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Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.001/LBA1

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS Kakenhi 20H00483
JSPS Kakenhi 22H05169
JST SPRING Grant
JSPS Kakenhi 23KJ1280

Title: Nesprin-2 coordinates opposing microtubule motors to generate nuclear movements during neuronal migration

Authors: *C. ZHOU[1], Y. K. WU[2], T. FUJIWARA[3], M. KENGAKU[2,3];
[1]Grad. Sch. of Biostudies, Kyoto Univ., Kyoto, Japan; [2]Grad. Sch. of Biostudies, Kyoto Univ., Kyoto, Japan; [3]Inst. for Integrated Cell-Material Sci. (WPI-iCeMS), Kyoto Univ., Kyoto, Japan

Abstract: Movement of the nucleus is critical for the proper positioning of neurons in the developing brain. During neuronal migration, nuclear movements are generated by cytoskeletal motor moelcules, among which dynein is widely recognized as the major player. Our previous study found that both dynein and kinesin-1, a pair of opposing microtubule motors, are required for forward nuclear movements in mouse cerebellar granule neurons, but the mechanism remains unknown. Here, we propose that dynein and kinesin-1 function in a coordinated manner for nuclear transport via a nuclear-membrane protein Nesprin-2. We demonstrated that Nesprin-2 serves as a cargo-motor adaptor by recruiting kinesin-1 and dynein-dynactin-BicD2 complex onto the nuclear envelope through independent but physically close motifs. Loss of function of Nesprin-2 in vivo caused delayed nuclear migration in cerebellar granule cells and impaired cerebellum layer formation. Intriguingly, both motors are indispensable for rescuing the impaired nuclear movements in Nesprin-2 mutant granule cells, supporting a co-dependent relationship. By reconstituting cargo dynamics using an intracellular cargo trafficking assay, we found that Nesprin-2 drives continuously active bidirectional movements along microtubules. Furthermore, while keeping the nucleus at a mobile state, Nesprin-2 physically links the nucleus with the forward-moving peri-nuclear microtubule tracks to facilitate forward nuclear translocation during neuronal migration. These results reveal the role of Nesprin-2 in mediating coordination between opposing motors as well as coupling of nuclear-microtubule movements.

Disclosures: C. Zhou: None. **Y.K. Wu:** None. **T. Fujiwara:** None. **M. Kengaku:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.002/Web Only

Topic: A.01. Neurogenesis and Gliogenesis

Support: PRODEP [CA UDG 700]
PROSNI-UDG-CUSUR
Neurobiology Institute, UNAM.

Title: Low protein diet intake during pregnancy and lactation promotes differential cellularity differences in dentate gyrus cells of hippocampus in male and female offspring

Authors: *M. NAVARRO MEZA[1], D. E. ALMARAZ[2], D. P. OCHOA[3], P. C. BELLO-MEDINA[4], M. DIAZ-MUÑOZ[5];
[1]Promoción, preservación y desarrollo de la salud. Ciencias Clínicas, Ctr. Universitario Del Sur/ Univ. De Guad, Ciudad Guzman/Jalisco, Mexico; [2]Promoción, preservación y desarrollo de la salud. Ciencias Clínicas, Univ. de Guadalajara, Jalisco, Mexico; [3]Promoción, preservación y desarrollo de la salud. Ciencias Clínicas, Univ. of Guadalajara, University of Guadalajara, Mexico; [4]Inst. de Educación a Distancia IDEAD, Univ. del Tolima, Ibagué, Tolima, Colombia, Tolima, Colombia,, Univ. del Tolima, Ibagué, Tolima, Colombia, Colombia, Colombia; [5]Inst. de Neurobiología, Univ. Nacional Autónoma de México, Querétaro, Querétaro, México., Queretaro, Inst. de Neurobiología UNAM, México, Queretaro, Mexico

Abstract: Brain development during pregnancy and lactation depends on factors such as mother's diet and postnatal development is necessary for proper execution of cognitive processes. The dentate gyrus (DG) is a gyroconvolution in cortex and temporal lobe of the hippocampus; and participates in consolidation and recovery of memory. Few studies have evaluated the effect of maternal diets on the neurodevelopment of DG within the progeny. Mother rats (Wistar) were divided in two groups: control (18% protein diet) and experimental (6% protein diet), food and water intake were quantified until day 10 of lactation; brain slices of male and female pups were obtained and used to detect 4',6- diamidino-2-fenilindol (DAPI) and neural nuclear protein (NeuN) in the DG by immunohistochemistry as markers of cellularity and mature neurons. The images obtained by fluorescence microscopy were assessed in ImageJ Software using double-blind method; two-way ANOVA and post hoc Bonferroni tests were performed. Offspring male in experimental group showed a 45% increase in DAPI area ratio hilus versus control male; a 71% increase in DAPI signal in experimental males versus experimental females; an increase of 35% in the number of cells (DAPI+) in females compared to males in infrapyramidal layer. Data indicate that male pups under low protein diet at day PND10 show more cells in DG hippocampus pyramidal area versus male of control group as well as female, as a sex-dependent compensatory mechanism to ensure the correct development of DG. Acknowledgements:The Authors would like to thank the following persons and institutions for their assistance and support of this study: José Martín García Servín, MVZ, for the handling and care of the experimental model; the Animal Care Facility of the Neurobiology

