-field (FEF) in narrow and broad spiking cells. Two male macaque monkeys were trained in a covert top-down attention task, where a central color cue indicated on a trail by trial basis where to attend to. The animals had to detect a change of the cued stimulus and ignore changes in un-cued stimuli. They responded by releasing a touch bar to obtain a fluid reward. Attention to the neuron's receptive/movement field significantly increased firing rates ($p<0.05$). These effects were significantly larger in narrow than in broad spiking cells ($p<0.05$). Application of muscarinic and nicotinic antagonists significantly reduced neuronal activity (irrespective of the attention condition) in both cells types ($p<0.05$). The effect of muscarinic blockade on firing rate reduction was significantly larger in narrow spiking cells than in broad spiking cells ($p<0.05$). Attentional rate modulation in narrow spiking cells significantly depended on the availability on muscarinic and nicotinic receptors, while it only depended on the availability of muscarinic receptors in broad spiking cells. Attention significantly reduced gain variability (rate variance) in both cell types ($p<0.05$), while muscarinic and nicotinic blockade increased rate variability ($p<0.05$). Thus, acetylcholine affects

attentional control in FEF through muscarinic and nicotinic receptors (albeit differently in broad vs. narrow spiking cells) and it also aids reduction of rate variability in both cell types. Supported by the Wellcome Trust. 1.Herrero JL, et al. (2008) Acetylcholine contributes through muscarinic receptors to attentional modulation in V1. Nature 454(7208):1110-1114. 2.Herrero JL, Gieselmann MA, Sanayei M, & Thiele A (2013) Attention-induced variance and noise correlation reduction in macaque V1 is mediated by NMDA receptors. Neuron 78(4):729-739.

Disclosures: **A. Thiele:** None. **C. Brandt:** None. **S. Gotthardt:** None.

Nanosymposium

747. Spatial and Feature Based Attention

Location: S402

Time: Wednesday, October 21, 2015, 1:00 PM - 3:00 PM

Presentation Number: 747.08

Topic: D.04. Vision

Support: NDSEG Fellowship (CG)

NSF Fellowship (CG)

NIH R21-EY19992 (MAS)

Gustavus and Louise Pfeiffer Research Foundation (MAS)

Title: Cholinergic, but not dopaminergic or noradrenergic, enhancement sharpens behavioral spatial tuning

Authors: ***M. A. SILVER**[1], C. GRATTON[3], S. YOUSEF[1], E. AARTS[4], D. WALLACE[2], M. D'ESPOSITO[1];
[1]Univ. of California, Berkeley, CA; [2]Univ. of California, San Francisco, CA; [3]Washington Univ., St. Louis, MO; [4]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ., Nijmegen, Netherlands

Abstract: The neuromodulators acetylcholine, dopamine, and norepinephrine have each been implicated in aspects of attentional function. In particular, the cholinergic system is thought to mediate attention effects by shifting cortex towards feedforward processing, enhancing bottom-up inputs and suppressing lateral interactions. Dopamine and noradrenaline have been proposed to influence prefrontal cortical mechanisms of attention, perhaps by altering the relative gain of target and distractor responses. However, it remains unclear how these neuromodulators specifically influence visual spatial interactions in attention tasks. Here, we examine this

question using systemic pharmacological enhancement in two double-blind, placebo-controlled crossover human behavioral studies. In each study, participants were asked to maintain attention on a flashing low-contrast target that was centered between two high-contrast distractors, and they performed a contrast decrement task at the target location. Importantly, on separate trials, distractors were presented at one of four different distances from the target, allowing the spatial extent of target-distractor interactions to be determined. In one study, 28 participants were administered the cholinesterase inhibitor donepezil on one experimental day and placebo on the other. Donepezil improved overall target detection, and modeling of the spatial profile of drug effects with a difference of Gaussians suggested that donepezil reduced the spatial extent of excitatory interactions. This result is consistent with previous neurophysiological evidence that acetylcholine decreases receptive field size and spread of fMRI responses in early visual cortex. In a second study, a new group of 23 participants were administered a dopamine D2 receptor agonist (bromocriptine), a noradrenergic alpha-2a receptor agonist (guanfacine), or placebo on three separate experimental days. Bromocriptine tended to decrease performance for distractors at intermediate distances and to improve performance at shorter and farther distances. Guanfacine, instead, showed a trend towards decreased baseline performance at all distances. Modeling indicated that neither drug systematically altered the spatial extent of excitatory or inhibitory interactions. These results demonstrate that cholinergic enhancement improves target processing among distractors and are consistent with previous neurophysiological data showing a narrowed spatial profile of activation. This cholinergic effect contrasted substantially with the impairments in performance observed following dopaminergic and noradrenergic enhancement.

Disclosures: **M.A. Silver:** None. **C. Gratton:** None. **S. Yousef:** None. **E. Aarts:** None. **D. Wallace:** None. **M. D'Esposito:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.01

Topic: D.18. Brain-Machine Interface

Support: Stanford Institute for Neuro-Innovation and Translational Neuroscience

Stanford BioX/NeuroVentures

Stanford Office of Postdoctoral Affairs

Garlick Foundation

Craig H. Neilsen Foundation

National Institutes of Health: NIDCD (R01DC009899), NICHD (R01HD077220), NICHD-NCMRR (N01HD53403 and N01HD10018), NINDS-Javits (R01NS25074)

Office of Research and Development,Rehabilitation R&D Service, Department of Veterans Affairs (B6453R)

Title: A bluetooth wireless brain-machine interface for general purpose computer use

Authors: *P. NUYUJUKIAN[1,2,3], C. PANDARINATH[1,2,3], C. BLABE[1], L. HOCHBERG[7,8,10,11,9], K. SHENOY[2,3,4,5,6], J. HENDERSON[1,3];
[1]Neurosurg., [2]Electrical Engin., [3]Stanford Neurosciences Inst., [4]Neurosciences Program, [5]Dept. of Neurobio., [6]Bioengineering, Stanford Univ., Stanford, CA; [7]Ctr. for Neurorestoration and Neurotechnology, Rehab. R&D Service, Veterans Adminstration, Providence, RI; [8]Sch. of Engin., [9]Inst. for Brain Sci., Brown Univ., Providence, RI; [10]Neurol., Massachusetts Gen. Hosp., Boston, MA; [11]Neurol., Harvard Med. Sch., Boston, MA

Abstract: Advances in brain-machine interfaces (BMIs) have demonstrated the potential of these systems to serve as important communication avenues. We recently demonstrated the highest performing BMIs for communication in clinical trial participants (Nuyujukian*, Pandarinath*, et al., SfN 2014 & Pandarinath*, Nuyujukian*, et al., SfN 2014). As is the case with most BMIs to date, this system was comprised of custom software packages and the interface was not user-updatable. The next step in the design of practical BMIs for communication would be to create a system that is broadly usable, similar to how computer peripherals can interface to a variety of computers through common interfaces (e.g., USB). Additionally, wireless transmission of control signals would simplify the interface, facilitating portability and ease of use. We addressed both of these issues by developing a general purpose BMI interface for communication which outputs signals using the Bluetooth (mouse) standard. In this fashion, the wireless BMI could pair with many types of standard computing hardware, ranging from computers to tablets. We tested this general purpose interface with participant T6 of the BrainGate2 pilot clinical trial. T6 is a 52 year old woman diagnosed with ALS who was implanted with a multielectrode array in motor cortex. After training a two-dimensional cursor and click decoder as reported last year, she used the wireless BMI to control an unmodified Android tablet. We conducted an experimental session with this system and she navigated the Android operating system interface, browsed the web, searched for and played online videos, searched for and played music, and composed three emails to researchers. This proof-of-concept demonstration illustrates one potential use for communication BMIs that uses wireless signal transmission to control off-the-shelf consumer hardware.

Disclosures: P. Nuyujukian: None. **C. Pandarinath:** None. **C. Blabe:** None. **L. Hochberg:** None. **K. Shenoy:** None. **J. Henderson:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.02

Topic: D.18. Brain-Machine Interface

Support: Stanford Institute for Neuro-Innovation and Translational Neuroscience

Stanford BioX/NeuroVentures

Stanford Office of Postdoctoral Affairs

Garlick Foundation

Craig H. Neilsen Foundation

National Institutes of Health: NIDCD (R01DC009899), NICHD (R01HD077220), NICHD-NCMRR (N01HD53403 and N01HD10018), NINDS-Javits (R01NS25074)

Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (B6453R)

Title: Dynamic dimensionality reduction of human motor cortical activity using recurrent neural networks

Authors: *C. PANDARINATH[1,2,3], D. SUSSILLO[2], B. L. SORICE[7], A. A. SARMA[8,11,9,7], E. N. ESKANDAR[12], L. R. HOCHBERG[11,8,7,13,10], L. F. ABBOTT[14], J. M. HENDERSON[1,3], K. V. SHENOY[2,3,4,5,6];
[1]Neurosurg., [2]Electrical Engin., [3]Stanford Neurosciences Inst., [4]Neurosciences Program, [5]Dept. of Neurobio., [6]Bioengineering, Stanford Univ., Stanford, CA; [7]Neurol., Massachusetts Gen. Hosp., Boston, MA; [8]Sch. of Engin., [9]Brown Inst. for Brain Sci., [10]Inst. for Brain Sci., Brown Univ., Providence, RI; [11]Ctr. for Neurorestoration and Neurotechnology, Rehab. R&D Service, Dept. of VA Med. Ctr., Providence, RI; [12]Dept. of Neurosurg., Harvard Med. Sch. and Massachusetts Gen. Hosp., Boston, MA; [13]Neurol., Harvard Med. Sch., Boston, MA; [14]Dept. of Physiol. and Cell. Biophysics, Columbia Univ., New York, NY

Abstract: Several recent studies have revealed new insights relating motor cortical population activity to motor behavior using dimensionality reduction techniques (e.g. Afshar et al. 2011, Churchland et al. 2012, Kaufman et al. 2014, Sadtler et al. 2014). While these techniques often uncover structure in the population activity that is not apparent from single neuron responses,

most involve smoothing neural activity in time, and often require averaging over multiple trials. Such treatments can obscure important features (e.g. fine temporal structure and trial-to-trial variability). We present an alternative approach to dimensionality reduction, called Latent Factor Analysis of Dynamical Systems (LFADS), that uses recurrent neural networks (RNNs; e.g. Sussillo & Abbott, 2009) to characterize dynamic structure in neural population activity. In this approach, an RNN is trained to reproduce time varying, simultaneously recorded, single trial spiking activity. To constrain the RNN to find a dimensionality-reduced representation of the spiking activity, its output is forced through a low dimensional layer of hidden units (10-20 dim). Activity in this layer serves as the basis for the predicted firing rates. In summary, LFADS produces a dynamic, low-dimensional estimate of the population activity that is consistent with recorded spiking data. We applied LFADS to intracortical recordings from human primary motor cortex during movements, recorded from participant T7 in the BrainGate2 clinical trial (ClinicalTrials.gov ID: NCT00912041). We show that the network's output captures fine temporal features of the recorded spike trains and reproduces known dynamic features of motor cortical activity on multiple timescales. For example, motor cortex exhibits beta band oscillations (e.g. 15-40 Hz) in local field potentials (LFP), and phase-synchronized spiking activity, often occurring in the pre-movement period and stopping before movement onset (e.g. Donoghue et al., 1998). Although LFADS is trained to model only the spiking activity, the estimated population state successfully predicts single-trial recorded LFP activity during the pre-movement period. Furthermore, it also shows the presence of slower oscillations (1-2 Hz), consistent with structure demonstrated using trial-averaged analyses (Churchland et al., 2012). These results show that LFADS reveals dynamic features of population activity on single trials. This knowledge may lead to a better understanding of trial-to-trial variability, which is central to motor control and higher-performance Brain-Machine Interfaces (Kao et al., SfN 2013).

Disclosures: **C. Pandarinath:** None. **D. Sussillo:** None. **B.L. Sorice:** None. **A.A. Sarma:** None. **E.N. Eskandar:** None. **L.R. Hochberg:** None. **L.F. Abbott:** None. **J.M. Henderson:** None. **K.V. Shenoy:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.03

Topic: D.18. Brain-Machine Interface

Support: Research supported by Stanford Electrical Engineering Departmental Fellowship

National Science Foundation Graduate Research Fellowship

NSF IGERT

NIH Pioneer Award 8DP1HD075623

DARPA REPAIR award N66001-10-C-2010

NIH T-RO1 award NS076460

Title: Increasing brain machine interface performance by online auto-delete based on motor cortical activity

Authors: *N. EVEN-CHEN[1], J. C. KAO[1], S. D. STAVISKY[2], S. I. RYU[3,1], K. V. SHENOY[1,4,5,2];
[1]Electrical Engin., [2]Neurosciences Grad. Program, Stanford Univ., Stanford, CA; [3]Neurosurg., Stanford Univ., Palo Alto, CA; [4]Bioengineering, [5]Neurobio., Stanford Univ., Stanford, CA

Abstract: Brain machine interfaces (BMIs) aim to provide greater independence for people with paralysis (e.g., communicating via cortical control of a computer cursor). Currently, a BMI user must correct on-screen keyboard typing errors, by subsequently selecting the "delete" key. Error detection based on neural activity alone could be used to automatically delete incorrect selections by decoding the user's recognition of the error. To pursue this idea we asked (1) if motor cortical activity correlates with task outcome and, if so, (2) can we decode outcome on single-trials to increase BMI performance? We trained a rhesus macaque (J) to control a BMI cursor and acquire a color-tagged target in an 8×8 keyboard-like target grid. The monkey selected the correct target by holding the cursor over it for 250 ms. He received feedback of the task outcome (via auditory tone and a liquid reward on successful trials) 600 ms after target selection. We delayed this feedback in order to separate neural signals reflecting the monkey's recognition of the task outcome from neural signals related to explicit task feedback. To address (1) above, we decoded the task outcome using a support vector machine to classify neural activity's principal components (PCs). Across four days (10,500 trials), his success rate was 80 ± 0.01% (mean ± SEM). When error detection was not used ("ED-off"), the monkey had to undo incorrect selections by selecting the "delete" target. When error detection was used ("ED-on"), detected errors were "auto-deleted." Thus, when incorrectly selected targets were detected as errors based on neural activity, the same target would be re-prompted (as opposed to the "delete" key), thereby circumventing manual deletion. We alternated ED-off and ED-on trial blocks. During ED-on blocks, we detected 93 ± 0.5% of incorrect selections with 3 ± 0.4% false detection, thereby addressing (2) above. Error detection increased the correct target selection rate by 16 ± 0.01%, approaching the ceiling imposed by initial selection success rate. In order to better understand the sources of neural activity that enabled us to distinguish between correct and incorrect selections, we examine the two leading PCs of the difference between the outcome-averaged selection-aligned neural activity. These two PCs capture 75% of the neural variance,

with weights concentrated in PMd. The subspace of the two PCs reveals dynamical differences between the two conditions in different phases of the task: movement to target, target-holding and waiting for reward. These results show that a signal correlated with task outcomes is present in motor cortex and can be used to increase the performance of BMIs.

Disclosures: **N. Even-Chen:** None. **J.C. Kao:** None. **S.D. Stavisky:** None. **S.I. Ryu:** None. **K.V. Shenoy:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.04

Topic: D.18. Brain-Machine Interface

Support: NSF Graduate Research Fellowship

Defense Advanced Research Projects Agency (DARPA) Reorganization and Plasticity to Accelerate Injury Recovery (REPAIR) N66001-10-C-2010

US National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (NINDS) Transformative Research Award R01NS076460

US National Institutes of Health (NIH) Director's Pioneer Award 8DP1HD075623-04

Title: "Neural hysteresis": incorporating historical knowledge of neural dynamics to rescue decoder performance

Authors: *J. C. KAO[1], S. I. RYU[6,1], K. V. SHENOY[1,2,3,4,5];
[1]Electrical Engin., [2]Neurobio., [3]Bioengineering, [4]Neurosciences Program, [5]Stanford Neurosciences Inst., Stanford Univ., Stanford, CA; [6]Dept. of Neurosurg., Palo Alto Med. Fndn., Palo Alto, CA

Abstract: Intracortical brain-machine interfaces (BMIs) convert spiking activity from neurons in motor cortex into control signals to guide prosthetic devices (e.g., a computer cursor or robotic arm). However, over time, the number of recorded spiking signals will decrease due to electrode array and biological failure (e.g., Barrese et al., JNE 2013). This decline reduces the performance (speed and accuracy) of the BMI to the point where a clinical intervention, such as replacing the electrode array, may be necessary. We asked if an algorithmic intervention, performed entirely in software, can rescue BMI performance and thereby postpone potential clinical intervention? To

address this question, we sought to include historical data, recorded from an earlier point in the array lifetime when more neurons were observed, as additional prior information to augment the BMI decoder. We term this concept "neural hysteresis," because historical neural observations (memory) are used to improve the current decoder. We implemented this idea by using a decoder that models the dynamical properties of neural population responses in motor cortex (the neural dynamical filter or NDF, Kao et al., SFN 2013). We posit that if the neural dynamics accurately reflect properties of motor cortex, then having a better estimate of these dynamics should result in a better decoder. To obtain a "best estimate" of these dynamics, we used a historical training set (when more neurons were available) to learn a neural dynamical model. This neural dynamical model constituted our "memory" from a prior state. We performed an offline experiment where we simulated array failure by artificially removing neural channels. Beginning with 192 channels (all channels available), we proceeded to drop channels (in increments of 10), re-building the NDF with the remaining channels. Therefore, for the NDF, the neural dynamical model was inferred from only the remaining channels available. We observed a substantial decrease in performance as channels were lost. To test our approach to "neural hysteresis," we built a hysteresis-NDF (HNDF) that incorporated the neural dynamical model learned from a historical training set. Thus, the difference between the HNDF and the NDF is that the HNDF incorporates a better neural dynamical model, learned from many more neurons. We found that when 82 or fewer channels remained, the HNDF significantly outperformed the NDF in offline performance ($p < 0.01$, paired t-test). These results suggest that neural dynamics capture important features of the neural population responses in motor cortex, and that knowledge of these dynamics may rescue BMI performance as array signal quality degrades.