Institute, UNAM; Nydia Hernández in the Microscopy and PhD, Luna Moreno D, Vázquez-Martínez O for expert technical support, GA Reynaga-Macias and GS de la Cruz Rivas for their support in databases and to make figures, and expert technical support.

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Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.003/LBA3

Topic: A.01. Neurogenesis and Gliogenesis

Support: JPMJSP2146

Title: Overexpression of motopsin, the loss of which functions causes intellectual disability, decreases locomotor activity in mice

Authors: *Y. TANAKA, F. YOKOI, S. MITSUI;
Dept. of Rehabil. Sci., Gunma Univ. Grad. Sch. of Hlth. Sci., Maebashi/Gunma, Japan

Abstract: Motopsin, also known as neurotrypsin (PRSS12), is a serine protease secreted from excitatory neuronal cells in some brain regions (Brain Research 66, 141, 1999). A truncating mutation in motopsin gene is associated with intellectual disability (Science 298, 1779, 2002). Motopsin knockout mice exhibit prolonged social interaction and reduced spine density in hippocampal CA1 (Eur J Neurosci 30, 2368, 2009). Recently, using a Tet-off system, we reported that motopsin overexpression (OE) enhances neurogenesis in the dentate gyrus of adult mice (Mol Neurobiol 61, 4929, 2024). In this study, we investigated cognitive functions of motopsin OE mice. Motopsin OE mice (male, n =6, female, n = 6) were created by crossing C57BL/6 Tg(Camk2a-tTA)1Mmay/J mice and C57BL/6 TRE-motopsin mice. Administration of doxycycline (DOX) for over 3 weeks suppressed motopsin overexpression to the basal level in these mice (motopsin SO mice, male, n =6, female, n = 6). Wild-type (WT) mice given water (WT, male, n = 5, female, n = 5) or DOX (WT-DOX, male, n = 6, female, n = 6) served as controls. A subject mouse (16.1 ± 4.2 week old) was placed in an open field (50 × 50 × 50 cm) for 10 min to explore (open field test, OFT), which was repeated over three consecutive days for habituation. Novel object recognition test (NOR) and novel location recognition test (NLR) were each conducted in the open field with a 72 h intersession interval. Brains were collected 24 h after intraperitoneal injection of 5-bromo-2'-deoxyuridine. In the OFT, motopsin OE mice showed significantly decreased total distance traveled compared to other groups (p=0.010), though no significant differences were observed in center time. In the NOR, all experimental groups exhibited no preference for the novel object. In the NLR, motopsin OE mice showed a

trend towards preferring to investigate the object in the same location as in the previous session ($p = 0.051$), while the other groups showed no location preference. Our results suggest that motopsin overexpression may affect locomotor activity and spatial memory. Further measurement of adult neurogenesis in the dentate gyrus will be presented.

Disclosures: Y. Tanaka: None. **F. Yokoi:** None. **S. Mitsui:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.004/LBA4

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI JP20H05688
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Title: Importance of maternal immunoglobulins for postnatal maintenance of cortical interneurons

Authors: K. MORIMOTO[1], R. TAKAHASHI[1], G. TAKAHASHI[1], M. MIYAJIMA[1,2], ***K. NAKAJIMA**[1];
[1]Keio Univ. Sch. Med., Tokyo, Japan; [2]PRESTO, JST, Tokyo, Japan

Abstract: Embryos and newborns are highly sensitive to a variety of stimuli, and they are protected by maternal molecules that cross the placenta. One such molecule thought to be important in preventing infection is immunoglobulin (Ig). However, the transfer of maternal Igs to the brain is fraught with risk: for example, maternal brain-reactive antibodies such as anti-contactin-associated protein-like 2 (Caspr2; CNTNAP2) and collapsin response mediator proteins 1 and 2 (CRMP1, CRMP2), and Y-box-binding protein 1 (YBX1) have been identified, and maternal brain-reactive antibodies are present in 10-20% of mothers of children with autism spectrum disorders. Therefore, we hypothesized that there might be an unknown benefit to the offspring brain that outweighs these risks because embryos are nearly sterile and lack infection and inflammation during the normal development. Using an IgG production deficient model

(Rag2 mice) and IgG transport impaired model (Fcgrt KO mice), we found that IgG in the developing brain is of maternal origin, and the amount of IgG is high in embryonic stages and just after birth, but it decreases dramatically after birth and almost disappears by 3 weeks postnatally because maturation of blood-brain barrier blocks the entry of IgG. They accumulate at the meninges and axon bundles, and P2RY12-positive microglia and CD206-positive border-associated macrophages (BAMs) are strongly stained for IgG. Using Fcer1g KO mice, we found that microglia and BAMs use FcγR to take up IgG, but deposition of IgG on the meninges and axon bundles is FcγR-independent. We examined the phenotype of maternal IgG-deficient mouse models and found that the number of interneurons were decreased in Fcgrt KO mice and pups from Rag2KO dams raised by ICR wild-type mice to eliminate the potential influence of the maternal genotype after birth. These results suggest that maternal IgG is important for the postnatal maintenance of interneurons.

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Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

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Topic: A.01. Neurogenesis and Gliogenesis

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HHMI
NINDS R01NS032457
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R01 HG012573
R01 CA269805

Title: Genetically Unstable Single-Neuron Genomes During Human Brain Development

Authors: *D. SHAO[1], Y. ZHAO[4], U. GHOSH[2], J. BREW[4], P. PARK[4], C. A. WALSH[3]; [1]Dept. of Neurol., Boston Children's Hosp., Boston, MA; [2]Boston Children's Hosp., Newark, DE; [3]Genet. and Genomics, Boston Children's Hosp., Boston, MA; [4]Dept. of Biomed. Informatics, Harvard Med. Sch., Boston, MA

Abstract: The conventional view that genome fidelity is paramount for neurons has been challenged by recent findings showing that both neuronal progenitors and post-mitotic neurons accumulate somatic single-nucleotide variants (SNVs) with aging and neurodegenerative diseases. During neurodevelopment, the human brain undergoes cellular expansion more rapidly than in other tissues of the body, and more so than during brain development of any other

species. Such rapid expansion has been shown to be a key driver of genetic instability in other systems, such as during early post-zygotic development and in cancer.To explore genome-level effects in individual neurons during human brain development, we conducted single-cell whole genome sequencing on over 1,500 neurons derived from human fetal and postnatal human brains. Individual fetal neurons or postnatal neurons were isolated using florescence activated nuclear sorting, after dissection of the cortical plate or NeuN-staining, respectively, and single-cell whole genome amplification was performed using Tn5-transposase. We developed a novel analytical method to detect copy-number alterations (CNAs), leveraging molecular overlap patterns created by Tn5 to improve call accuracy. Our findings reveal that fetal neurons frequently exhibit multiple CNAs. These aberrant genomes reflected recurrent patterns of genomic instability as evidenced by the mutational spectrum of CNAs and immunohistochemistry identifying micronuclei in neurodevelopment, a biological indicator of genetic instability.Genomic instability affected a significant subset of fetal neurons, but surprisingly, this proportion is reduced in postnatal neurons. Postnatal neurons show fewer aberrant genomes and a reduced percentage of CNAs compared to their fetal counterparts. Moreover, postnatal neurons are less likely to show CNAs affecting genes crucial for neuronal function, suggesting a selection process that eliminates mutated genomes. Additionally, using single-cell DNA/RNA multiomic methods, we observed that neurons with pronounced aneuploidy exhibit alterations in gene sets associated with apoptosis. These findings reveal a complex etiology of CNA during brain development and highlight an unexpected mechanism of genetic diversity. This study suggests that cellular mechanisms for genetic control are crucial in shaping the final neuronal complement in the human brain, impacting both neurodevelopment and potentially long-term cognitive health.

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Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.006/LBA6

Topic: A.01. Neurogenesis and Gliogenesis

Title: Spatiotemporal and hierarchical diversification of MGE-derived GABAergic neurons

Authors: *Z.-L. LI[1,2], X. LI[1,2], D. MI[1,2], S.-H. SHI[1,2,3,4];
[1]IDG/McGovern Inst. for Brain Research, Tsinghua University, Tsinghua-Peking Joint Ctr. for Life Sci., Beijing, China; [2]Tsinghua Univ., Beijing, China; [3]Beijing Frontier Res. Ctr. for Biol. Structures, Beijing, China; [4]New Cornerstone Sci. Lab., Beijing, China