Disclosures: J.C. Kao: None. **S.I. Ryu:** None. **K.V. Shenoy:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.05

Topic: D.18. Brain-Machine Interface

Support: DARPA Grant N66001-10-C-4056

NIH Grant 1F32NS092430-01

Title: Engineered learning toward improved brain-machine interface and rehabilitation training

Authors: *J. J. WILLIAMS[1,2], R. N. TIEN[3,2], Y. INOUE[1], A. B. SCHWARTZ[1];
[1]Systems Neurosci. Inst., [2]Ctr. for the Neural Basis of Cognition, [3]Dept. of Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The field of brain-machine interfaces (BMI) has developed dramatically over the past two decades with recent demonstration of control of up to 10 degrees of freedom by a human tetraplegic subject. During this time, much effort has rightfully been directed toward improving the decoding algorithms that drive the movement of a prosthetic effector. For example, several studies have examined adapting a BMI's decoding algorithm to the estimated neural strategy of the user at different timescales. However, in many of these studies, the inherent difficulty of the BMI task throughout the learning trajectory remained unchanged or was altered in an ad-hoc fashion, potentially hindering the learning trajectory and impairing the experience of the BMI user. In this study, we chose to focus on improving the learning trajectory and experience of the BMI user by designing and implementing a framework that tailors the difficulty of a given BMI task to the skill and learning trajectory of the user. Recent work from our lab has outlined a framework for systematically adjusting the difficulty of a BMI task. Included in this framework are methods for defining the difficulty of a parameterized task, modeling and estimating the real-time skill of a BMI user, and adjusting the difficulty of the task to maintain subject motivation while still providing sufficient error feedback to promote further skill acquisition. To date, we have employed this algorithm in two non-human primates performing a progression of BMI tasks with 1 to 4 controllable degrees of freedom using intracortical neural signals. Here, we will present evidence that this system generalizes well across subjects and tasks, demonstrating both intra- and inter-session task adaptation and skill acquisition by the subject. In addition to examining the learning trajectories observed using such a system, we also examine the neural correlates of motor learning that accompany this BMI skill acquisition. Overall, our results suggest practical training principles for both BMI and rehabilitation purposes as well as insights into the neural processes that may occur during natural motor skill development.

Disclosures: J.J. Williams: None. **R.N. Tien:** None. **Y. Inoue:** None. **A.B. Schwartz:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.06

Topic: D.18. Brain-Machine Interface

Support: NSF GRFP Grant DGE-1247842

DARPA Award No N66001-10-C-4056

Title: Modulation of somatosensory cortex during brain control of an anthropomorphic robotic limb

Authors: *S. N. FLESHER[1], A. B. SCHWARTZ[2], R. A. GAUNT[3];
[2]Dept. of Neurobio., [3]Dept of Physical Med. and Rehabil., [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Primary somatosensory cortex (S1) is known to receive input from peripheral afferents and respond based on the location and modality of the peripheral stimulus. S1 also contains corticospinal neurons and can show changes in activity during real or attempted movements in the absence of somatosensory feedback. We use neural activity recorded from intracortical microelectrodes during a brain computer interface (BCI) paradigm to study how S1 activity is modulated during prosthetic limb movements controlled using neural activity decoded from primary motor cortex (M1). This gives us the unique opportunity to study S1 during control of a device while the subject receives no task-relevant cutaneous feedback. An 88-electrode intracortical microelectrode array was placed in M1 and a 32-electrode intracortical microelectrode array was placed in area 1 of S1 in a non-human primate (NHP). The M1 array was placed in the upper arm representation of M1 and the S1 array was placed in the hand and finger representation of area 1. Placement of the S1 arrays was verified by receptive field mappings. The subject was trained on a series of reach to grasp and carry tasks using his native upper limb. Kinematics of the subject's movements and manipulation of the object were recorded with motion capture and a triple axis accelerometer mounted on the object. In a second experiment, the subject used a BCI that used decoded neural activity recorded from the array in M1 to control a robotic limb to perform the same reaching and grasping tasks. When the subject used his native limb, we found sharp peaks of neural activity in S1 shortly after object contact and object release, consistent with the expected behavior of somatosensory cortical neurons. In the BCI paradigm, when the subject used the robotic limb, spiking activity of some S1 neurons continued to modulate in a similar fashion. Activity peaks in the BCI case showed modulation of S1 in the absence of peripheral cutaneous input. Based on the modulation of S1 during the BCI task, we found that area 1 of S1 responds during the control of a robotic hand interacting with an object. This modulation of S1 could suggest a mirror-neuron like phenomenon in S1. It is also possible that the S1 activity reflects a portion of the motor command, or an efference copy of the motor command in M1 representing attempted grasp.

Disclosures: **S.N. Flesher:** None. **A.B. Schwartz:** None. **R.A. Gaunt:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.07

Topic: D.18. Brain-Machine Interface

Support: DARPA contract N66001-10-C-4056

DARPA ARM-S program

NSF Grant DGE-1252522

Title: Blending of brain-machine interface and vision-guided autonomous robotics improves neuroprosthetic arm performance during grasping

Authors: *J. E. DOWNEY[1,4], J. WEISS[2], K. MUELLING[5], A. VENKATRAMAN[5], J.-S. VALOIS[5], A. BAGNELL[5], A. B. SCHWARTZ[1,5,3], J. L. COLLINGER[1,2,6];
[1]Dept. of Bioengineering, [2]Dept. of Physical Med. and Rehabil., [3]Dept. of Neurobio., Univ. of Pittsburgh, Pittsburgh, PA; [4]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [5]Robotics Inst., Carnegie Mellon Univ., Pittsburgh, PA; [6]VA Pittsburgh Healthcare Syst., Pittsburgh, PA

Abstract: Recent studies have shown that brain-machine interfaces (BMIs) offer great potential for restoring upper limb function, however a number of factors may limit the capacity of the control signal acquired from the brain. In particular, grasping and manipulating objects requires very accurate control of the arm and hand. This accuracy can be accomplished by blending brain-derived intended movement signal with vision-guided autonomous robot control. We describe a shared control framework where the goal is inferred from the BMI-decoded velocity commands and the vision information of an RGB-D camera. By rating the confidence of each control signal, the framework smoothly blends them together. The autonomous robot control assists in positioning the hand at a suitable grasp position, in preventing the subject from knocking over the object, in opening and closing the hand, and it ensures a compliance appropriate for the inferred task. Two human subjects with tetraplegia used an intracortical BMI to control a robotic arm to complete object transport tasks both with and without shared control. The computer vision system identified objects in the workspace in real time and defined stable grasp positions. Once the user approached the object with the robotic arm, the system guided the movements to ensure a stable grasp. Computer assistance was also used to maintain a grasp during transport. Care was taken to adjust the amount of shared control to provide an optimal balance between BMI control and computer assistance. The two subjects combined to complete an object transfer task successfully 65% of the time with shared control, and 13% of the time without ($p < 0.001$, Fisher's Test). During the shared control trials, arm speed was lower while it moved near the objects, but trial completion times did not increase. When asked to rank the difficulty of using the arm on a 10 point scale (1 - extremely easy to 10 – extremely difficult) the subjects reported an average difficulty of 4.2 with shared control vs. 7.9 without shared control (both subjects: $p <$

0.02, Wilcoxon signed-rank test). One participant attempted a task that required the selection of one of two objects. He achieved a success rate of 92% with shared control demonstrating the potential to allow the user to maintain autonomy while using shared control. Integration of BMI control with computer vision-based assistance led to improved performance on object transfer tasks while maintaining the user's autonomy. Providing assistance without removing generalizability will make BMI systems more attractive to potential users.

Disclosures: J.E. Downey: None. **J. Weiss:** None. **K. Muelling:** None. **A. Venkatraman:** None. **J. Valois:** None. **A. Bagnell:** None. **A.B. Schwartz:** None. **J.L. Collinger:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.08

Topic: D.18. Brain-Machine Interface

Support: EC grant VERE

Title: Brain computer interface assisted stroke rehabilitation with multimodal feedback

Authors: *C. GUGER[1], R. ORTNER[2], N. SABATHIEL[3];
[1]g.tec Guger Technologies OG, Schiedlberg, Austria; [2]g.tec medical engineering GmbH, Schiedlberg, Austria; [3]Guger Technologies OG, Schiedlberg, Austria

Abstract: A brain-computer interface (BCI) allows to analyze brain activity in order to control an avatar or rehabilitation training device. Important for a successful outcome of the rehabilitation procedure is that the mental activity is paired with the avatar movements or rehabilitation device movements. The study was performed with two patients who had a stroke 4 years earlier (P1, female, 40 years old) or 2 month earlier (P2, female, 61 years old). P1 suffered a complete paralysis of her left hand, but had normal right hand movements. The hand movement performance of P2 was measured with a 9 hole PEG test and showed that the right arm needed about twice as much time to complete the test. Both patients performed the motor imagery (MI) session by imagining left or right hand movements according to an instruction on a computer screen. Then the BCI system analyzed the EEG data and controlled the avatar hand movement on the computer screen and simultaneously controlled an functional electrical stimulator (FES) that stimulated the corresponding hand. Therefore the patient could see the virtual hand movement and his real hand was simultaneously also moving. After 10 training sessions of 30 min each with P1 and 21 training sessions with P2 the success of the procedure

could already be shown. P2 was able to move the paralyzed hand herself without the BCI and FES and P2 could perform the 9-hole PEG test with similar speed for both hands. This shows that the training is successful and more patients are undergoing currently further tests.

Table 1: Results of the two patients. The 9-hole PEG tests shows an improvement of the affected hand for P2 from 65 seconds before the treatment to 30 seconds after the last treatment. P1 was not able to perform the 9-hole PEG test, but improved in BCI control accuracy.

P2				P1	
Session	Control accuracy (%)	9-hole PEG test Left hand (s)	9-hole PEG test Right hand (s)	Session	Control accuracy (%)
0	-	31	65	1	63,7
3	95,0	32	54	4	86,2
6	91,2	32	45	7	96,2
9	92,5	31	42	10	96,2
12	95,0	31	42		
15	91,2	29	38		
18	91,2	29	34		
21	88,7	29	30		

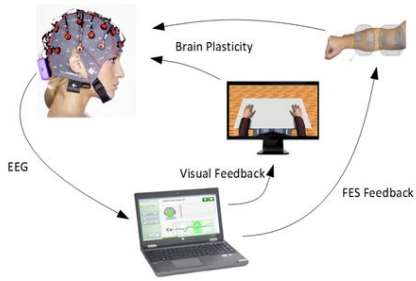


Figure 1: System overview. The EEG is acquired on 32 positions over the cortex. The BCI drives the two feedback modalities, the visual feedback and the FES feedback.

Disclosures: C. Guger: None. **R. Ortner:** None. **N. Sabathiel:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.09

Topic: D.18. Brain-Machine Interface

Support: DARPA MTO SPAWAR Pacific Grant/Contract No. N66001-15-C-4017

NIH 1ULTR001067

Title: Using multiple Utah Slanted Electrode Arrays (USEAs) to control 5-degrees-of-freedom of a virtual prosthetic hand and provide sensations in the phantom hand for a human, transradial amputee

Authors: *S. WENDELKEN[1], D. M. PAGE[1], T. DAVIS[2], D. J. WARREN[1], C. DUNCAN[3], D. HUTCHINSON[4], G. A. CLARK[1];
[1]Bioengineering, [2]Neurosurg., [3]Physical Med. and Rehabil., [4]Orthopedic Surgery, Univ. of Utah, Salt Lake City, UT

Abstract: To date, commercially available myoelectric prosthetics are not capable of measuring sufficiently unique signals needed for individual and articulate digit control, and do not provide naturalistic sensory feedback. We are developing an improved interface for a prosthetic hand that will use highly selective intraneural and intramuscular recordings from the residual limb for the control signals and that will provide sensory feedback via microstimulation of residual peripheral nerves. Previously, we demonstrated 1-Degree-of-Freedom (DoF) closed-loop control of a virtual prosthetic hand (VPH) using an electromyographic (EMG) control signal recorded from one Utah Slanted Electrode Array (USEA), and sensory feedback provided by microstimulation through another USEA, both implanted into the residual arm nerves of a human, transradial amputee [1]. Here we present results from a recent study in which we used neural signals from USEAs implanted into the peripheral arm nerves of a human amputee to control up to 5 or more DoFs of a VPH in real-time. In this IRB-approved study, 2 USEAs were implanted in the residual ulnar and median arm nerves (one per nerve) of a human, transradial amputee for 5 weeks. Experiments involved a training phase, in which USEA data were collected to train a decode algorithm, and a testing phase, in which the subject attempted to control the VPH to touch or follow targets in virtual space. A Kalman filter was used to decode the position of the VPH from the neural firing rates in real time. The subject successfully completed a 5-DoF target touching task (20/21 successful trials, flexion of digits 1-4 in addition to wrist flexion/extension). This level of control exceeds that achieved in previous investigations using peripheral nerve interfaces. Additionally, this subject could intuitively combine individual DoF movements into novel grasp movements (e.g., forefinger-thumb “pinch”) without further training. During an informal free-form session, this subject demonstrated 10-12 DoF control. However, this session did not allow a quantified determination of the error rate. In microstimulation experiments, the subject reported up to 131 localized proprioceptive and cutaneous percepts spanning the fingers, palm, and posterior of the hand. Results from these studies support the use of USEAs signals to provide unique and intuitive control signals for a prosthetic hand. In upcoming studies, we will combine EMG and simultaneous stimulation and recording from USEAs using the Grapevine system (Ripple, Salt Lake City, UT) into a hybrid, bi-directional control system. [1] Clark, G.A., et al. 2014 36th Annual International Conference of the IEEE EMBC, 1977-80

Disclosures: S. Wendelken: None. **D.M. Page:** None. **T. Davis:** None. **D.J. Warren:** None. **C. Duncan:** None. **D. Hutchinson:** None. **G.A. Clark:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.10

Topic: D.18. Brain-Machine Interface

Support: APL Graduate Fellowship

NIH Grant 1R01NS088606

Title: Online control over individual finger movements with the modular prosthetic limb using high-density electrocorticography in a human subject

Authors: *G. HOTSON[1], D. P. MCMULLEN[2], M. S. FIFER[3], K. D. KATYAL[4], M. S. JOHANNES[4], W. S. ANDERSON[2], N. V. THAKOR[3], B. A. WESTER[4], N. E. CRONE[3]; [1]Dept. of Electrical and Computer Engin., [2]Dept. of Neurosurg., [3]Dept. of Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [4]Johns Hopkins Univ. Applied Physics Lab., Laurel, MD

Abstract: Brain-machine interfaces have made great strides towards restoring the ability to reach to objects and perform simple grasping movements. Users have simultaneously controlled many degrees of freedom afforded by prosthetic devices using only their cortical signals. However, dexterous control over individual finger movements has remained elusive. This has left paralyzed BMI users incapable of performing tasks requiring the fine level of finger manipulation often taken for granted by able bodied persons. Here we show online neural control over the individual fingers of the Johns Hopkins University Applied Physics Lab (JHU/APL) Modular Prosthetic Limb (MPL). This was accomplished by using the high gamma responses extracted from high-density electrocorticography (ECoG) in a human subject moving his corresponding native fingers. The classification finger movements from the high gamma signal was performed through hierarchical linear discriminant analysis with a Markovian prior on a gating classifier. The subject was able to use this system to fully flex only the desired finger in 57% of trials (chance 20%). The pinky and ring fingers were often confused for one another, and the success rate would have improved to 76% (chance 25%) had those fingers been treated as one. The gating classifier was able to correctly distinguish between movement and rest with an accuracy of 89% (chance 50%). Peak online classification accuracy of individual fingers reached 80.5% (chance 20%), and 93.7% with ring and pinky fingers coupled. This shows the ability of high-density ECoG to control a high degree of freedom brain machine interface in order to actuate individual finger movements. This was accomplished through the use of the native cortical representation of finger movements, without the need for any unintuitive operant conditioning.

Disclosures: **G. Hotson:** None. **D.P. McMullen:** None. **M.S. Fifer:** None. **K.D. Katyal:** None. **M.S. Johannes:** None. **W.S. Anderson:** None. **N.V. Thakor:** None. **B.A. Wester:** None. **N.E. Crone:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.11

Topic: D.18. Brain-Machine Interface

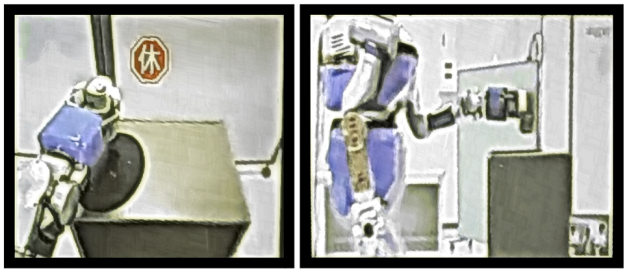
Support: EU FP7 Project VERE (No. 257695)

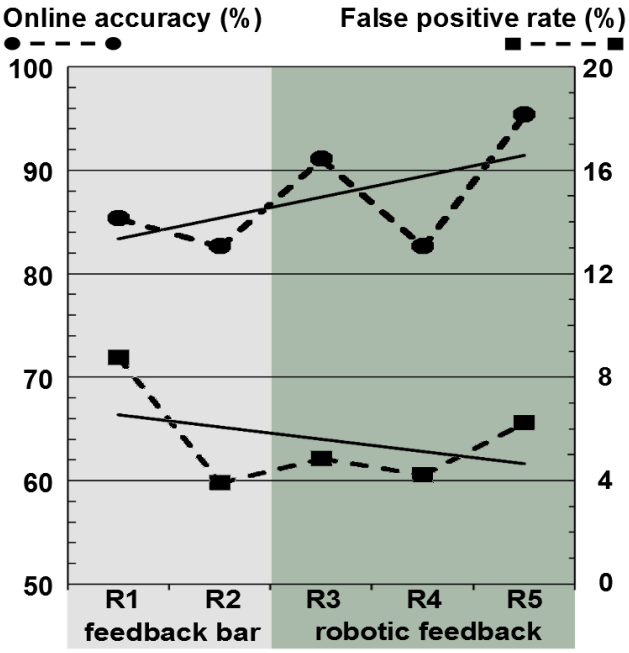
ENIAC Project DeNeCoR (No. 324257)

Title: A motor imagery BCI for online control of a humanoid robot using electrocorticograhpic signals

Authors: ***C. KAPELLER**[1], P. GERGONDET[2], K. KAMADA[3], H. OGAWA[3], F. TAKEUCHI[3], R. ORTNER[1], R. PRUECKL[1], A. KHEDDAR[2], C. GUGER[1];
[1]G.Tec Med. Engin. Gmbh, Schiedlberg, Austria; [2]CNRS-AIST Joint Robotics Lab., Tsukuba, Japan; [3]Dept. of Neurosurg., Asahikawa Med. Univ., Asahikawa, Japan

Abstract: Decoding brain activity could lead to a powerful and independent Brain-Computer-Interface (BCI) allowing for intuitive control of devices like robots. Electrocorticography (ECoG) allows extracting robust features and easy introduction of an idle state. Common spatial patterns (CSP) provide a powerful tool for feature optimization and dimensionality reduction, especially for multi-channel ECoG recordings. This work focuses on an ECoG motor imagery BCI that allows triggering from an idle state, and therefore facilitates tele-operation of an HRP-2 humanoid robot (Kawada Industries, Japan) (see Figure 1). The experiment contained six runs separated into three phases, (i) training (R0), (ii) online classification with a feedback bar (R1 and R2) and (iii) online classification with robotic feedback (R3, R4 and R5). Each run consisted of 20 active trials to lift a can and 20 idle trials. One subject, who had a 60 channel high-density subdural grid implanted over the right motor cortex, participated in the study. Data were sampled with 1200 Hz and band pass filtered at 0.5-500 Hz. After each run the best two feature-enhancing and -suppressing CSPs were determined for the frequency band of 8-32 Hz and a linear classifier was computed based on the band power values of a 1.0 s signal buffer. In the last run the subject reached 95.4 % mean online accuracy over 40 trials (see Figure 2). To our knowledge, this is the first online experiment with a motor imagery BCI using CSPs from ECoG signals.





Disclosures: **C. Kapeller:** None. **P. Gergondet:** None. **K. Kamada:** None. **H. Ogawa:** None. **F. Takeuchi:** None. **R. Ortner:** None. **R. Prueckl:** None. **A. Kheddar:** None. **C. Guger:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.12

Topic: D.18. Brain-Machine Interface

Support: The US taxpayers

NIH Common Fund Transformative R01 Research Award Grant 1R01NS081710 – 01

Alberta Innovate Health Solution Graduate Scholarship Grant AIHS GS 201400077

Natural Sciences and Engineering Research Council of Canada Grant PGSD3-460264-2014

Title: Engineering perceptual illusions of hand movement to sense the activity of bidirectionally integrated bionic limbs

Authors: *P. D. MARASCO[1,2], J. S. HEBERT[3], J. S. SCHOFIELD[4], Z. C. THUMSER[2], J. P. CAREY[4], B. M. ORZELL[2];
[1]Biomed. Engin., Cleveland Clinic, Lerner Res. Inst., Cleveland, OH; [2]Advanced Platform Technol. Ctr., Louis Stokes Cleveland VA Med. Ctr., Cleveland, OH; [3]Dept. of Med., [4]Mechanical Engin., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Individuals with amputation cannot feel their prosthetic limbs. Despite advances in technology, artificial hands are still insensate tools that must be carefully watched at all times to perform even simple tasks. A principal reason older cable-actuated prosthetic split-hook grippers and body-powered elbows still see widespread use is because the joint movements can be intuitively felt through the cable system. The loss of meaningful proprioceptive feedback is a critical drawback preventing intuitive use of advanced prosthetic limbs. Kinesthesia, the sense of limb movement, is fundamentally important to restoring the sense of natural prosthetic movement. The kinesthetic illusion, a joint-specific illusionary perception of movement generated by vibrating limb tendons at 70 to 115 Hz, is a perceptual phenomenon with applicability as the missing element for effective bidirectionally integrated prosthetic limbs. By examining prosthetic feedback within a new perceptual cognitive framework we show that it is possible to engineer perception of specific illusionary active hand movements with functionally relevant grip conformations for human amputees. Targeted reinnervation was used to reassign the sensory-neural structure of the remaining proximal post-amputation musculature. Vibrational input was used to activate the kinesthetic movement illusion in rewired muscles to systematically generate complex cognitive percepts of dynamic hand grips in the absence of the actual wrist and hand. Six human amputee study participants with a bidirectional neural-machine-interface independently reported many similar complex synergistic movement percepts that appeared to be representative of basic coordinated actions required for dexterous manipulation. Movement sensations were independent of whether the overlying skin was natively innervated or reinnervated with the restored sensory hand map of the study subjects; suggesting activity of the reinnervated muscle sensory receptors alone is sufficient for the perception of active hand movements. Frequency-displacement curves with respect to magnitude of illusionary strength indicated the strongest responses to illusionary input at measured frequencies between 70 and 90 Hz; which falls within the 70-115 Hz band of the kinesthetic illusion reported for able bodied. These illusionary perceptual sensations were mapped directly to the movement of commercially-available dexterous robotic hands to provide real-time simultaneous volitional motor control and

active kinesthetic perceptual sensory feedback for prosthetic limbs through a bidirectional neural-machine-interface.

Disclosures: **P.D. Marasco:** None. **J.S. Hebert:** None. **J.S. Schofield:** None. **Z.C. Thumser:** None. **J.P. Carey:** None. **B.M. Orzell:** None.

Nanosymposium

748. Controlling Prostheses with Brain Machine Interfaces

Location: N226

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 748.13

Topic: D.18. Brain-Machine Interface

Support: FRM foundation (DBS20140930785)

Title: Real-time articulatory speech synthesis for brain-computer interfaces

Authors: ***F. BOCQUELET**[1,2], T. HUEBER[2], L. GIRIN[2], C. SAVARIAUX[2], B. YVERT[1]; [1]CLINATEC, Grenoble Cedex 9, France; [2]Gipsa-Lab INP/CNRS, Grenoble, France

Abstract: Brain-Computer Interfaces (BCIs) typically propose typing strategies to restore communication for paralyzed and aphasic people. A more natural way would be to directly control an artificial speech synthesizer. Such approach requires a synthesizer that can be controlled in real time to produce intelligible speech. In a recent work, we used an existing corpus of French articulatory-acoustic data to build an articulatory speech synthesizer based on Deep Neural Networks that mapped movement trajectories of the jaw, tongue, and lips recorded by electromagnetic articulography (EMA) to speech signals, and showed that this mapping approach ensured robust speech synthesis. Here, we first developed a new model providing more intelligible speech synthesis. For this purpose, we recorded from a reference speaker a new articulator-acoustic corpus made of 712 French sentences of variable lengths (4531 words in total) using nine 3D EMA sensors located on the tongue, lips, jaw, and velum. A DNN model was built that allowed transforming this EMA data into clearly intelligible speech in real time. In a second step, we tested to which extent this synthesizer could be controlled in real time to produce continuous speech. Four different subjects participated in the study. For each subject, EMA trajectories of 6 sensors located on the tongue, lips and jaw were recorded. A calibration model was built on 50 short sentences of the corpus to map this EMA data to the EMA data of the reference speaker. Then new incoming EMA data was converted in real time with this model and then streamed to the speech synthesizer. The auditory feedback was given in real-time to the subject who was silently articulating to produce artificial speech. All subjects were able to

control the synthesizer in real-time. The intelligibility of vowels and vowel-consonant-vowel sequences was assessed. Interestingly, spontaneous conversations with the experimenters were possible with several subjects. This real time speech synthesis approach could further be used in BCI paradigms for direct speech production from cortical signals.

Disclosures: F. Bocquelet: None. **T. Hueber:** None. **L. Girin:** None. **C. Savariaux:** None. **B. Yvert:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.01

Topic: E.05. Stress and the Brain

Support: US Army Grant DM102281

Title: Locus coeruleus noradrenergic system response to traumatic stress in PTSD model and early intervention with intranasal NPY

Authors: *E. L. SABBAN, L. I. SEROVA, M. LAUKOVA, L. G. ALALUF, E. OLSSON; Dept Biochem & Mol Biol, New York Med. Coll, Valhalla, NY

Abstract: Dysregulation of central noradrenergic system, one of the core features in PTSD, may mediate heightened stress sensitivity, hyperarousal and re-experiencing symptoms. The locus coeruleus (LC), origin of majority of noradrenergic neurons in the brain, mediates a variety behaviors such as arousal, memory acquisition, attention, vigilance, and responses to stress. Here we examined molecular changes in LC triggered by single prolonged stress (SPS) PTSD model, and their response to early intervention with intranasal NPY infusion, at the time in which the PTSD-related symptoms are manifested, with specific attention to changes which might mediate heightened stress sensitivitiy. Male SD young adult rats were exposed to SPS stressors and immediately afterwards given intranasal infusion of vehicle or 150 µg NPY and left undisturbed. Seven days later, at time when behavioral symptoms are manifested, TH protein, but not mRNA, was elevated compared to unstressed controls only in LC of vehicle-infused rats. Although 90% of TH positive cells also expressed GR, its levels were unaltered. In LC, mRNA levels for CRH receptor 1 (CRHR1) mRNA were elevated by SPS in subset of animals and Y2 mRNA reduced, while CRH expression was higher in the central nucleus of amygdala (CeA) compared to unstressed controls. These changes were not present in animals given intranasal NPY. The LC of SPS animals were found to have enhanced sensitivity to mild trauma related (forced swim) or

unrelated (EPM) stressors. Testing for anxiety on EPM of SPS treated, but not previously unstressed, animals triggered more than 5-fold increase in TH, DBH and NPY mRNAs. Wide variations in response of TH and DBH mRNA levels in LC of SPS treated animals to the mild stress of EPM suggested differences in susceptibility or resilience. The results show that SPS triggers long term noradrenergic activation with increased expression of NE biosynthetic enzymes and heightened sensitivity to mild stressor. This may be mediated by enhanced CRH input from CeA and elevated CRHR1 gene expression and reduced Y2R presynaptic inhibition in LC. Results demonstrate therapeutic potential for early intervention with intranasal NPY for traumatic elicited noradrenergic impairments.

Disclosures: **E.L. Sabban:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stressout Inc. **L.I. Serova:** None. **M. Laukova:** None. **L.G. Alaluf:** None. **E. Olsson:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.02

Topic: E.05. Stress and the Brain

Support: DA09082

Title: Neuroanatomical Interactions of NPY and CRF Systems in the amygdala

Authors: ***N. ENMAN**, B. A. REYES, E. J. VAN BOCKSTAELE;
Pharmacol. and Physiol., Drexel Univ., Philadelphia, PA

Abstract: Neuropeptide Y (NPY) has been identified as a neurochemical mediator of stress resilience. NPY is abundant within the central nucleus of the amygdala (CeA), a brain region directly involved in integrating stress responses and eliciting emotional reactivity to environmental cues. The CeA sends afferents of the pro-stress peptide corticotropin-releasing factor (CRF) to the locus coeruleus (LC)-norepinephrine (NE) system in a circuit that is proposed to mechanistically link limbic and arousal centers during stress. Overlap of the NPY and CRF systems in the CeA bears significance, as NPY is hypothesized to promote stress resilience by functionally opposing the excitatory effects of CRF. However, the anatomical organization of the NPY system as it relates to the CRF system in the CeA, which may influence LC-NE mediated functions, remains unstudied. We hypothesize that NPY promotes stress resilience by impacting on the function of the LC-NE system, potentially through direct

neuroanatomical interactions with amygdalar CRF circuitry. To investigate cellular sites for interactions between the NPY and CRF systems, coronal sections through the CeA were processed for immunocytochemical detection of NPY or NPY receptors (Y1R or Y2R) and CRF in tissues obtained from male rats. Examination of the CeA using immunofluorescence microscopy demonstrated co-localization of Y1R and Y2R subtypes with CRF-expressing cell bodies. High-resolution immunoelectron microscopy using gold-silver labeling for Y1R and Y2R and immunoperoxidase labeling for CRF confirmed that CRF-immunoreactive dendrites express Y1R and Y2R. Further examination for NPY and CRF peptidergic interactions by electron microscopy indicated that NPY was frequently co-localized within dendrites and soma expressing CRF in the CeA. These findings provide indirect evidence for the modulation of the LC-NE system through potential interactions of amygdalar NPY and CRF systems. Delineating interactions between neurochemical mediators of stress resilience and components of the LC-NE system is critical to our continued understanding of the cellular mechanisms underlying effective coping to stress.

Disclosures: N. Enman: None. **B.A. Reyes:** None. **E.J. Van Bockstaele:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.03

Topic: E.05. Stress and the Brain

Title: CRH neurons encode different acute stress levels by activity changes in individual cells and alteration in coordinated population response

Authors: *C. M. VOM BERG - MAURER[1], C. A. TRIVEDI[2], J. H. BOLLMANN[2], R. J. DE MARCO[1], S. RYU[1];
[1]Max Planck Inst. For Med. Res., Heidelberg, Germany; [2]Neural Circuits and Behavior Res. Group, Dept. of Biomed. Optics, Max Planck Inst. for Med. Res., Heidelberg, Germany

Abstract: An integrated stress response is triggered when animals face a state of threatened homeostasis. Corticotropin-releasing-hormone (CRH) released from the paraventricular nucleus (PVN) of the hypothalamus lies at the apex of the hypothalamo-pituitary-adrenocortical (HPA) axis, which initiates a hormonal cascade to regulate diverse aspects of stress physiology and behavior. To achieve an optimally tuned adaptive response, it is critical that the magnitude of the endocrine stress response matches the severity of the threat. However, how the activity of CRH neurons relates to the level of acute stress *in vivo* is currently not known. We characterized for

the first time activity of CRH cells in intact animals using two-photon calcium imaging in larval zebrafish with transgenic label of CRH cells while simultaneously applying stressful input of different intensity. Perturbations of the environment such as salinity change and pH fluctuation increase whole body cortisol, and lead to behavioral stress reactions in larval zebrafish. In response to these stressors, our results reveal that CRH neurons alter their activity at both the individual and the population level. Under unstimulated conditions, CRH cells are either active or inactive, while stress exposure can lead to clear increase in activity in some CRH neurons. Such stressor-induced activity changes in the frequency and amplitude of Ca2+-transients of individual CRH neurons co-vary with stressor intensity. Strikingly, stressor exposure also induces broadening of the responsive pool of CRH cells through recruitment of previously inactive CRH neurons in an intensity-dependent manner. pH drop leads to greater HPA axis activation than salinity change, reflected in a greater number of responsive CRH cells, higher whole body cortisol levels and more pronounced avoidance behavior. Stressor-induced activity among CRH neurons is highly synchronized suggesting the existence of a tight coordination mechanism at the population level. Thus, our results provide first *in vivo* assessment of the acute stress response of CRH cells and reveal how different acute stress levels are encoded by CRH neurons.