Abstract: The medial ganglionic eminence (MGE)-derived GABAergic neurons of great diversity are essential for the operation and function of all brain areas of the mammalian telencephalon, including the cortex and various subcortical nuclei; however, the mechanisms that control the diversification and distribution of these GABAergic neurons remain elusive. In this study, we systematically investigated the production and diversification of MGE-derived GABAergic neurons by integrating scRNA-seq, spatial transcriptomics, and genetics across the entire MGE neurogenic phase in the mouse brain. We found that different types of GABAergic neurons progressively emerge from distinct spatiotemporal niches of MGE. The diversification process proceeds in a hierarchical manner, with the major types specified in the progenitor stage, while the fine subtypes further defined in the post-mitotic stage. In particular, we identified the progenitor origin and developmental path of striatal Parvalbumin (PV)+ and Thyrotropin-releasing hormone (TRH)+ interneurons. Genetic ablation of these interneurons leads to obsessive-compulsive disorder (OCD)-like behavioral defects. Together, these findings provide a comprehensive developmental framework for the organized generation and distribution of highly diverse GABAergic neurons in the mammalian telencephalon.

Disclosures: Z. Li: None. **X. Li:** None. **D. Mi:** None. **S. Shi:** None.

Late-Breaking Poster

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Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.007/LBA7

Topic: A.01. Neurogenesis and Gliogenesis

Support: ARC Grant DP200102363
Washington University in St Louis laboratory startup funds

Title: Nuclear factor one genes regulate radial glia differentiation during early cortical development

Authors: *J. W. C. LIM[1], N. A. MUNDELL[1], E. HOSSEN[1], S. PAL[1], J. BUNT[2], L. J. RICHARDS[1];
[1]Dept. of Neurosci., Washington Univ. in St. Louis, Saint Louis, MO; [2]Princess Máxima Ctr. for Pediatric Oncology, Utrecht, Netherlands

Abstract: The nuclear factor one (NFI) transcription factors are a family of transcription factors consisting of the genes *NFIA*, *NFIB*, *NFIC*, and *NFIX*. Haploinsufficiency of *NFIA*, *NFIB*, or *NFIX* in people causes neurodevelopmental syndromes characterized by similar phenotypes, implying that they function similarly to regulate cortical development. These phenotypes include macrocephaly, intellectual disability, corpus callosum dysgenesis, and enlarged lateral ventricles. In mice, NFIA, NFIB, and NFIX are highly expressed in most cell types during cortical

development and in the adult cortex. Previous studies using mouse models have shown that *Nfi* genes regulate progenitor cell differentiation, but the underlying molecular mechanisms remain unclear. Aside from being expressed in most cell types, single-gene mouse mutants have overlapping phenotypes making it difficult to determine their cell type-specific functions. To address this, we utilized a single-cell multiomics approach coupled with detailed histological analyses of an Emx1-Cre-driven conditional mouse model where we removed *Nfia*, *b*, and *x* in different combinations in the dorsal forebrain. Focusing our current study on radial glial cells where these genes are first expressed, we found that upon *Nfi* deletion, radial glial cells divided symmetrically to give rise to more radial glial cells at the expense of generating intermediate progenitors and postmitotic neurons. Our single-cell data further demonstrates that NFIs regulate this process by binding at distal regulatory elements, resulting in the subsequent activation or repression of complementary gene regulatory networks underlying the switch between symmetric and asymmetric cell divisions. Whilst further work is required to determine how NFI binding at distal regulatory elements result in different outcomes on gene expression (activation versus repression), this study uncovers the molecular mechanisms through which NFI transcription factors regulate radial glial cell differentiation.

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Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.008/LBA8

Topic: A.01. Neurogenesis and Gliogenesis

Title: Evolutionarily conserved ventral program drives neocortical astrocyte diversification

Authors: *X. YU[1,2,3], Q. ZHANG[1,2,3], J. MA[1,2,3], S.-H. SHI[1,2,3];
[2]Tsinghua-Peking Joint Ctr. for Life Sci., [3]IDG/McGovern Inst. for Brain Research, School of Life Sci., [1]Tsinghua Univ., Beijing, China

Abstract: Astrocytes account for a fundamental population of cells in the neocortex and play numerous essential roles in neocortical development and function. Accumulating evidence suggests that neocortical astrocytes are diverse in morphological, molecular, and functional features; yet, little is known about the developmental program underlying neocortical astrocyte diversity. Here, by integrating systematic single-cell RNA-seq analysis across species, in vivo lineage tracing, and mouse genetics, we show that the evolutionarily conserved ventral program drives the progressive ventralization of dorsal radial glial progenitors (RGPs) and the generation of diverse astrocytes in the neocortex. Astrocytes or astrocyte-like glia represent a highly conserved cell type with an enrichment of smoothened signaling, the major ventralizing

signaling of the telencephalon. Interestingly, in the developing mouse neocortex, systematic reconstruction of the developmental trajectory atlas of RGPs reveals a progressive ventralization and detachment of RGPs from the ventricular zone at the late stage to generate diverse grey matter astrocytes as well as oligodendrocytes, whereas the remaining non-ventralizing RGPs preferentially give rise to ependymal cells and adult neural stem cells. Moreover, upon generation, astrocytes exhibit distinct differentiation patterns. While many astrocytes downregulate ventralization gene expression and become enriched with brain-blood barrier-related genes, others maintain ventralization gene expression and are enriched with synaptic function-related genes. Notably, similar astrocyte generation and diversification programs also exist in primates and is linked to glioblastoma formation. Together, these results define an evolutionarily conserved developmental program for the generation of diverse astrocytes in the neocortex.