Disclosures: C.M. Vom Berg - Maurer: None. **C.A. Trivedi:** None. **J.H. Bollmann:** None. **R.J. de Marco:** None. **S. Ryu:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.04

Topic: E.05. Stress and the Brain

Support: CIHR Grant

Title: Hypothalamic CRH neurons balance inward and outward behavior

Authors: *T. FUZESI, J. I. WAMSTEEKER CUSULIN, N. DAVIU, J. S. BAINS; Hotchkiss Brain Inst., Hotchkiss Brain Inst., Calgary, AB, Canada

Abstract: In the absence of tasks requiring immediate attention or an external focus, animals, including humans, shift to behaviors that are self-referential and inwardly focused. How the brain regulates the shifts between these distinct behavioral states is not known. In order to investigate this, we used short exposure to stress which triggers outward, goal-directed behavior

and reliably followed by inward, repetitive and stereotyped behaviors. One of the best-studied inward behavior in rodents is self-grooming and is widely observed in response to stressful stimuli in natural and experimental settings. Classical electrical stimulation studies implicated the paraventricular nucleus of the hypothalamus (PVN) as a locus for intensive self-grooming behavior. The PVN houses corticotropin releasing hormone (CRH) synthesizing neurons that are endocrine command cells and activated during stress raising the possibility that PVN CRH neurons play a role in the stress induced shift between outward and inward behavior. To address this we used an approach that combines optogenetics, electrophysiology, anatomical tracing and behavior. After confirming that exposure to an acute external challenge is followed by a context-dependent switch to inward behavior, we utilized a transgenic CRH-Cre mouse line combined with optogenetical tools. First, inhibition of PVN CRH neurons by Archaerhodopsin revealed that persistent activity of CRH neurons following footshock is necessary for stress induced shift to inward behavior. Next, we found that channelrhodopsin 2 mediated optical stimulation of PVN CRH neurons launches robust and extensive self-grooming. In addition we found evidence that the activation of CRH neurons controls the balance between outward and inward behaviors with higher activation rates favouring inward behaviors at the expense of outward exploratory behaviors. We next conducted a series of experiments to elucidate the neural pathway(s) responsible for the shift to inward behavior. First, we identified CRH fibers in the lateral hypothalamus (LH) arising from the PVN and showed that selective optical activation of PVN CRH fibers in the LH is sufficient to trigger grooming response. Next, we used *in vitro* whole cell patch clamp recordings from LH neurons and demonstrated that CRH neurons in the PVN send direct excitatory projection to the LH. To further explore the links between context, external/internal behavior and CRH neuron activation, we performed the optical stimulation of CRH neurons in contexts of different threat levels and found that that the shift to inward behavior following activation of CRH neurons is sensitive to the requirement of outward focus.

Disclosures: **T. Fuzesi:** None. **J.I. Wamsteeker Cusulin:** None. **N. Daviu:** None. **J.S. Bains:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.05

Topic: E.05. Stress and the Brain

Support: Defense Advanced Research Projects Agency (DARPA) and the U. S. Army Research W911NF1010093

T32 Training Grant in Neurodevelopmental Disabilities (2T32NS007413-16)

Title: The role of orexins in sex differences in the stress response and in cognitive function

Authors: *L. GRAFE[1], A. CORNFELD[2], S. LUZ[1], S. BHATNAGAR[1,2];
[1]Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Stress-related psychiatric disorders, such as post-traumatic stress disorder (PTSD) and depression, are serious mental illnesses that occur twice as frequently in women compared to men. Despite this disparity, we do not fully understand the biological basis of these sex differences. Human studies have revealed differences in levels of the neuropeptides orexins in anxious and depressed patients compared to controls. Additionally, previous work from our lab has revealed that orexins contribute to the stress response and anxiety-like behavior in rats. In the studies described here, we explored sex differences in orexin expression, the stress response, and cognitive function in order to better define the role of these neuropeptides in stress-related phenotypes. Our data indicate that female rats exhibit higher orexin mRNA, neural activation, and concentrations in the cerebrospinal fluid compared to male rats under basal conditions. In stressed individuals, an important adaptation is the ability to habituate with repeated exposure to the same stress, a process that is impaired in disorders such as PTSD. We observed that, compared to males, females do not habituate as fully to five days of repeated restraint as assessed by: 1) sustained plasma levels of corticosterone and adrenocorticotropin hormone (ACTH) 2) persistent activation in the paraventricular nucleus (PVN) of the hypothalamus, and 3) continued struggle behavior displayed by females while in the restrainer on day 5. We then asked whether differential activation of orexin neurons in females compared to males could underlie the lack of habituation in female rats. Data indicate that stimulating orexin neurons (via DREADDS) during acute restraint increased plasma ACTH and corticosterone levels in male rats to the levels of control females. We next tested cognitive flexibility after repeated restraint stress using an Attentional Set Shifting (AST) paradigm, since stress related pathologies cause cognitive impairments. In the Side Reversal Task, stress increased the number of trials to criterion and errors in females, whereas stress improved male performance. cFOS expression in the orbitofrontal cortex (OFC), known to mediate Side Reversal, revealed less activation in females after stress, but more activation in males after stress, consistent with behavioral performance on the task. Future experiments will determine if orexins are important for the sex differences observed in this cognitive flexibility task. As orexins regulate stress responses, cognitive function, autonomic responses, and emotional memory, targeting orexins may impact a range of psychiatric symptoms in a sex-specific manner.

Disclosures: **L. Grafe:** None. **A. Cornfeld:** None. **S. Luz:** None. **S. Bhatnagar:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.06

Topic: E.05. Stress and the Brain

Support: Merck & Co LKR136861

Title: Orexin 2 receptor regulation of the Hypothalamic-Pituitary-Adrenal (HPA) response to acute and repeated stress

Authors: *D. EACRET[1], L. GRAFE[1], S. LUZ[1], L. N. WILSON[1], A. GOTTER[2], C. WINROW[2], S. BHATNAGAR[1,3];
[1]Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Merck & Co, West Point, PA; [3]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Orexin antagonists are used as alternatives to GABA modulators for the pharmacological treatment of insomnia. Beyond their contribution to arousal, orexins are known to play a role in the regulation of the stress response. However, the specific contribution of the orexin 1 and orexin 2 receptors is unclear. To examine the role of the orexin 2 receptor in the stress response, we administered MK-1064 (a selective orexin 2 receptor antagonist) prior to 5 days of daily 30min restraint with and without stimulating orexin neurons via DREADDs (Designer Receptors Exclusively Activated by Designer Drugs). Male Sprague-Dawley rats were injected bilaterally with orexin DREADDs virus into the lateral hypothalamus 4 weeks prior to the start of the experiment for maximal virus expression. Animals were administered vehicle, 10mg/kg MK-1064, or 30mg/kg MK-1064 orally, followed by vehicle or Clozapine N-Oxide (CNO) intraperitoneally to activate the DREADDs 90 minutes prior to the start of restraint. In rats without DREADDs-induced activation of orexins, rats displayed habituation of both ACTH and struggle behavior from day 1 to day 5 of restraint, as expected. Both doses of MK-1064 reduced only day 1 ACTH levels compared with vehicle treated rats but did not have an additional effect on day 5. These data suggest that the orexin 2 receptor contributes to the HPA response to acute stress. In the rats in which orexins were stimulated by CNO, the 30mg/kg dose decreased ACTH levels on day 5 beyond the habituated ACTH levels. These data suggest that when the majority of orexin neurons are stimulated throughout 5 days of restraint, orexins acting via the orexin 2 receptor limit the magnitude of habituation. Blocking orexin 1 receptors is unlikely to produce a further enhancement of habituation. Lastly, rats given CNO lost more body weight during the 5 days of restraint than vehicles, and MK-1064 prevented this body weight loss, indicating that the orexin 2 receptor might contribute to broader effects of repeated stress. Collectively, these results provide insight into the role of both the orexin 1 and orexin 2 receptors in regulating the response to acute and to repeated stress.

Disclosures: **D. Eacret:** None. **L. Grafe:** None. **S. Luz:** None. **L.N. Wilson:** None. **A. Gotter:** A. Employment/Salary (full or part-time); Merck & Co. **C. Winrow:** A. Employment/Salary (full or part-time); Merck & Co. **S. Bhatnagar:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Merck & Co.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.07

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant DP2MH104119

NIH Grant RO1EB018297

Title: Parvalbumin positive interneurons in CA1 play a role in coordinating theta frequency oscillations and sleep-dependent memory consolidation

Authors: ***N. OGNJANOVSKI**[1], S. SCHAEFFER[1], D. MARUYAMA[2], S. MOFAKHAM[2], M. ZOCHOWSKI[2], S. ATON[1];
[1]Molecular, Cellular, and Developmental Biol., Univ. of Michigan Aton Lab., Ann Arbor, MI;
[2]Physics, Biophysics Program, Univ. of Michigan, Ann Arbor, MI

Abstract: Human neuropathologies like epilepsy, Alzheimer's disease, and schizophrenia have both cognitive (e.g. long-term memory) defects as well as disrupted sleep patterns. Consolidation of contextual fear memory (CFM) in mice is dependent on sleep, although the network-level mechanisms are unknown. In C57Bl/6 mice, during CFM consolidation there are increases in CA1 neuronal firing and in hippocampal theta (4-12 Hz) oscillations during post-training rapid eye movement (REM) sleep. We tested the role parvalbumin-expressing (PV+) interneurons play in state-specific patterns of hippocampal activity (e.g. REM theta), and whether this coordination facilitates memory consolidation. Pharmacogenetic tools in combination with chronic *in vivo* recording were used to characterize neuronal and network activity changes during CFM consolidation. Adeno-associated virus (AAV) was used to express the inhibitory designer receptor hM4Di in a CRE-dependent manner in hippocampal CA1 in Pvalb-CRE mice. Following single-trial contextual fear conditioning (CFC), PV+ cells were silenced via systemic administration of an hM4Di-selective agonist, CNO; control mice were treated with vehicle.

CFM consolidation was measured 24 hours later. CA1 recordings were carried out during a 24h baseline period, and for 24h following CFC. Functional connectivity was assessed over time in CA1 based on spike timing relationships among recorded neurons. Stability of connectivity was assessed by comparing connectivity maps across successive 1-min recording intervals throughout baseline and post-CFC periods. Silencing of PV+ FS-interneurons led to impaired CFM consolidation (assessed by quantification of context-specific freezing behavior) in hM4Di-expressing mice. While CNO treatment caused no significant changes in sleep architecture, inhibiting PV+ interneurons in CA1 attenuates post-CFC theta activity increases associated with learning in control mice. Functional connectivity within CA1 also becomes unstable following PV+ interneuron silencing. Taken together, these data suggest that activity among CA1 PV+ interneurons is required for establishing network dynamics that underlie sleep-dependent CFM consolidation.

Disclosures: N. Ognjanovski: None. **S. Schaeffer:** None. **D. Maruyama:** None. **S. Mofakham:** None. **M. Zochowski:** None. **S. Aton:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.08

Topic: E.05. Stress and the Brain

Support: CIHR 045004

NSERC 400708

Title: Deficiency of Luman, a transcription factor that alters glucocorticoid signaling, results in stress resilience in mice

Authors: *R. LU[1], M. ZENG[1], K. TRAN[1], J. LYMER[2], A. CARUSO[3], P. TURNER[4], E. CHOLERIS[2], N. MACLUSKY[3];
[1]Mol. and Cell. Biol., [2]Psychology, [3]Biomed. Sci., [4]Pathobiology, Univ. of Guelph, Guelph, ON, Canada

Abstract: The hypothalamic-pituitary-adrenal (HPA) axis is a major branch of the neuroendocrine system that regulates the stress response; dysregulations of this axis can lead to a number of common pathologies including depression. Luman (CREB3) is a transcription factor involved in the unfolded protein response. Recent evidence suggests that Luman plays a role in

glucocorticoid receptor (GR) regulation. In order to elucidate the biological function of Luman we characterized a Luman knockout (KO) mouse line. These mice displayed a severe maternal defect. We assessed the level of stress in our Luman KO mice through a variety of behavior tests, in all of which they exhibited stress resilience. Luman was found to be highly expressed in neuroendocrine tissues including the hypothalamus, hippocampus, pituitary and adrenal glands. The hormone profiles of these Luman KO mice have chronically low corticosterone, testosterone and prolactin levels, while they displayed an exaggerated response to the dexamethasone suppression test. In addition, GR signaling is altered in the Luman KO mice, and the activity and expression of GR is increased at both the cellular and tissue level. The mutant mice also showed defects in glucocorticoid production/secretion in adrenal gland, neurogenesis in dentate gyrus and dendritic morphology of hippocampal neurons. Previously we have found that the knockout mice of the Luman-recruitment factor (LRF, or CREBRF) also have dysregulation of glucocorticoid activity accompanied by similar but less severe phenotype. We therefore propose that Luman is a key regulator of the glucocorticoid signaling in the hypothalamus-pituitary-adrenal (HPA) axis and is important for the function of adrenal gland and hippocampus; and Luman may be involved in stress-related pathologies such as depression and anxiety disorders.

Disclosures: **R. Lu:** None. **M. Zeng:** None. **K. Tran:** None. **J. Lymer:** None. **A. Caruso:** None. **P. Turner:** None. **E. Choleris:** None. **N. MacLusky:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.09

Topic: E.05. Stress and the Brain

Title: Dynamic endocannabinoid responses to stress are influenced by both sex and stressor intensity

Authors: *H. A. VECCHIARELLI[1,2,3], T. T. Y. LEE[4], M. MORENA[2], J. M. GRAY[2], M. N. HILL[2];
[1]Neurosci., Univ. of Calgary, Calgary, AB, Canada; [2]Hotchkiss Brain Inst., Calgary, AB, Canada; [3]Mathison Ctr. for Mental Hlth. Res. and Educ., Calgary, AB, Canada; [4]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Sex differences heavily influence many neurobehavioral responses to stress. While estradiol is known to influence this sex difference, neurochemical systems which regulate stress have been largely unexplored in this context. In this regard, the endocannabinoid (eCB) system is

interesting as there are known sex differences in the expression of cannabinoid receptors throughout the brain and it has been well established that the eCB system, especially in corticolimbic brain structures (such as the amygdala, hippocampus, hypothalamus and prefrontal cortex) is involved in activation and termination of the stress response. While cannabinoid receptor expression has been reported to differ between males and females following chronic stress, to date there is no evidence of whether dynamic eCB changes in response to stress differ between males and females. In order to investigate this, we measured the endocannabinoid system ligands (anandamide (AEA) and 2-arachidonylglycerol (2-AG)) in corticolimbic brain regions following acute exposure to a relatively mild and commonly used psychological stress (restraint) or a more robust, mixed physical/psychological stressor (forced swim). Consistent with previous reports, we found that AEA levels within the amygdala, prefrontal cortex and hypothalamus were reduced in males following exposure to both restraint and forced swim stress and that hippocampal AEA levels were reduced only following forced swim stress. In response to forced swim stress, females exhibited a relatively similar pattern to males with reductions of AEA within the hippocampus, prefrontal cortex and amygdala, but had no changes within the hypothalamus. Interestingly, in response to restraint stress, females showed a consistent decrease in prefrontal cortical AEA content, but exhibited a differential response than males by exhibiting no changes in AEA within the hypothalamus and a surprising increase in amygdala AEA levels. With respect to 2-AG, however, females and males largely exhibited similar responses both showing increases 2-AG in the amygdala in response to forced swim, but not restraint. Restraint stress increased 2-AG content in the hypothalamus of both males and females, but forced swim had no effect. Neither stressor had any effect on 2-AG levels in the hippocampus of either males or females. Finally, forced swim stress increased 2-AG content in the prefrontal cortex of males, but not females. Collectively, these data highlight that dynamic eCB responses to stress are influenced by both sex and stressor intensity. Ongoing work is seeking to determine the relationship of these differences to reproductive hormone status.

Disclosures: **H.A. Vecchiarelli:** None. **T.T.Y. Lee:** None. **M. Morena:** None. **J.M. Gray:** None. **M.N. Hill:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.10

Topic: E.05. Stress and the Brain

Support: Patterson Trust Award Program in Clinical Research

NIH Grant K08MH-086812

Title: IL-6 mediation of prenatal stress effects on embryonic microglia morphology but not anxiety-like behavior

Authors: S. B. GUMUSOGLU[1], R. S. FINE[2,3], S. J. MURRAY[2], *H. E. STEVENS[4,2];
[1]Neurosci. Program, Univ. of Iowa, Iowa City, IA; [2]Child Study Ctr., Yale Sch. of Med., New Haven, CT; [3]Harvard Univ., Cambridge, MA; [4]Univ. of Iowa Col. of Med., Iowa City, IA

Abstract: Objective: Prenatal stress (PS) exposure has been linked to neurodevelopmental phenotypes and psychiatric disorders, including anxiety, autism, schizophrenia and attention hyperactivity deficit disorder (ADHD). PS has also been shown to result in multiple behavioral phenotypes in mice, including increased anxiety-like behavior. Additionally, PS has been linked to changes in microglia. The mechanisms responsible for these outcomes are not clear. Maternal immune activation (MIA) has also been shown to cause increased anxiety-like behavior and altered microglia in offspring. The actions of the proinflammatory cytokine interleukin 6 (IL-6) may be a common mechanism underlying the effects of both PS and MIA pathways. Method: To determine if IL-6 plays a key role in the conference of PS effects from mother onto offspring, restraint stressed CD1 female mice were concurrently injected with anti-IL6 antibody or saline for the last week of pregnancy. As controls, non-stressed pregnant dams were injected with anti-IL6 antibody or saline. Male offspring brain tissue was collected at embryonic day 14 (E14) and analyzed for microglia number and morphology using stereological counting. Other male offspring were tested in adulthood for anxiety-like behavior via the elevated plus maze (EPM). Results: Maternal IL-6 blockade was found to rescue the effects of PS on microglia morphology, such that no increase in phagocytosing forms of microglia were found in PS offspring brains when anti-IL-6 antibody was administered concurrently. Saline-injected PS animals did not see this return to control levels of phagocytosing microglia. In contrast to this, prenatally stressed adult male offspring showed elevated anxiety, as indicated by more restricted exploration of the open arm of the EPM regardless of whether their mothers were injected with saline or anti-IL6 antibody. Conclusions: These findings suggest that there are multiple mechanisms for the effects of prenatal stress on male offspring. Cytokines such as IL-6 may play a large role in initial impacts on embryonic microglia changes while other mechanisms may be responsible for anxiety-like behavior in adult offspring.

Disclosures: S.B. Gumusoglu: None. **R.S. Fine:** None. **S.J. Murray:** None. **H.E. Stevens:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.11

Topic: E.05. Stress and the Brain

Support: FAPESP 2014/22226-0

NIH/NIHM R01-MH-093473

NIH/NIHM R01-MH-093472

Title: Repeated social defeat stress induced activation of immune system and monocyte trafficking to the brain of mice is attenuated by a non-selective cannabinoid agonist

Authors: *S. F. LISBOA[1,2], D. SHEA[2], F. S. GUIMARÃES[1], J. P. GODBOUT[2,3,4], J. F. SHERIDAN[2,3,5];
[1]Pharmacol., Univ. of São Paulo - FMRP, Ribeirao Preto, Brazil; [2]Inst. for Behavioral Med. Research, Ohio State Univ., Columbus, OH; [3]Ctr. for Brain and Spinal Cord Repair, Ohio State Univ., Columbus, OH; [4]Neurosci., [5]Div. of Oral Biol., Ohio State Univ., Columbus, OH

Abstract: Repeated social defeat (RSD) is a model of social stress that promotes microglia activation, myeloid cell trafficking, and prolonged anxiety-like behavior. Pharmacological agents that target cells of both the peripheral and central immune system may be beneficial in the treatment of stress-related disorders, especially stressors that promote a pro-inflammatory response. Several lines of evidence indicate that the induction of the cannabinoid system dose-dependently attenuates behavioural effects of stress. While cannabinoids have several effects within the central nervous system, they can have potent anti-inflammatory effects on innate immune cells including monocytes, macrophages and microglia. Therefore, the purpose of this study was to determine the degree to which treatment with a cannabinoid agonist during RSD attenuated neuroinflammation and trafficking of myeloid cells to the brain. To address this objective, C57BL/6 mice were injected i.p. with a non-selective cannabinoid agonist, WIN55,212-2, 30 minutes prior to each of the six exposures to social defeat. Samples were collected 14 h after the last exposure to social defeat. Here we show that RSD-induced myelopoiesis and the release of inflammatory monocytes (CD11b+/Ly6Chi) into circulation were decreased by systemic cannabinoid activation. Moreover, the administration of the cannabinoid agonist also limited RSD-induced splenomegaly with reduced accumulation of granulocytes in the spleen. Furthermore, RSD-induced trafficking of inflammatory monocytes to the brain was blocked by the cannabinoid agonist. These reduced immune effects of the cannabinoid agonist were associated with a reversal of RSD-induced anxiety. Collectively, these results indicate that intervention with a cannabinoid agonist during repeated social defeat attenuated the activation of immune system and reduced the corresponding enhancement of

neuroinflammation that influences behaviour. These studies were supported by FAPESP (2014/22226-0 to SFL) and NIH/NIMH (R01-MH-093473; R01-MH-093472 to JFS).

Disclosures: **S.F. Lisboa:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Post-doctoral fellowship (FAPESP -2014/22226-0). **D. Shea:** None. **F.S. Guimarães:** None. **J.P. Godbout:** None. **J.F. Sheridan:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.12

Topic: E.05. Stress and the Brain

Support: NIH Grant MH059911

Title: Overnight fasting blunts anxiety-like behavior in rats due to "silencing" of central glucagon-like peptide 1 (GLP-1) neural signaling pathways

Authors: *L. M. RINAMAN[1], H. ZHENG[2];
[1]Univ. Pittsburgh, Pittsburgh, PA; [2]Dept. of Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: GLP-1 expressing neurons in the caudal nucleus of the solitary tract and medullary reticular formation are sensitive to metabolic state, and participate in behavioral and physiological responses to stress. Previously-published research findings indicate that caloric restriction attenuates behavioral responses to acute stress in adult rats, and also blunts stress-induced release of adrenocorticotropic hormone. We reported that overnight food deprivation attenuates anxiety-like behavior assessed in the elevated plus maze, and blunts stress-induced recruitment of hindbrain GLP-1 neurons and their hypothalamic and limbic forebrain targets. Our new results indicate that overnight fasting also reduces acoustic startle amplitude (a non-exploratory-based measure of anxiety), and markedly attenuates light-enhanced startle (LES). Further, the ability of anxiogenic LES testing to activate cFos expression by hindbrain GLP-1 neurons and their hypothalamic/limbic forebrain targets is significantly reduced in overnight fasted rats compared to ad lib-fed controls. Similar to the effects of fasting, baseline startle and LES was reduced in ad lib-fed rats after i.c.v. infusion of GLP-1 receptor antagonist (Exendin-9; 100 μg), which also significantly suppressed the ability of LES testing to activate neural cFos expression within stress-related hindbrain and limbic forebrain regions of interest. Collectively, our novel findings implicate central GLP-1 signaling pathways in driving behavioral and

physiological responses to acute stress, and further suggest that short-term fasting attenuates these stress responses, at least in part, by suppressing central GLP-1 signaling.

Disclosures: L.M. Rinaman: None. **H. Zheng:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.13

Topic: E.05. Stress and the Brain

Support: FAPESP Felloship 2013/00249-9

FAPESP Grant 2012/09300-4

FAPESP Grant 2012/17626-7

CNPq Grant 474477/2013-4

Title: κ-opioid and Orphan Opioid Receptor Like-1 receptors in the medial amygdaloid nucleus modulate the neuroendocrine responses to acute restraint stress

Authors: *A. FASSINI, A. SCOPINHO, E. FORTALEZA, L. RESSTEL, F. CORREA; Univ. of Sao Paulo, Ribeirao Preto, Brazil

Abstract: Introduction: The medial amydaloid nucleus (MeA) modulates several physiological and behavioral processes, including autonomic and endocrine changes during aversive situations. The restraint stress (RS) causes significant increase in neuronal activity of the MeA when compared to other amygdaloid nuclei. In addition, lesions in MeA reduced the RS-activated neurons in PVN. The opioid system participates of the mediating neuroendocrine responses, including those associated with aversive situations. Furthermore, it was showing the presence of peptides and opioid receptors in amygdala, suggesting the existence of a functional opioid neurotransmission on that structure. Based on the facts mentioned above, the hypothesis of this study is that the MeA opioid neurotransmission is involved in the modulation of hormonal responses evoked by RS. Methods: Male Wistar rats (240-280g) were used. Guide cannulae were implanted bilaterally in the MeA for drug or vehicle (artificial cerebrospinal fluid, aCSF, 100nL) microinjection. 10 minutes before microinjection of drugs or vehicle into the MeA, rats were subjected to RS. For collect of samples to corticosterone assays, rats were decapitated at time 0, 20 or 60min of restraint stress and the blood were collected in EDTA tubes (1mg/mL of blood).

Plasma samples were used to measured the corticosterone level by enzyme immunoassay. Results: The MeA pretreatment with 0.03nmol of nor-BNI (κ-opioid antagonist - (F1,29=39,86, P<0,0001) or 0.03nmol of UPF-101 (ORL-1 antagonist - F1,26=24,46, P<0,0001) potentiated the increase in corticosterone levels, while the microinjection of 0.03nmol of cyprodime (μ-opioid antagonist - F1,28=0,51, P=0,48) or 0.03nmol of naltrindole (δ-opioid antagonist - F1,29=0,24, P=0,62) did not change de neuroendocrine and cardiovascular responses induced by RS when compared with vehicle group. Conclusion: The current results demonstrate that opioid neurotransmission mediates the MeA inhibitory influence on restraint-evoked neuroendocrine changes. Financial Support: FAPESP and CAPES

Disclosures: **A. Fassini:** None. **A. Scopinho:** None. **E. Fortaleza:** None. **L. Resstel:** None. **F. Correa:** None.

Nanosymposium

749. Stress Peptides and Factors

Location: S405

Time: Wednesday, October 21, 2015, 1:00 PM - 4:30 PM

Presentation Number: 749.14

Topic: E.05. Stress and the Brain

Support: DA032194

Mayo Foundation

Title: Characterizing vertebrate stress response with mutant zebrafish strains in the hypothalamic-pituitary-adrenal axis

Authors: ***H. LEE**[1], T. L. POSHUSTA[2], R. G. KRUG, II[1], M. R. BERG[2], K. J. CLARK[2,1]; [1]Neurobio. of Dis., Mayo Grad. Sch., Rochester, MN; [2]Biochem. and Mol. Biol., Mayo Clin., Rochester, MN

Abstract: Stress-related neuropsychiatric disorders (ND), such as major depressive disorder, are leading causes of disability worldwide. A hallmark physiological change in patients with NDs is alterations in the hypothalamic-pituitary-adrenal (HPA) axis activity that manifest as hyper- or hypo-cortisolemia. Vertebrate-specific systemic stress response (SR) signals through the neuroendocrine HPA axis and sympathetic nervous system (SNS). However, we only have limited knowledge on how molecular components in the HPA axis and SNS interact to produce an integrated behavioral response. Hyperosmotic stress (100 mM NaCl) invokes an increased locomotor response in larval zebrafish within minutes. We hypothesized that zebrafish locomotor

response to hyperosmotic stimulation is a behavioral SR that is composed of multiple molecular pathways. We have begun our genetic analysis by examining key receptors in the HPA axis. By injecting highly efficient TALENs (transcription activator-like effector nucleases) that target genes in the HPA axis and generate DNA lesions in both chromosomes (bi-allelic), we have found that locomotor response to hyperosmotic stress is significantly influenced by *crhr1* (corticotropin releasing hormone receptor 1), *mc2r* (melanocortin receptor 2; receptor for adrenocorticotropic hormone (ACTH)), and *nr3c1* (glucocorticoid receptor), but not by mineralocorticoid receptor (MR; *nr3c2*). In addition, *mc2r* germline mutants showed a significant decrease in locomotor response. To our surprise, an *nr3c1* germline mutant that results in a frameshift-induced truncation of the glucocorticoid receptor did not show any deficits in locomotor response. We are currently investigating potential compensatory mechanisms by characterizing locomotor response in *nr3c1* mutants with pharmacological MR down-regulation and alternative alleles of *nr3c1* mutants. Understanding how multiple signaling systems contribute to this seemingly simple behavioral response will help us better model vertebrate-specific SR.

Disclosures: H. Lee: None. **T.L. Poshusta:** None. **R.G. Krug:** None. **M.R. Berg:** None. **K.J. Clark:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.01

Topic: F.01. Human Cognition and Behavior

Support: NSF Grant BCS-1354350

NSF Grant SMA-1041755

NIH Grant T32GM081760

Title: Electrophysiological profiles of word and face recognition in neurodevelopmental disorders

Authors: *E. M. DUNDAS[1], M. BEHRMANN[1], E. COLLINS[1], Y. GABAY[2], D. C. PLAUT[1]; [1]Psychology, Carnegie Mellon Univ., Pittsburgh, PA; [2]Dept. of Communication Sci. and Disorders, Univ. of Haifa, Haifa, Israel

Abstract: Extensive evidence gleaned from investigations reveals the existence of highly specialized and seemingly independent neural mechanisms for visual word recognition in the left hemisphere (LH), and for visual face recognition in the right hemisphere (RH) of adults. Emerging evidence suggests, however, that these two domains are not independent and that word lateralization is driving the emergence of face lateralization. An account offered to explain these findings (Plaut & Behrmann, 2011) predicts that, in individuals with disrupted word processing, such as those with developmental dyslexia (DD), or disrupted face processing, such as those with congenital prosopagnosia (CP), the typical hemispheric organization of word and face recognition should be disrupted. The current study employs behavioral and electrophysiological measures to compare the hemispheric superiority for face and word recognition in adults with DD or with CP, with persistent reading or face recognition difficulties, to matched control participants. In the control subjects, performance is better in the RVF than LVF and the N170 is stronger in the LH than the RH for words, and conversely, performance is better in the LVF than RVF and the N170 is stronger in the RH than the LH for faces, replicating the standard, well-established result. In adults with DD or with CP, however, behavioral performance differed from the controls and there was atypical hemispheric difference in the strength of N170 with abnormal lateralization of representations. In both the DD and CP, there was no hemispheric difference in the strength of N170 for words or for faces. These findings suggest that the hemispheric organization of face and word processing do not develop independently, and that, when there is a failure to develop coherent word processing or face processing, there are adverse consequences for recognition of stimuli in the other domain. A theoretical account in which competition for visual representations unfolds over the course of development is proposed to account for the findings.

Disclosures: E.M. Dundas: None. **M. Behrmann:** None. **E. Collins:** None. **Y. Gabay:** None. **D.C. Plaut:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.02

Topic: F.01. Human Cognition and Behavior

Support: NSERC RGPIN 251070-13

CIHR MOP 201209

Canadian Research Chair 201104

Title: Eye movement repetition effects do not require the hippocampus or explicit recognition

Authors: *R. K. OLSEN[1], V. SEBANAYAGAM[2], B. R. BUCHSBAUM[2,3], Y. LEE[2], R. ROSENBAUM[5,2], C. L. GRADY[2,3,4], M. MOSCOVITCH[2,3], J. D. RYAN[2,3,4];
[1]Rotman Res. Inst., North York, ON, Canada; [2]Rotman Res. Inst., Toronto, ON, Canada; [3]Psychology, [4]Psychiatry, Univ. of Toronto, Toronto, ON, Canada; [5]Psychology, York Univ., Toronto, ON, Canada

Abstract: It is well established that eye movements change as a function of repetition--that is, the number of fixations directed toward a novel image is higher than the number of fixations made to subsequent presentations of that image. However, questions remain regarding the nature of the memory representations and the corresponding neural regions which drive these eye movement repetition effects. For example, while some research has reported that eye movement repetition effects are observed only for information that can be explicitly (consciously) recognized (Smith et al., 2008) others have reported that eye movement repetition effects can occur without conscious awareness (see Hannula et al., 2010 for a review). To investigate this issue, we examined the relationship between eye movement repetition effects for single faces and subsequent recognition memory in three groups: healthy young adults (n=32, 24 female; mean age=23), healthy older adults (n=32, 25 female; mean age=74), and two young adults with developmental amnesia. All three groups demonstrated an equivalent eye movement repetition effect for repeated faces; however, explicit recognition memory for studied faces was significantly reduced in older adults and for the developmental amnesia cases compared to younger adults. A follow-up neuroimaging study was next conducted in which eye movements were recorded during fMRI scanning of healthy young adults (n=20) while they viewed faces that repeated up to four times within a block. Statistical analyses were designed to probe for brain areas in which the magnitude of the eye movement repetition effect was correlated with the magnitude of the neural repetition effect across subjects. Brain regions which exhibited a significant correlation were located in regions which have previously been related to face processing within the ventral visual processing stream. Taken together, these results indicate that eye movement repetition effects are driven by memory representations that are not necessarily available for conscious access and that this type of eye movement repetition effect is associated with neural changes in extra-hippocampal neocortical regions, such as those within the ventral visual processing stream.

Disclosures: **R.K. Olsen:** None. **V. Sebanayagam:** None. **B.R. Buchsbaum:** None. **Y. Lee:** None. **R. Rosenbaum:** None. **C.L. Grady:** None. **M. Moscovitch:** None. **J.D. Ryan:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.03

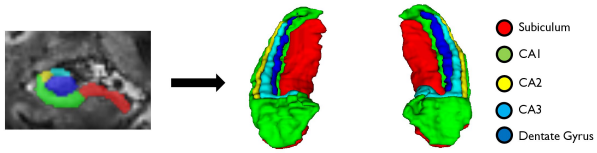
Topic: F.01. Human Cognition and Behavior

Support: MRC Grant G1002149

Title: Investigating the role of hippocampal subfields in complex scene perception

Authors: ***C. J. HODGETTS**[1,2], N. L. VOETS[3], A. G. THOMAS[4,3], A. D. LAWRENCE[1,2], K. S. GRAHAM[1,2];
[1]Sch. of Psychology, [2]Cardiff Univ. Brain Res. Imaging Ctr., Cardiff Univ., Cardiff, United Kingdom; [3]Oxford Ctr. for Functional MRI of the Brain, Univ. of Oxford, Oxford, United Kingdom; [4]Section on Functional Imaging Methods, NIMH, Bethesda, MD

Abstract: Recent 3T functional neuroimaging studies of the medial temporal lobe suggest that the hippocampus (HC) is important for forming complex and conjunctive representations of visual scenes. While these studies have been informative in terms of characterising HC representations more broadly, they have lacked the image resolution necessary to accurately delineate - and determine the functional contribution of - different HC subfields. In the current study, we investigated the response of subfields within the HC during perceptual discrimination of stimuli from different visual categories (scenes, faces, objects) by applying a 7-Tesla imaging protocol alongside a perceptual odd-one-out task that has been shown to be sensitive to HC lesions in humans (e.g., Lee et al., 2005). Based on a protocol by Wisse et al. (2012), HC subfields (CA1, CA2, CA3, subiculum, dentate gyrus) were manually delineated on high-resolution T2*-weighted images (0.6mm isotropic; Fig. 1) and registered to individual functional data (1.2mm isotropic). Contrasting scene trials with difficulty-matched face and objects trials, revealed significant clusters in the HC ($Z > 3.1$, $p = 0.05$), which were predominantly located in anterior subiculum bilaterally. Further, this response was robust at the individual level: 25/26 participants possessed significant HC voxels, and probabilistic overlap maps revealed that the majority of individual-level scene responses (65%) overlapped in right anterior subiculum. By applying ultra high-resolution imaging techniques, these results point toward a potential key role for the subiculum in perceptually discriminating complex scene stimuli, which may be shaped - in part - by its extrinsic connectivity with other regions implicated in spatial processing in humans and animals (e.g., posterior cingulate cortex, retrosplenial cortex; Aggleton et al., 2012).