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Program #/Poster #: LBA001.009/LBA9

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH NS117804
NIH NS117804-05S1

Title: Functional role of oligodendroglial progenitor cell-encoded Stearoyl-CoA desaturase 1 in developmental myelination

Authors: *I. N. FARNUM[1], M. CHAVALI[2];
[1]Pediatrics, Oregon Hlth. & Sci. Univ., Portland, OR; [2]Pediatrics/Neuroscience, Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Neonatal white matter injury (NWMI) is a major cause of motor and cognitive abnormalities in infants born pre-term, as well as in full-term births with complications such as intrauterine growth restriction, placental abruption, and birth asphyxia. Cerebral hypoxia and altered fetal circulation cause myelination defects in these conditions. However, the underlying mechanisms that disrupt the myelination by oligodendrocytes in hypoxic injury are not completely clear. Here, we found that neonatal hypoxia leads to a reduction in oligodendroglial stearoyl-CoA desaturase (Scd1) expression levels in a HIF-signaling dependent manner. Stearoyl-CoA desaturase is a rate-limiting enzyme in the synthesis of monounsaturated fatty acids, which are highly important for the formation and maintenance of the myelin membrane. Using inducible conditional knockout models of *Scd1*, we tested its functional impact on

oligodendroglial survival and maturation. We found that oligodendrocyte progenitor (OPC)-*Scd1 cKO* (*PDGFRa-Cre^{ERT2}/Scd1 (fl/fl)*) mice showed developmental hypomyelination with reduced myelin protein levels and mature oligodendrocyte cell numbers in various CNS white matter tracts. Additionally, systemic administration of a Scd1-specific pharmacological antagonist during neonatal development also resulted in a similar oligodendrocyte maturation deficit and hypomyelination in normoxic conditions and exacerbated the hypomyelination phenotype in a hypoxic injury setting. Interestingly, loss of mature oligodendrocyte specific-*Scd1* (in *PLP-Cre^{ERT2}/Scd1 (fl/fl)*) did not result in any myelination defects or outward behavioral deficits, suggesting a stage-specific role for OPC-Scd1. We are currently investigating the downstream mechanism through which Scd1 regulates oligodendrogenesis and myelination.

Disclosures: I.N. Farnum: None. **M. Chavali:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.010/LBA10

Topic: A.02. Postnatal Neurogenesis

Support: R21NS130290

Title: Astrocytic glycolysis regulates activity-induced hippocampal neurogenesis in the adult brain

Authors: *X. WANG[1], S. GE[2];
[1]Stony Brook Univ., Stony Brook, NY; [2]Neurobio. and Behavior, State Univ. of New York At Stony Brook, Stony Brook, NY

Abstract: Within the hippocampal neurogenic niche, nestled beneath the dentate granule cell layer, neural progenitors tirelessly generate newborn neurons in the adult brain. These fledgling cells face a pivotal early phase of competitive selection, characterized by active tangential migration and exuberant neurite extension towards the granule cell layer. However, in contrast to the well-characterized intrinsic molecular and circuit mechanisms governing this integration process, how these newborn neurons compete for their energy supply in this competitive environment remains unknown. Astrocytes are recognized as crucial conductors of brain glucose metabolism. Whether and how astrocytes regulate glucose metabolism and affect the activity-induced survival of newborn neurons remains unknown. To investigate the role of glucose metabolism in the activity-dependent survival of newly born neurons, we first performed single-cell RNA profiling and observed a marked reduction in glycolytic capacity in newborn neurons compared to neural progenitors and mature neurons. To examine the dynamics of cellular glucose metabolism during enriched contextual exploration (EE), a behavior that can specifically

affect the survival of newborn neurons, we established an optical glucose imaging technique with a genetic glucose sensor. We analyzed astrocytic glucose dynamics during EE, and found a rapid decrease in astrocytic glucose levels during exploration, with a quick return to baseline upon returning to the home cage. Importantly, when genetically depleted glucose transporter 1 from astrocytes, the EE-induced survival was impaired. To further explore how astrocytic glucose metabolism affects newborn neuron survival, we measured both extracellular and intracellular dynamics of lactate, an energy metabolite that can be shuttled between cells. Interestingly, intracellular and extracellular lactate levels initially increased during EE and can quickly recover to baseline. To elucidate the functional role of lactate, we genetically depleted Ldha (impairing lactate production) or MCT1 (impairing lactate shuttle). Both manipulations compromised the activity-induced survival of newborn neurons. Importantly, disrupting MCT1 in newborn neurons, thereby blocking lactate uptake, also impaired their survival. This groundbreaking discovery unveils a captivating link between environmental stimulation, astrocyte metabolism, and hippocampal neurogenesis, paving the way for understanding how brain activity shapes neuronal survival.