Disclosures: **C.J. Hodgetts:** None. **N.L. Voets:** None. **A.G. Thomas:** None. **A.D. Lawrence:** None. **K.S. Graham:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.04

Topic: F.01. Human Cognition and Behavior

Support: NSERC Discovery + Accelerator Grant (249877-2006-RGPIN)

Title: fMRI reveals different activation patterns for real objects vs. photographs of objects

Authors: ***J. C. SNOW**[1], S. D. SQUIRES[2], K. M. STUBBS[2], J. C. CULHAM[2];
[1]Psychology, The Univ. of Nevada, Reno, NV; [2]The Brain and Mind Inst., Univ. of Western Ontario, London, ON, Canada

Abstract: Hundreds of functional magnetic resonance imaging (fMRI) experiments have revealed the neural substrates of object processing using photos of objects. Here we used univariate and multivariate pattern analysis (MVPA) of fMRI responses to determine whether photos are represented similarly to real objects in the human brain. The objects were either tools (plastic whisks, toothbrushes or hammers) or non-tools of comparable size and elongation (socks, sunglasses and candles). The photos were matched closely to the real objects for size and viewpoint. The stimuli were presented in rapid succession in the fMRI scanner using a custom-designed conveyor belt. We used a block design in which subjects viewed four exemplars (of different color, form, etc.) of one object type (e.g., whisks) in either real or photo format in each block. Univariate subtraction analysis revealed higher activation for real objects than photos in object-selective areas of the ventral visual stream (including the middle temporal gyrus and fusiform gyrus), and dorsally in primary somatosensory cortex and the anterior intraparietal sulcus -an area involved in object grasping. Conversely, univariate subtraction analysis revealed greater activation for photos than real objects in anterior cingulate cortex -possibly reflecting the presence of conflicting depth cues in the photos (but not real objects). Surprisingly, MVPA showed that early visual areas and lateral and ventral occipitotemporal cortex were sensitive to the format in which stimuli were viewed. Specifically, although the representations of individual objects were similar for real stimuli and photos, objects in the same format were represented more similarity than those in different formats. For example, in comparing activation patterns between even and odd runs, whisks were more similar to whisks than the other five types of objects (regardless of format) but real whisks were more similar to real whisks than photos of

whisks. Taken together, our results indicate that the human brain does not treat photographs as being equivalent to real objects. First, real objects can invoke greater activation than photos. Second, although areas within the ventral visual system represent object identity, these representations are not identical across real versus photo formats. Real objects might elicit different brain-based responses to photos because they provide richer visual information, they have definite haptic qualities, and they afford genuine action.

Disclosures: **J.C. Snow:** None. **S.D. Squires:** None. **K.M. Stubbs:** None. **J.C. Culham:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.05

Topic: F.01. Human Cognition and Behavior

Support: Swiss National Science Foundation

NSF Grant BCS1025149

NSF Grant BCS0923763

NSF Science of Learning Center Grant SMA-1041755

Title: Dorsal object representations in the absence of ventral object vision

Authors: *T. KASSUBA[1], M. BEHRMANN[2], S. KASTNER[1];
[1]Princeton Univ., Princeton, NJ; [2]Dept. of Psychology, Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Primate visual processing has been traditionally assigned to two segregated functional pathways: a ventral stream serving object perception, and a dorsal stream serving spatial and action perception. Recent studies in humans, however, have demonstrated the existence of a human-specific, hierarchically organized dorsal object vision system in the posterior intraparietal sulcus (pIPS), remarkably similar to the ventral one. It remains unclear whether these dorsal object representations are propagated directly from early visual cortex to parietal cortex, or whether they depend on ventral object vision. To address this question, we explored the response properties of the dorsal system in the absence of normal input from ventral object representations. We studied the dorsal system of patient SM, who suffers from profound object agnosia and prosopagnosia following a focal lesion in his right lateral fusiform gyrus. We have previously shown that the topographic organization and activation profile of SM's early visual

cortex is intact, but that object-related responses in regions surrounding the lesion and in corresponding locations in the structurally intact left hemisphere are compromised (Konen et al. 2011). Here, in a series of fMRI-adaptation experiments, we tested whether and how SM's circumscribed ventral lesion affects the selectivity of intermediate (MT+, V3A, V7) and higher-order (pIPS) processing stages of the dorsal stream for different types of object stimuli (2D-objects, 3D-objects, line drawings) and moving dots as non-object control stimuli. SM's visually evoked responses of all dorsal areas in the left hemisphere to both 2D-objects and line drawings were impaired, relative to healthy control subjects, and/or as compared to SM's right hemisphere. In addition, left MT+ and V7 showed impaired selectivity for line drawings and 2D-objects. On the other hand, visually evoked responses and stimulus-selective responses to 3D-objects and motion stimuli were comparable to the control group. The functional connectivity between SM's ventral (V4, LOC) and dorsal (MT+, V3A, V7, pIPS) regions was disrupted in various ways, but most severely for SM's right V4. Overall, we found more disruptions in functional connectivity for 2D-objects and line drawings than for 3D-objects. Together, the results show that the ventral lesion mostly affects dorsal processing of 2D-objects and line drawings. On the other hand, the representation of 3D-structure of an object, which is needed for object grasping and manipulation, might not depend on ventral object vision.

Disclosures: T. Kassuba: None. **M. Behrmann:** None. **S. Kastner:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.06

Topic: F.01. Human Cognition and Behavior

Support: National Science Foundation grant to MB

NSF TDLC to MB

The Binational Scientific Foundation (Israel-USA) travel grant to EF

Title: Object 3D structure representations in the dorsal pathway is not dependent on the ventral pathway: Evidence from visual agnosia

Authors: *E. FREUD[1,2], G. AVIDAN[1], T. GANEL[1], M. BEHRMANN[2];
[1]Ben Gurion Univ. of the Negev, Beer-Sheva, Israel; [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: According to the 'two visual pathways' hypothesis, the ventral pathway mediates object perception while the dorsal pathway supports spatial- and visually-guided action. Nevertheless, recent evidence shows that the dorsal pathway is also engaged in the perception and representation of object shape, even in tasks that do not require actions. The critical question is whether these dorsal, object-based representations are independent of ventral representations, and whether the dorsal representations contribution plays a functional role in object recognition or are merely epiphenomenal. To this end, we examined the neural and behavioral profile of a group of patients with an object recognition impairment resulting from focal damage to the occipitotemporal cortex. In an fMRI experiment, control participants evinced sensitivity to the 3D structure of objects in object-selective regions, along both the ventral and dorsal cortices. The patients revealed reduced sensitivity to object structure in the ventral pathway, but preserved sensitivity in the dorsal pathway. The behavioral significance of this latter sensitivity was further investigated in a series of psychophysics experiments. Although profoundly impaired in tasks related to object perception, the patients still demonstrated residual sensitivity to object structural information. We argue that this residual sensitivity is a function of their intact dorsal pathway - as even the patient with the most severe agnosia following extensive occipitotemporal damage showed such sensitivity to object structure. Taken together, our findings suggest that object representations in the dorsal pathway are independent from those in ventral pathway and while these dorsal representations are unable to support normal object perception, they may support a coarse description of object structure.

Disclosures: **E. Freud:** None. **G. Avidan:** None. **T. Ganel:** None. **M. Behrmann:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.07

Topic: F.01. Human Cognition and Behavior

Support: DFG Grant Ka 1258/10-1

ERC Grant StG 211078

Title: Contralateral preference in object recognition - evidence from visual hemiagnosia

Authors: ***J. RENNIG**[1,2,3], M. HIMMELBACH[1], H. WILHELM[4], H.-O. KARNATH[1,5];
[1]Div. of Neuropsychology, Ctr. of Neurology, Univ. of Tübingen, Tuebingen, Germany;
[2]Neurocognition Lab., Knowledge Media Res. Ctr., Tuebingen, Germany; [3]Dept. of Neurosurg.,

Baylor Col. of Med., Houston, TX; [4]Ctr. for Ophthalmology, Univ. of Tuebingen, Tuebingen, Germany; [5]Dept. of Psychology, Univ. of South Carolina, Columbia, SC

Abstract: Patients suffering from visual agnosia show remarkable impairments in visual object recognition despite of intact primary visual functions. Visual agnosia usually emerges after extensive bilateral lesions to ventral visual pathways. In contrast, symptoms of visual agnosia are rarely reported after unilateral lesions. We presumed that unilateral lesions are largely compensated by the intact hemisphere. Therefore, associated sub-clinical deficits cannot be detected in standard tests of object recognition. This assumption was based on neuroimaging studies that mapped the topographic organization of higher object sensitive areas of the ventral pathway. These studies reported some lateralization in this area. However, such lateralization was rather weak in comparison to earlier visual areas. Applying short unilateral presentations of everyday objects we found significant impairments of object recognition in the contralesional visual hemifield in a group of patients with unilateral lesions to the ventral pathway in comparison to healthy controls and patients with unilateral brain-damage beyond the ventral visual systems. This first group study on visual hemiagnosia confirmed a weak lateralization of the topographic organization of higher object sensitive areas that was found in correlative neuroimaging and non-human primate studies. In contrast to these existing studies, our patient study demonstrates a causal link between neuroanatomy and behavioral performance.

Disclosures: J. Rennig: None. **M. Himmelbach:** None. **H. Wilhelm:** None. **H. Karnath:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.08

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant AG009253

NIH Grant MH092953

Title: Subjective vividness ratings of pictures predict exemplar-specific similarity between encoding and recall activity patterns

Authors: *M. R. JOHNSON[1,2], K. J. MITCHELL[3], M. K. JOHNSON[1];
[1]Dept. of Psychology, Yale Univ., New Haven, CT; [2]Dept. of Psychology, Univ. of Nebraska, Lincoln, NE; [3]Dept. of Psychology, West Chester Univ., West Chester, PA

Abstract: Several previous neuroimaging studies have demonstrated that brain activity patterns during remembering of visual items are similar to the initial patterns during perception of those items. Furthermore, pattern similarity may represent information about the item at both the general category level (e.g., face, scene, object), and the exemplar level (i.e., the specific individual item within that category). We hypothesized that the degree of pattern similarity between encoding and recall for a given item would be associated with a greater sense of subjective vividness during recollection. During fMRI scanning, participants (N=61) saw several colored pictures (objects, scenes), presented individually and each accompanied by a written label; after a short delay, they saw the labels presented alone and were instructed to recall the relevant item. Participants performed vividness ratings during both perception (they indicated the vividness of the visual experience) and the later recollection task (they indicated the vividness of their mental representation). A multivariate pattern analysis (MVPA) assessed the similarity between brain activity patterns during perception and recollection of the same item. These pattern similarity scores were then regressed against the vividness ratings. For objects, we found that vividness ratings during recollection were significantly better predictors of exemplar-specific pattern similarity than vividness ratings during perception in prefrontal, temporal, parietal, and occipital regions of interest. The same was true for scenes in prefrontal and parietal regions. Although vividness ratings for perception and recollection were positively correlated with one another (i.e., items that were perceived more vividly tended also to be recalled more vividly), these results suggest that they are nonetheless dissociable. That is, subjective vividness during remembering is more tightly linked to "objective" vividness (i.e., amount of pattern similarity between encoding and recall) than can be predicted from the perceptual vividness of stimuli alone.

Disclosures: **M.R. Johnson:** None. **K.J. Mitchell:** None. **M.K. Johnson:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.09

Topic: F.01. Human Cognition and Behavior

Support: NIH R01 MH092345

Title: Category learning biases representations of orientation in early human visual cortex

Authors: *E. F. ESTER, T. SPRAGUE, J. SERENCES;
Psychology, Univ. of California San Diego, La Jolla, CA

Abstract: The ability to rapidly and accurately categorize sensory representations is an essential component of many everyday tasks. Electrophysiological and human neuroimaging studies suggest that categorization is mediated by a network of prefrontal and posterior parietal cortical areas. Here, we ask whether and/or how learning to categorize visual stimuli biases sensory representations in human visual cortex. We trained human observers to sort specific orientation values (e.g., 12° or 120°) into two arbitrary categories (A and B) until they reached near-ceiling levels of performance. After behavioral training, we used fMRI and an inverted encoding model to reconstruct representations of an attended orientation in multiple regions of early visual cortex (V1-hV4v/V3a) while participants performed the same speeded categorization task. Across trials, reconstructions of the attended orientation were biased away from the boundary separating categories A and B towards exemplars of the category to which they belonged. This occurred even though we could not reliably decode category membership from activation patterns in any of the same visual areas. These results suggest that category learning biases representations of sensory information, even at very early stages of visual processing.

Disclosures: E.F. Ester: None. **T. Sprague:** None. **J. Serences:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.10

Topic: F.01. Human Cognition and Behavior

Support: British Academy Postdoctoral Fellowship

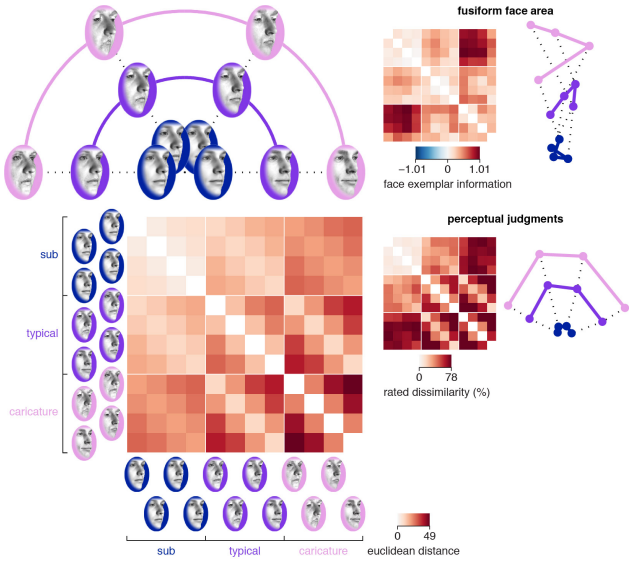
ERC Grant 261352

Darwin College Charles and Katharine Darwin Research Fellowship

Title: A warped face space in human cortical and perceptual representations

Authors: *J. D. CARLIN, N. KRIEGESKORTE;
MRC Cognition and Brain Sci. Unit, Cambridge, United Kingdom

Abstract: Face recognition appears effortless, but the cortical representation that supports this ability remains poorly understood. According to a classic account, individual exemplars are encoded as vectors in a norm-based face space where distinctiveness is associated with eccentricity and identity with direction. However, it is unclear how eccentricity and direction contribute to face exemplar similarity in human visual cortex, or how such cortical face spaces compare to spaces estimated from perceptual judgments. Here, we used a principal components analysis model of 3D face shape and texture to generate a reference face space against which representational distances estimated from human fMRI response patterns and perceptual judgments could be compared. Although the reconstructed face spaces correlated with the reference space, the cortical face spaces systematically over-represented distances associated with eccentricity compared to direction. This eccentricity bias was less evident in the perceptual face space. Importantly, multiple brain regions including the fusiform face area discriminated face space direction reliably when eccentricity was held constant, thus confirming that both eccentricity and direction are represented in fMRI response patterns, albeit to different extents. Although an over-representation of identity-preserving distinctiveness information may appear a surprising property for a face representation, we show that a computational model readily exhibits a similarly warped representational space. This model offers an explanation for why cortical face spaces over-represent eccentricity while retaining some direction information, and suggests that sensitivity to face space eccentricity at the level of fMRI responses can arise as an emergent property from a model where no individual unit encodes distinctiveness as such.



Disclosures: J.D. Carlin: None. **N. Kriegeskorte:** None.

Nanosymposium

750. Visual Imagery

Location: N228

Time: Wednesday, October 21, 2015, 1:00 PM - 3:45 PM

Presentation Number: 750.11

Topic: F.01. Human Cognition and Behavior

Support: Medical Research Council UK

Title: A novel paradigm to study the effect of selective adaptation of different levels of the visual hierarchy on binocular rivalry

Authors: *J. FREYBERG[1], C. E. ROBERTSON[3], S. BARON-COHEN[2];
[2]Dept. of Psychiatry, [1]Univ. of Cambridge, Cambridge, United Kingdom; [3]Harvard Univ., Cambridge, MA

Abstract: Onset Rivalry - the first period of binocular rivalry - differs from sustained rivalry in multiple aspects. It is often biased towards a particular percept, and affected by factors such as stimulus location in the visual field, stimulus contrast, and context. These biases can be strong enough to produce exclusive dominance of one image, something not seen in sustained rivalry. Here, we outline how selective adaptation of different levels of the visual hierarchy affect onset rivalry. 31 healthy participants completed 92 trials of binocular rivalry (6s duration). We included an additional 23 participants with an autism spectrum condition (ASC) in the study, as individuals with ASC have been shown to exhibit different dynamics of sustained binocular rivalry. We presented different object stimuli on green or red squares. Rivalry was achieved using a mirror stereoscope. Participants reported dominant or mixed percepts during 6s trials. 20 trials occurred without prior adaptation (baseline). To measure the influence of adaptation on onset rivalry, 36 trials each were preceded by presenting one of the stimuli for 2s, either to the eye that will go on to view the stimulus during rivalry (full adaptation) or the opposite eye (high-level adaptation). We hypothesised that in full adaptation trials, both early stages of the visual hierarchy (driven by monocular input) and later stages (driven by binocular input) of the visual hierarchy are adapted, while in high-level adaptation trials, only later stages are adapted to the stimulus. We compared the two adaptation conditions to baseline. Both adaptation conditions strongly reduced the number of times the adapted image was the first image perceived by participants (all $p < 0.001$). The reduction was significantly stronger in the full adaptation condition, as evidenced by a significant main effect of stimulus type in a 2x2 ANOVA with diagnosis of ASC as between-subject factor ($F(1, 33) = 15.952$, $p < 0.001$; full adaptation: -15.7% ± 16.9%, high-level adaptation: -9.3% ± 13.6%). We find similar results for the average duration of dominant percepts reported by participants. No effect of Group was observed either at baseline or in the adaptation condition (all $p > 0.2$), indicating that the effects of adaptation on onset rivalry are unremarkable in autism. In summary, we provide evidence that there is a strong effect of adaptation on onset rivalry, and that this effect stems from both early and late stages of

visual processing. We also show that individuals with autism, known to perform differently in sustained rivalry, perform similarly to individuals without autism during onset rivalry.