Disclosures: X. Wang: None. **S. Ge:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

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Topic: A.02. Postnatal Neurogenesis

Support: NSF-IOS-1456918
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Hubel Neuroscience Summer Research Fellowship awarded by Wellesley College

Title: Longitudinal tracking of hemocyte populations in vivo indicates lineage relationships and supports neural progenitor identity in adult neurogenesis

Authors: *A. J. EDWARDS[1,2], B. S. BELTZ[2];
[1]The Ken and Ruth Davee Dept. of Neurol., Northwestern University, Feinberg Sch. of Med., Chicago, IL; [2]Neurosci., Wellesley Col. Neurosci. Program, Wellesley, MA

Abstract: Adult neurogenesis, which takes place in both vertebrate and invertebrate species, is the process by which new neurons are born and integrated into existing functional neural circuits, long after embryonic development. Most studies in mammals suggest that self-renewing stem cells are the source of the new neurons, although the extent of self-renewal is a matter of debate. In contrast, research in the crayfish *Procambarus clarkii* has demonstrated that the neural progenitors producing adult-born neurons are capable of both self-renewing and consuming

(non-self-renewing) divisions. However, self-renewing divisions are relatively rare, and therefore the production of adult-born neurons depends heavily on progenitors that are not replenishing themselves. Because the small pool of neural progenitors in the neurogenic niche is never exhausted throughout the long lives of these animals, we hypothesized that there must also be an extrinsic source of these cells. It was subsequently demonstrated that the neural progenitors originate in hemocytes (blood cells) produced by the immune system that travel in the circulation before ultimately integrating into niches where the neural lineage begins. The current study examines the developmental lineage of the three hemocyte types — hyaline (HC), semigranular (SGC) and granular (GC) cells — with the goal of understanding the origins of the progenitor cells that produce adult-born neurons. Longstanding qualitative metrics for hemocyte classification were validated quantitatively. Then, in a longitudinal study, proliferation markers were used to label the hemocytes *in vivo*, followed by sampling the circulating hemocyte population over the course of two months. Hemolymph samples were taken at intervals to track the frequencies of the different hemocyte types. These data reveal sequential peaks in the relative frequencies of HCs, SGCs and GCs, which were identified using qualitative and quantitative measures. These findings suggest that the three hemocyte types comprise a single cellular lineage that occurs in the circulation, with each type as a sequential progressive stage in hemocyte maturation beginning with HCs and ending with GCs. When combined with previously published data, this timeline provides additional evidence that HCs serve as the primary neural progenitor during adult neurogenesis in *P. clarkii*.
This work has been peer-reviewed and was published in Neural Development on June 20, 2024. It can be found at the following link:
https://neuraldevelopment.biomedcentral.com/articles/10.1186/s13064-024-00185-3.

Disclosures: A.J. Edwards: None. **B.S. Beltz:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.012/LBA12

Topic: A.03. Stem Cells and Reprogramming

Title: Schwann cell precursors alter motor neuron activity in hiPSC-derived co-cultures from healthy and ALS donors

Authors: *A. HUNTEMER-SILVEIRA, M. DAU, G. MCCABE, V. TRUONG, P. WALSH; Anatomic Inc., Minneapolis, MN

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized primarily by the loss of motor neurons (MNs), leading to muscle weakness and eventual paralysis. Other cell types are also affected, including Schwann cells, which are

responsible for trophic support and myelination of peripheral nerves, as well as modulation of neuromuscular junction transmission. People with ALS typically die within five years of diagnosis, and there is currently no effective treatment that can reverse or halt the progression of ALS. In 2024 alone, two clinical trials to treat ALS failed due to lack of efficacy. This presents an urgent need to expand and improve current models for the study and treatment of ALS. We report here the development of a fully human induced pluripotent stem cell (hiPSC) based co-culture system to study the effects of Schwann cell precursors (SCPs) on MN pathology in ALS. Utilizing rapid directed differentiation protocols, hiPSCs from both a mutant TDP-43 ALS patient and healthy control donor were differentiated into SCPs and MNs. Healthy MNs, ALS MNs, healthy MN/SCPs, ALS MN/SCPs, healthy MN/ALS SCPs, and ALS MN/healthy SCP co-cultures were seeded on commercially available microelectrode arrays and spontaneous and evoked activity measured. In healthy co-cultures, MNs are spontaneously active within 7 days in vitro (DIV) and SCPs rapidly align with MN axons. ALS MNs show decreased spontaneous baseline activity compared to healthy MNs. Co-culture with SCPs increases spontaneous ALS MN activity and may also promote a hyperactive phenotype reported by similar ALS models, based on significant increases in spiking and bursting activity compared to healthy co-cultures. Evoked activity as measured following application of glutamate agonists/antagonists demonstrates altered functional activity in ALS co-cultures. These results demonstrate that integration of Schwann cell precursors into ALS models offers a unique opportunity to study mechanisms of TARDBP mutation in ALS and screen for therapeutic agents. Human models provide a promising avenue for the study of degenerative diseases, drug screening, and tissue engineering applications.

Disclosures: **A. Huntemer-Silveira:** A. Employment/Salary (full or part-time):; Employee at Anatomic Incorporated. **M. Dau:** None. **G. McCabe:** A. Employment/Salary (full or part-time):; Anatomic Inc. **V. Truong:** A. Employment/Salary (full or part-time):; Anatomic Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ownership and stock in Anatomic Incorporated. **P. Walsh:** A. Employment/Salary (full or part-time):; Anatomic Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Inc.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.013/LBA13

Topic: A.03. Stem Cells and Reprogramming

Support: 5056

Title: Dose-dependent effects of supernumerary sex chromosomes on brain organoid architecture and function

Authors: *A. ADAMO[1], V. ASTRO[3], G. HERRERA-LÓPEZ[4], P. J. MAGISTRETTI[2], A. R. MUOTRI[5];
[2]BESE, [1]King Abdullah Univ. of Sci. and Technol., Thuwal, Saudi Arabia; [3]King Abdullah Univ. of Sci. and Engin., Thuwal, Saudi Arabia; [4]KAUST, Thuwal, Saudi Arabia; [5]Pediatrics/Cellular Mol. Med., UCSD, La Jolla, CA

Abstract: Klinefelter syndrome (KS) is the most prevalent aneuploidy in males and is characterized by a 47,XXY karyotype. Less frequently, higher-grade sex chromosome aneuploidies (HGAs) can also occur. KS and HGA patients display a broad spectrum of neuronal clinical manifestations, including cognitive deficits, seizures, autistic traits, and delays in motor, speech, and language skills. The severity of cognitive impairment directly correlates with the number of additional sex complements. Despite the significant incidence of sex chromosome disorders, there has been a sustained demand for cellular models that elucidate the transcriptional and epigenetic consequences of X chromosome aneuploidies and their implications for human health. We previously generated a paradigmatic cohort of KS and HGA iPSCs to investigate the transcriptional consequences of X chromosome overdosage in 49,XXXXY, 48,XXXY, and 47,XXY patients. Leveraging this cohort, we modeled the impact of sex-chromosome aneuploidies during early neurodevelopment using iPSCs-derived X aneuploid cortical brain organoids. Intriguingly, X aneuploid brain organoids retain the epigenetically determined inactivation status of supernumerary X chromosomes during extended differentiation periods thus serving as an ideal 3D neurodevelopmental model. Through a comprehensive analysis integrating morphological, transcriptomic, and functional assessments, we demonstrated that supernumerary sex chromosomes detrimentally affect neural patterning, cortical architecture, and electrophysiological properties of brain organoids in a dose-dependent fashion. Thus, our study underscores the use of brain organoids as a valuable platform for modeling the molecular and cellular consequences of X chromosome overdosage during early neurodevelopment.

Disclosures: A. Adamo: None. **V. Astro:** None. **G. Herrera-López:** None. **P.J. Magistretti:** None. **A.R. Muotri:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.014/LBA14

Topic: A.03. Stem Cells and Reprogramming

Support: FAPESP 2014/50931-3
FAPESP 2020/09702-1

CNPq 465355/2014-5
CNPq 404134/2020-3

Title: Distinct Immunological Profiles in Centenarian iPSC-Derived Astrocytes Reveal Potential Mechanisms of Resilience to SARS-CoV-2 Infection

Authors: *M. V. DE CASTRO, D. OLIVEIRA, A. FARIA ASSONI, J. ESPOSITO, M. SILVA, F. CHIANCA, A. BARRETO DE PAIVA, M. CASTRO AMARANTE, M. SILVA, L. DE MENDONÇA OLIVEIRA, L. CORDEIRO MARTINS, M. SATO, L. FERREIRA, M. ZATZ;
Univ. of Sao Paulo (USP), São Paulo, Brazil