Disclosures: J. Freyberg: None. **C.E. Robertson:** None. **S. Baron-Cohen:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.01

Topic: F.01. Human Cognition and Behavior

Title: Delineating Default mode and Central Executive Control network in subjects exposed to high altitude

Authors: *T. K. GANDHI[1], S. CHOUHAN[2], S. B. SINGH[3];
[1]Defence Inst. of Physiol. & Allied Sci. (DIPAS), New Delhi, India; [2]Biomed. Engg, [3]DIPAS, New Delhi, India

Abstract: Effect of high altitude hypoxia on brain plasticity is well documented in animal model. However, the effect of hypobaric hypoxia on human brain for a prolonged period is not well understood. A large body of research on high altitude residents has reported the impairment in cognitive functions. Prolonged exposure to hypobaric hypoxia has devastating consequences to brain architecture and functions. Previous studies have reported the alternation of brain structure and consequently the functions just after the exposure to high altitude. The results are not very consistent across subject populations and the duration of exposure. Here, we have an unique opportunity to work with a group of seven subjects, who were born and brought up in sea level but were exposed to high altitude (12,000-15,000 feet) for a period of 24-36 months and living in sea level last three years. Both neuropsychological test (WAIS IV) and the resting state functional connectivity (RSFC) was conducted during the de-induction period on experimental as well as age matched control subjects. Functional connectivity analysis was performed using seed-based approaches with MATLAB based custom software package: CONN. For seed-based analysis, sources are defined as multiple seeds corresponding to the pre-defined seed regions for: (i) Default mode network (DMN) and (ii) Executive control network (ECN). Seeds for DMN and ECN were chosen to be 10-mm spheres centered on previously published foci. The cognitive performance of experimental (high altitude exposed) subjects was lower ($p<0.01$) than the age matched controls in neuropsychological test. In RSFC analysis, we use DMN seeds (LLP, MPFC, PCC, RLP) and ECN seeds (Dorsal medial PFC, Right anterior PFC, Left superior parietal, Right superior parietal) as regions of interest (ROIs). The connectivity in executive

control network is significantly higher ($p<0.01$) in controls compared to high altitude exposed subjects group. Both the behavioral and neuroimaging studies point the impaired resting state executive network in human expose to hypobaric hypoxia condition even shorter than three years. Additional studies are underway to understand the limit of plasticity in these subject groups during de-induction stages longitudinally.

Disclosures: **T.K. Gandhi:** None. **S. Chouhan:** None. **S.B. Singh:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.02

Topic: F.01. Human Cognition and Behavior

Title: Antisaccade practice improves efficiency in cognitive control behavior and associated circuitry

Authors: *A. RODRIGUE[1], B. AUSTIN[3], J. MCDOWELL[2];
[1]Psychology, [2]Univ. of Georgia, Athens, GA; [3]Univ. of Wisconsin, Madison, WI

Abstract: Cognitive control includes operations like attention, inhibition, and working memory. Integrity of cognitive control is also related to the ability to perform basic aspects of everyday functions. As such, there are substantial efforts to improve cognitive control via practice-related paradigms. Antisaccades are reliable measures of cognitive control and require the inhibition of a prepotent response in order to generate a more task-relevant response. We hypothesized that practice of an antisaccade task would improve cognitive control performance and also alter underlying neural circuitry. Healthy subjects completed an 8 day antisaccade practice trial. Practice was conducted in a laboratory setting and lasted an hour each day. Before and after the practice trial, subjects completed an fMRI scanning session while performing antisaccades. For antisaccade behavior during the scanning session, we measured reaction time for correct antisaccades and error rate. To evaluate changes in antisaccade behavior with practice we performed a linear mixed model analysis with time as a repeated measure. To evaluate the effect of practice on brain variables, we measured the BOLD signal with fMRI. We performed a repeated measures ANOVA on the results of a standard GLM analysis to quantify changes in brain activation, and did the same with the results of a psychophysiological interaction (PPI) to quantify changes in brain connectivity with practice. To evaluate the transfer of antisaccade practice effects, subjects also performed the Wisconsin Card Sorting Task (WCST), an alternative measure of cognitive control, before and after the practice trial. Results across all

analyses indicated an increase in efficiency in antisaccade performance and brain variables. At post-test, subjects had lower error rates and were faster at performing the antisaccade task. Neural changes included decreases in activation in cognitive control regions (prefrontal cortex) and regions involved in saccade planning and generation (supplementary and frontal eye fields). There were also increases in efficiency in connectivity of control regions with the rest of the brain, with connections becoming more lateralized and refined. We also saw a transfer effect of antisaccade practice. People completed more conceptual level responses and had fewer errors on the WCST. Overall, antisaccade practice increased efficiency in both antisaccade behavior and the neural circuitry supporting antisaccade performance. Effects of practice also transferred to other aspects of cognition. This may aid in constructing remediation strategies for populations that have deficits in cognitive control.

Disclosures: **A. Rodrigue:** None. **B. Austin:** None. **J. McDowell:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.03

Topic: F.01. Human Cognition and Behavior

Title: Brain dynamics during cognitive conflict: insights from human intracranial recordings

Authors: *E. BARTOLI, C. CONNER, N. TANDON;
Neurosurg., Uthealth Sci. Ctr. At Houston, Houston, TX

Abstract: The inhibition of a prepotent response represents a particular skill within the broad domain of cognitive control, defined as the ability to continually control and adapt behavior to task rules and goals. A classic cognitive control experiment is the Stroop task, which requires participants to inhibit an automatic and overlearned process, such as reading a word, in order to accomplish task rules, i.e., naming the color in which the word is printed. The brain dynamics underpinning the execution of this task have been widely studied, however, the roles played by distinct regions within the prefrontal cortex are difficult to disentangle, mainly because of the trade-off between temporal and spatial resolution of non-invasive neuroimaging techniques. We used intracranial EEG recordings (icEEG), a technique with high spatiotemporal resolution during a Stroop task in a cohort 12 patients (6 with left hemisphere coverage, 2 right and 4 bilateral) undergoing intracranial monitoring for their epilepsy. Participants were required to name the color of words presented on a screen and icEEG data were collected during the whole task duration together with behavioral measures (reaction times, accuracy). Percent power

changes in gamma (60-120 Hz) and beta (13-30 Hz) frequency bands are calculated in a time window locked to stimulus onset (0-2000 ms, where word onset = 0 ms) with respect to a pre-stimulus baseline (-700-200 ms). By examining the percent power changes in these frequency bands we were able to describe the time-course of activity throughout a distributed cortical network. There was initial recruitment of posterior fusiform cortex (~180 ms), followed by a set of medial prefrontal (pre-supplementary motor area and supplementary motor area), and lateral prefrontal (middle frontal gyrus - MFG) and subcentral regions (~200-300 ms). MFG activity was maintained until the onset of response. Precentral regions exhibited peaks of gamma power locked to response time, reflecting the articulatory network underlying color naming. Reaction times were significantly slower when the word-color associations were incongruent compared to congruent associations, due to the increased response conflict ($t(11)=-7.755$, $p<0.001$). This interference effect was correlated to a sustained response in lateral prefrontal cortex. Overall, our results provide new insights into the early and close interplay between medial and lateral prefrontal regions during the resolution of conflicting cognitive inputs.

Disclosures: **E. Bartoli:** None. **C. Conner:** None. **N. Tandon:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.04

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R21 NS085543

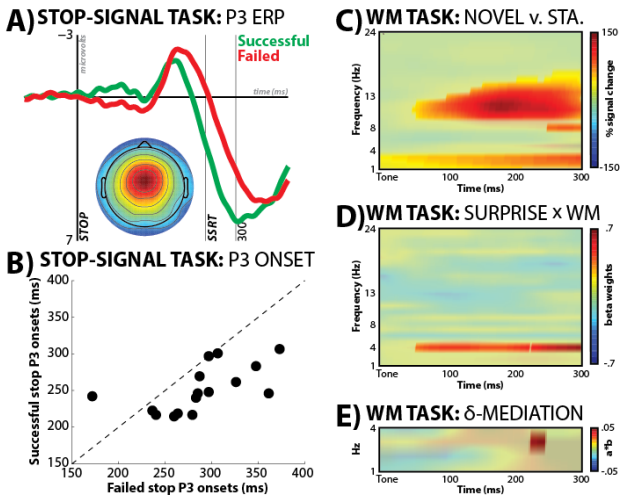
James S McDonnell Grant #220020375

Title: Surprise recruits a neural suppressive mechanism that generates broad motor response inhibition and also disrupts working memory

Authors: ***J. R. WESSEL**, A. R. ARON;
Psychology, UC San Diego, La Jolla, CA

Abstract: An everyday observation is that a surprising event interrupts one's train of thought. We hypothesized that such forgetting reflects an interruption of ongoing cognitive activity, generated by a suppressive mechanism. This hypothesis was motivated by the following. First, surprising events recruit the same suppressive neural mechanism as outright action-stopping in motor-inhibition tasks. Second, this mechanism has broad skeletomotor effects: action-stopping

causes reduced corticomotor excitability in task-unrelated effectors, and similar broad motor suppression follows surprising events. Third, action-stopping also has suppressive non-motor effects: it reduces stimulus value and memory encoding. We developed a task in which working memory (WM) was interrupted by surprising events. Participants were presented with tones during WM maintenance, most of which were not surprising (sine-wave, standard, p=80%), and some of which were surprising (unique birdsong segment, novel, p=20%). Novels lead to reduced WM accuracy ($p = .002$), and novels that lead to WM errors were more surprising than novels that did not ($p < .05$). We measured EEG during this task, followed by a motor stop-signal task (SST). Using independent component analysis, we identified a suppressive brain component that indexed successful action-stopping in the SST (motor suppression independent component, MS-IC, Fig. Panel A,B), and then investigated its activity in the WM task. Surprising events in the WM task indeed recruited the MS-IC, specifically in the lower frequency bands (1-13Hz, Panel C). Crucially, the degree of surprise-related MS-IC delta-band (1-4Hz) activity was negatively correlated with WM accuracy (Panel D). Furthermore, MS-IC delta-band activity was a significant mediator of the degree to which surprise disrupted WM (Panel E). Thus, surprise interrupts cognition via the same suppressive mechanism that interrupts action. This mechanism may produce a cognitive and motor 'refresh' after salient events, which could enable an attentional shift to the event, and new goal encoding.



Disclosures: **J.R. Wessel:** None. **A.R. Aron:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.05

Topic: F.01. Human Cognition and Behavior

Support: EFRO

Food Cognition Model Systems

Title: Disentangling effects of aging on proactive and reactive response inhibition

Authors: ***M. BLOEMENDAAL**[1], B. B. ZANDBELT[1], J. B. T. WEGMAN[1], O. VAN DE REST[2], R. COOLS[1,3], E. AARTS[1];
[1]Radboud University, Donders Inst. for Brain, Cognition and Behaviour, Ctr. for Cognitive Neuroimaging, Nijmegen, Netherlands; [2]Div. of Human Nutr., Wageningen Univ., Wageningen, Netherlands; [3]Dept. of Psychiatry, Radboud Univ. Med. Ctr., Nijmegen, Netherlands

Abstract: Older adults can behave recklessly, for example in traffic, especially during information overload. Age impairments have been shown in response inhibition, but the processes underlying this deficit are unclear. Here we aim to examine two distinct forms of response inhibition in aging, as well as the effect of cognitive load. Reactive response inhibition is the process of stopping a response and can be measured with stop-signal tasks. Proactive response inhibition entails the preparation for stopping and is characterized by proactive slowing of reaction times. A group of young (n=25, age range 18-32) and older adults (n=23, 61-74) were tested using fMRI. We disentangled the effects of aging on both proactive and reactive inhibition using an adapted stop signal paradigm including different levels of cognitive load in which color cues signaled stop probability. Behaviorally, older adults had more difficulties cancelling a response (i.e. longer SSRT) relative to young adults, which was accompanied by increased medial frontal and occipital signal across level during reactive inhibition (Stop Success > Stop Failure). Moreover, SSRT was positively correlated with right inferior frontal gyrus (rIFG) signal. Thus, over-recruitment of the stop network during reactive inhibition was associated with impaired stop efficiency in older adults. During proactive response inhibition, the degree of proactive slowing was less in older than young adults in high relative to low cognitive load. This was reflected by increased IFG, fronto-polar and occipital signal in high relative to low cognitive load for young compared with older adults during proactive inhibition (parametric regressors for stop probability on Go trials). Thus, both at the neural and behavioral level, older adults did not engage in proactive inhibition during high cognitive load. Our findings suggest that reckless behavior in older adults might be due to a reduced ability to stop an action, as well as due to a diminished capacity to prepare for an upcoming stop in situations of information overload.

Disclosures: **M. Bloemendaal:** None. **B.B. Zandbelt:** None. **J.B.T. Wegman:** None. **O. van de Rest:** None. **R. Cools:** None. **E. Aarts:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.06

Topic: F.01. Human Cognition and Behavior

Support: NHMRC 10011008

Title: Controlling the impulse for reward: A fMRI study of inhibitory control over monetary reward in cigarette smokers

Authors: *R. HESTER[1], E. CHEN[2], K. CHARLES-WALSH[2];
[1]Univ. of Melbourne, Melbourne, Australia; [2]Psychological Sci., Univ. of Melbourne, Melboune, Australia

Abstract: Human research examining the neural mechanisms underlying inhibitory control has typically relied on paradigms (e.g., Stop signal, Go/No-go task) that require withholding a prepotent response to a neutral stimulus. While this approach has been invaluable, most clinical dyscontrol problems such as those found in addiction arise from the inability to control the impulse for reward. We administered a novel monetary reward task during fMRI data collection to dependent cigarette smokers (n = 22) and matched control participants. The task cued participants to expect a monetary reward. On a small proportion of trials, rather than making a button-press response to receive the monetary reward participants were shown a stop-signal that required them to withhold their response. To mimic real-world abstinence, successful response inhibition over a money-related stimulus received no financial reward, whereas the failure to withhold resulted in the expected monetary reward. BOLD activity for the response preparation and response inhibition epochs of successful inhibition over a reward-related stimulus, indicated hyperactivity in cognitive control regions (e.g., right inferior frontal gyrus, dorsal anterior cingulate gyrus) and hypoactivity in reward anticipation regions (e.g., striatum, nucleus accumbens). Significant differences were apparent between smokers and non-smokers during the response preparation period when successful control over reward was compared to either failures of control, or successful control over a neutral stimulus. Our results suggest that impulsiveness for reward in dependent smokers control is associated with both the up-regulation of reward-related anticipation and down-regulation of cognitive control-related processes. The results support the hypothesis that interventions for addiction targeting both reward sensitivity and cognitive control, rather than either individually, will have greater chances of achieving improved treatment outcomes.

Disclosures: R. Hester: None. **E. Chen:** None. **K. Charles-Walsh:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.07

Topic: F.01. Human Cognition and Behavior

Support: UK Medical Research Council Grant to MCA: MC-A060-5PR00

Title: Cognitive control of memory and action: A within subject fMRI study

Authors: *T. W. SCHMITZ[1], C. S. FERREIRA[2], M. C. ANDERSON[1];
[1]Med. Res. Council, Cambridge, United Kingdom; [2]Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Separate lines of research suggest that cognitive control over memories and actions may rely on overlapping neural systems. We therefore examined in the same individuals how these two modalities of cognitive control may alter cortical dynamics. To do so, we directly compared BOLD responses induced by retrieval suppression against those induced by motor suppression. Retrieval suppression was indexed from the Think/No-Think task (TNT), which assesses the level of subsequent forgetting induced by repeated suppression of episodic memories. Motor suppression was indexed from the Stop-Signal task (SST), which assesses the time required to cancel a motor response that is already in the process of execution. We first examined if behavioral indices of cognitive control in one modality were predictive of those in the other. For memory suppression, we used indices of suppression-induced forgetting, while for motor suppression we used stop-signal response time. We found that cognitive control between modalities was tightly correlated across individuals ($r = -0.66$), suggesting that the TNT and SST tasks index a common executive resource. To explore potential supramodal patterns of cortical response, we conducted a conjunction analysis of suppression-induced activity between modalities. We found significant supramodal activation at several nodes in the right lateral prefrontal cortex (RLPFC), including middle frontal gyrus activation (BA9/46), inferior frontal gyrus (BA44/45), and presupplementary motor area (BA6). To examine potential modality-dependent cortical responses, we performed a priori region of interest (ROI) analyses in the hippocampus (HC) and in primary motor cortex contralateral to the response hand (M1). We found a significant ROI (HC, M1) x Task (TNT, SST) interaction, driven by modality-dependent responses in each ROI. Specifically, retrieval suppression evoked significantly larger negative BOLD responses in HC compared to M1, whereas motor suppression evoked significantly larger negative BOLD responses in M1 compared to HC. We then examined with dynamic causal modeling (DCM) if cognitive control induces coupling between the observed supramodal nodes in RLPFC and downstream nodes in HC and M1. We found evidence that the same population of

supramodal neurons in the RLPFC is bi-directionally coupled with the HC during memory suppression and with M1 during motor suppression. Our results indicate that cognitive control of both memories and actions evokes a common supramodal RLPFC system, which in turn evokes modality-dependent coupling in anatomically distributed subsystems.

Disclosures: T.W. Schmitz: None. **C.S. Ferreira:** None. **M.C. Anderson:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.08

Topic: F.01. Human Cognition and Behavior

Support: US Army Medical Research:Neural Markers and Rehabilitation of Executive Functioning in Veterans with TBI and PTSD

Foundation of Hope

University of North Carolina Translational Medicine Program

Title: Cognitive control and affective processing dysregulation in veterans with comorbid ptsd and tbi: an fmri and resting state functional connectivity study

Authors: *M. WEBER[1], J. BIZZELL[2], J. JOHNSON[2], E. MELTON[2], E. ELBOGEN[2], A. BELGER[2];
[1]Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [2]UNC at Chapel Hill, Chapel Hill, NC

Abstract: Comorbid Post-traumatic Stress Disorder (PTSD) and mild traumatic brain injury (mTBI) represents a complex neuropsychological construct with impairments in executive functioning (EF) and emotional processing (EP), impacting social functioning, quality of life, and mental health. Understanding the underlying neurobiology of these deficits can significantly improve the efficacy of intervention in individuals with mTBI/PTSD. This study aims to identify underlying neurobiology of EF and EP deficits, and elucidate relationships between neural network function in fronto-limbic (FL) and front-striate (FS) regions and connectivity, symptom severity (SS) and neurocognitive (NC) impairments. We conducted functional (fMRI), resting state (rsfMRI) and diffusion tensor (DTI) magnetic resonance imaging in 95 veterans (ages 16-65) who met criteria for PTSD/mTBI. FMRI tasks included an affective face matching task (AFMT), affective 1-back task (A1BT), and a go-no-go inhibition task (GNGT). Subjects completed the Barratt Impulsivity Scale (BIS-11) and Clinician Administered PTSD Scale

(CAPS). Images were acquired on a 3T SIEMENS Tim Trio. Image analysis included whole-brain voxel-wise and region-of-interest (ROI) analyses performed using FMRIB's Software Library (FSL). Pearson's correlation coefficient was used to threshold and identify significance at $p<.05$ for mean % signal change VS. NC and SS scores. Resting state functional connectivity (rs-FC) was analyzed using Python/FSL. Pearson's R coefficient ($R>.33$) for the best linear fit of z-scores vs. NC scores ($p<.05$). ROI-based analyses revealed reduced amygdala and fusiform gyrus activation related to increased CAPS. Increased insula activity related to increased BIS-11 and CAPS during the AFMT. Increased cingulate gyrus activity related to increased CAPS and BIS-11, while increased middle frontal gyrus related to increased BIS-11 during the A1BT. During the GNGT, decreased inferior frontal gyrus activity related to increased BIS-11. Rs-FC analyses revealed decreased FS connectivity related to increased CAPS, and decreased FL rs-FC related to increased BIS-11. Overall, this study revealed that functional and rs-FC in FL and FS ROIs is aberrant in veterans with mTBI/PTSD. Hypo-activation in FL ROIs related to more severe CAPS during emotional face processing, while hyper-activation in these regions related to more severe CAPS and BIS-11. Rs-FC results could indicate networks being taken "off-line" more efficiently as severity increases. Future work will compare these data to healthy controls and correlate task-based activation to symptoms of hyper-arousal and emotional numbing.

Disclosures: M. Weber: None. **J. Bizzell:** None. **J. Johnson:** None. **E. Melton:** None. **E. Elbogen:** None. **A. Belger:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.09

Topic: F.01. Human Cognition and Behavior

Support: Wellcome Trust Senior Investigator Award to Professor Trevor Robbins 104631/Z/14/Z

Title: Impaired cognitive flexibility is associated with reduced functional connectivity of dorsal fronto-striatal loop circuits in patients with Obsessive Compulsive Disorder (OCD)

Authors: *M. M. VAGHI[1,2], P. KUNDU[3], P. E. VÉRTES[2], A. M. APERGIS-SCHOUTE[2,4], F. E. VAN DER FLIER[2], N. A. FINEBERG[5], A. SULE[4], A. X. PATEL[2], E. T. BULLMORE[2,4], T. W. ROBBINS[1,2];
[1]Dept. of Psychology, Cambridge, United Kingdom; [2]Behavioural and Clin. Neurosci. Inst., Cambridge, United Kingdom; [3]Brain Imaging Ctr. and Translational and Mol. Imaging Institute,

Icahn Inst. of Med. at Mt. Sinai, New York, NY; [4]Dept. Psychiatry, Cambridge, United Kingdom; [5]Hertfordshire Partnership Univ. NHS Fndn. Trust and Univ. of Hertfordshire, Hertfordshire, United Kingdom

Abstract: Obsessive Compulsive Disorder (OCD) is characterized by recurrent intrusive thoughts (obsessions) and repetitive rituals (compulsions), performed according to rigid rules. Executive impairment is evident in OCD and possibly dependent upon abnormalities within fronto-striatal circuitry. Thus, fundamental to the understanding of OCD, is a detailed knowledge of the patterns of connectivity between cortical and subcortical brain regions, building on the hypothesis that OCD is associated with dysfunctional interactions between nodes that should work in concert rather than from damage to individual brain regions. The present study was conducted to test the hypothesis of dysfunctional fronto-striatal loop circuits in OCD patients and to relate patterns of altered connectivity to cognitive mechanisms possibly underlying the perseveration demonstrable in the clinical behavior of OCD patients. We tested 44 OCD patients (27 medicated and 17 unmedicated) and 43 healthy controls on the Extradimensional / Intradimensional set shifting task from the CANTAB battery and collected multi-echo resting state data from the same subjects. In terms of neuropsychological performance, compared to controls, OCD patients made significantly more errors selectively at the extradimensional shift (EDs) stage. There were no differences in discrimination learning per se or at the intradimensional shift stage, demonstrating, that while being able to form an attentional set, patients were impaired when had to shift attention between stimulus dimensions. No significant differences were detected between medicated and unmedicated patients consistent with evidence that serotonergic mechanisms are not implicated in EDs performance. OCD patients showed functional abnormalities along the dorsal cortico-striatal axis, implicating significantly reduced functional connectivity (FC) between the caudate and lateral prefrontal cortex (LPFC). Reduced functional connectivity between the left caudate and the LPFC was significantly correlated with higher numbers of errors in the EDs stage. Current findings confirmed that OCD patients show marked impairment in cognitive flexibility, which previous studies demonstrated to have endophenotype qualities in OCD. Importantly, the study supported the hypothesis that OCD is associated with functional alterations of the dorsal fronto-striatal axis. Finally, the results suggested that reduced functional connectivity between the caudate and specific sectors of the frontal cortex might account for the rigid behavior observed clinically in OCD and possibly identified a valuable biomarker for this disorder.

Disclosures: **M.M. Vaghi:** None. **P. Kundu:** None. **P.E. Vértes:** None. **A.M. Apergis-Schoute:** None. **F.E. Van Der Flier:** None. **N.A. Fineberg:** None. **A. Sule:** None. **A.X. Patel:** None. **E.T. Bullmore:** None. **T.W. Robbins:** F. Consulting Fees (e.g., advisory boards); Cambridge Cognition (CANTAB), Lilly, Lundbeck, Osuka, Teva and Shire Pharmaceuticals, GSK. Other; Springer, Elsevier.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.10

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant NS082069

NIH Grant MH063901

Title: Causal evidence for the organization of prefrontal cortex by content and control

Authors: *D. E. NEE[1], M. D'ESPOSITO[2];
[2]Helen Wills Neurosci. Inst., [1]Univ. of California, Berkeley, Berkeley, CA

Abstract: The prefrontal cortex (PFC) is essential for higher-level cognition. However, understanding the functional organization of the PFC has been challenging given the widespread involvement of much of the PFC across a range of cognitive tasks. Focal disruption of distinct areas of the PFC can therefore provide a powerful means to causally tease apart the functions of distinct regions and elucidate the organizational structure of the PFC. Based on previous data, we hypothesized that the PFC has two axes of organization: a dorsal-ventral axis sensitive to content, and a rostral-caudal axis sensitive to levels of cognitive control. To causally test this proposal, participants performed a task that varied demands on content (verbal, spatial) and level of cognitive control (low, mid, high) after receiving continuous theta-burst transcranial magnetic stimulation (TMS) to either the rostral PFC (lateral frontal pole), mid-ventral PFC (ventrolateral prefrontal cortex), or caudal-dorsal PFC (caudal superior frontal sulcus). As predicted, TMS to different sites produced distinct patterns of impairment: 1) TMS to caudal-dorsal PFC impaired spatial processing generally; 2) TMS to mid-ventral PFC impaired verbal processing, especially at mid-levels of cognitive control; 3) TMS to rostral PFC produced no effect on content processing, but impaired high-levels of cognitive control. Notably, these results were partially hierarchical in that disruptions that produced impairments at lower levels of cognitive control also tended to produce impairments at higher levels of cognitive control, while the converse was not true. These results provide causal evidence for a dorsal-ventral content and rostral-caudal abstraction organization of the PFC, and support the idea that interactions within the PFC are hierarchical.

Disclosures: D.E. Nee: None. **M. D'Esposito:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.11

Topic: F.01. Human Cognition and Behavior

Support: NSERC Discovery Grant

Title: The what, where and when of executive function: dissociating cognitive control processes in the human brain

Authors: *S. LEMIRE-RODGER[1], R. N. SPRENG[2], W. D. STEVENS[1], G. R. TURNER[1]; [1]York Univ., Toronto, ON, Canada; [2]Cornell Univ., Ithica, NY

Abstract: Executive control processes have been found to cluster around three factors: updating, inhibition and task switching. Few neuroimaging studies have directly contrasted these processes in a single study. Here we examined convergent and divergent patterns of neural activity using a within-subject design and a novel paradigm that matched all non-executive demands across tasks. Participants underwent fMRI scanning while switching between updating, inhibition and control tasks. Our original analysis identified divergent patterns of activity related to each of the executive functions of interest. Working memory updating was associated with bilateral activity (right > left) in dorsolateral prefrontal and insular cortex as well as lateral parietal cortex. Inhibition was associated with activity in the right ventrolateral prefrontal cortex and frontal poles bilaterally as well as medial prefrontal cortex. Task switching was associated with a predominantly left-lateralized activation pattern including regions of the dorsolateral prefrontal cortex, superior medial prefrontal cortex, posterior cingulate cortex as well as lateral parietal cortices. A conjunction analysis revealed virtually no overlap in brain activity for the three tasks. These results provided strong evidence for the fractionation of executive control processes in the human brain. In the current study, we used a mixed block and event-related analysis to isolate brain areas associated with sustained and transient aspects of executive control (specifically updating and inhibition). This analysis revealed areas associated with trial-wise activation as well as the instantiation and maintenance of executive task-set. Brain areas involved in both the transient and sustained aspects of executive control remained distinct across conditions. Updating events were associated with bilateral insula activation while regions or lateral frontal and parietal cortices were active over condition blocks. Inhibition events were associated with activation of frontal polar cortices bilaterally as well as right inferior frontal gyrus. Sustained activity during inhibition blocks was associated with left superior parietal lobe, precentral gyrus, and cuneus. These results replicate our previous findings, demonstrating that executive control processes are dissociable in the brain. Here we extend these findings to suggest that this

distinction may be most robust for discrete events. In contrast, sustained activity in superior parietal cortices was observed for both tasks, and may reflect the maintenance of an executive control task set.

Disclosures: S. Lemire-Rodger: None. **R.N. Spreng:** None. **W.D. Stevens:** None. **G.R. Turner:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.12

Topic: F.01. Human Cognition and Behavior

Support: Sir Henry Wellcome Postdoctoral Fellowship

Title: A standardized decomposition of the posterior cingulate cortex: heterogeneous recruitment of subregions across cognitive tasks

Authors: *R. M. BRAGA[1,3,4], A. HAMPSHIRE[2], R. LEECH[2];
[2]Div. of Brain Sci., [1]Imperial Col. London, London, United Kingdom; [3]Ctr. for Brain Sci., Harvard Univ., Cambridge, MA; [4]Athinoula A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp. & Harvard Med. Sch., Charlestown, MA

Abstract: The posterior cingulate cortex (PCC) communicates with multiple sensory modalities and is implicated in a broad range of cognitive tasks and psychiatric conditions. We have previously shown that the PCC contains a 'local functional architecture' (LFA) of subregions. The existence of these subregions raises the possibility that the PCC is not uniformly recruited across different cognitive tasks. Further, the functional connectivity (FC) of each PCC subregion may dynamically alter during different task contexts. We analysed task and resting-state functional magnetic resonance imaging (fMRI) data from the Human Connectome Project (n=460) to parcellate the PCC into component subregions. Spatial independent component analysis was run in individual-subjects that included all 7 task fMRI datasets. The spatial correspondence of PCC network maps from each run was examined. We then assessed the FC of each PCC network with the rest of the brain, and tested the correspondence of the whole-brain FC maps. Finally, we examined the task-related contrasts to characterise the contributions of each PCC subregion to the task-based modulation of the PCC as a whole. The results showed that the PCC subregions are surprisingly robust to different task contexts, with similar subregion maps being obtained from different tasks. Connectivity to other regions of the brain was also

highly consistent across tasks. However, subregions of the PCC showed strikingly different task-based modulation depending on the task that was being performed. In contrast, when assessed as a whole the PCC showed the characteristic DMN pattern of function; with decreased activation for externally oriented tasks and increased activation for internally oriented tasks. Our results support the notion that the PCC can be decomposed into a set of task-invariant regions. Furthermore, these same regions, although consistently activated as a whole for many tasks, were differentially modulated across different tasks. This suggests that the PCC adopts different configurations of relative subregion activation during different task contexts. This may explain how similar activation of the PCC can subserve multiple cognitive tasks; through different local-scale modulation in subregions that are relatively specialized in their global connectivity. We propose that these local-scale features are integral to the role of the PCC, and propose that different neurological conditions (many of which implicate the PCC) may also be stratified by regarding the existence of these subregions.

Disclosures: **R.M. Braga:** None. **A. Hampshire:** None. **R. Leech:** None.

Nanosymposium

751. Human Cognition: Cognitive Control and Flexibility

Location: N227

Time: Wednesday, October 21, 2015, 1:00 PM - 4:15 PM

Presentation Number: 751.13

Topic: F.01. Human Cognition and Behavior

Support: Julius N. Frankel Foundation

Title: High-definition transcranial direct current stimulation to right inferior frontal cortex improves response inhibition

Authors: ***J. HOGEVEEN**[1,2], J. GRAFMAN[1,2,3], A. DAVID[4], M. BIKSON[4], K. K. HAUNER[1,2,3];
[1]Cognitive Neurosci. Lab., Rehabil. Inst. of Chicago, Chicago, IL; [2]Dept. of Physical Med. & Rehabil., [3]Dept. of Neurol., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [4]Dept. of Biomed. Engin., The City Col. of New York, New York, NY

Abstract: Transcranial direct current stimulation (tDCS) is a valuable tool for improving cognitive performance and elucidating causal brain-behavior relationships. However, conventional tDCS has a spatially diffuse effect on neural activity, reducing its utility to researchers interested in inducing targeted neurocognitive effects. The recent development of "high-definition" tDCS (HD-tDCS) enables researchers to modulate neuronal activity with an

increased focality relative to conventional tDCS. Heretofore, relatively few studies have utilized HD-tDCS to improve cognitive task performance, and almost no studies have compared HD-tDCS to non-HD (conventional) tDCS. In the present study, we determined whether HD-tDCS could be used to improve response inhibition, a critical executive function that is impaired in various clinical populations marked by heightened impulsivity. Through the use of predictive computational models, we designed an HD-tDCS montage to principally target the right inferior frontal cortex (rIFC), a brain region that is known to play a critical role in response inhibition. Participants performed a response inhibition task (the stop-signal task, SST) before, during, and after HD-tDCS (group 1) or conventional tDCS (group 2) was delivered to rIFC. Further, a third group of subjects completed the same pre-posttest design but received tDCS to a control site (mid-occipital cortex). SST performance was improved in both the HD-tDCS and conventional tDCS groups relative to the control group. Thus, we provide seminal evidence that HD-tDCS can be used to improve response inhibition, suggesting that it is possible to modulate executive functions using a method with purported improved spatial focality relative to conventional tDCS.

Disclosures: **J. Hogeveen:** None. **J. Grafman:** None. **A. David:** None. **M. Bikson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CUNY has patents on brain stimulation with MB as inventor. MB is co-founder of Soterix Medical Inc.. **K.K. Hauner:** None.