Abstract: One of the main challenges in science is to understand the diverse cellular and molecular mechanisms underlying resistance and susceptibility to SARS-CoV-2 infection and the significant clinical variability of COVID-19, which ranges from asymptomatic to lethal cases. Notably, the oldest individuals and those with comorbidities have been at the highest risk of developing severe COVID-19. However, there have been reports of unvaccinated centenarians worldwide who had asymptomatic infections or recovered from mild COVID-19. In this study, induced pluripotent stem cell-derived astrocytes were generated from Brazilian centenarians who recovered from COVID-19 before vaccination (n=4) and from young adults who recovered from critical COVID-19 (n=4). Astrocytes were infected with SARS-CoV-2 (Wuhan strain and Gamma P1 variant) at a multiplicity of infection (MOI) of 1.0 for 48 hours. All experiments were conducted in a biosafety level 3 laboratory. Consistent with previous findings, astrocytes were permissive to SARS-CoV-2 infection. Interestingly, although our data showed that the rate of cell-free infection of SARS-CoV-2 was similar in both experimental groups under the same conditions, the levels of CXCL8 (IL-8) and CXCL10 (IP-10) in the medium were significantly reduced following infection only in the centenarian group. The reduction in CXCL8 and CXCL10 levels in the centenarian astrocytes suggests that these individuals may possess unique immunological characteristics that enable them to better resist the excessive inflammation typically caused by SARS-CoV-2. Understanding these mechanisms could be crucial for developing new therapeutic strategies focused on modulating the immune response in COVID-19 patients, especially those at risk of developing severe forms of the disease. By uncovering these distinctive immune profiles, we can potentially identify biomarkers for resilience to COVID-19 and inform the design of treatments that could enhance immune regulation, thereby improving outcomes for patients across different age groups and clinical severities. The study was approved by the committee for ethics in Research of the Institute of Biosciences at the University of São Paulo (CAAE 34786620.2.0000.5464) and supported by the São Paulo Research Foundation (grant numbers 2014/50931-3, and 2020/09702-1), the National Council for Scientific and Technological Development (grant numbers 465355/2014-5 and 404134/2020-3).

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Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.015/LBA15

Topic: A.03. Stem Cells and Reprogramming

Title: Rapid and consistent generation of human iPSC-derived oligodendrocyte-like cells using opti-ox technology

Authors: M. HERRERA VAQUERO, L. FOULSER, S. MILDE, C. ARUTHAN, G. BELLI VALLETTA, J. HUNDLING, V. YIANNI, **B. HAUGEN**, I. FERREIRA, B. NEWMAN, T. OOSTERVEEN, G. MASTROGIOVANNI, *W. BERNARD, E. METZAKOPIAN, M. KOTTER;
bit.bio, Cambridge, United Kingdom

Abstract: Oligodendrocytes (OLs) are the myelinating cells in the central nervous system. By ensheathing axons, OLs enhance the action potential conduction velocity. OLs arise from oligodendrocyte precursor cells (OPCs) during pre- and postnatal development. The death of OLs and the impairment of differentiation of OPCs into OLs is a major pathological characteristic in demyelinating diseases.
The development of therapies that promote myelination in neurological conditions, particularly demyelinating diseases, is hampered by the limited translatability of existing preclinical animal models, and the lack of reliable in vitro models. Human induced pluripotent stem cells (hiPSCs) can be used to generate OLs for in vitro applications, however, current differentiation protocols are often lengthy, challenging to reproduce, and are difficult to scale. Our proprietary opti-ox™ (optimised inducible overexpression) technology enables highly controlled expression of transcription factors, deterministically programming hiPSCs into specific cell types of interest, to provide a robust, consistent, and reliable source of human cells for in vitro applications.
We have used opti-ox to rapidly program hiPSCs into oligodendrocyte-like cells (ioOligodendrocyte-like cells), a population of oligodendroglial cells resembling a pre-myelinating oligodendrocyte state. By day 1, the cells present an OPC-like morphology and are positive for oligodendroglial lineage markers OLIG2, SOX10 and O4. By day 8, the cells show increased complexity with an OL-like morphology, and increased expression of other mature oligodendrocyte markers such as MBP, MAL, CNP and MYRF, seen by qRT-PCR, bulk RNA and scRNAseq. Furthermore, whole transcriptome analysis demonstrates equivalent expression profiles between three different manufactured lots indicating consistency and experimental reproducibility.
ioOligodendrocyte-like cells provided a relevant, consistent, and scalable source of human cells that can be used for investigations into novel therapeutics and molecular mechanisms that regulate this critical glial cell type that is implicated in various human diseases.

Disclosures: **M. Herrera Vaquero:** A. Employment/Salary (full or part-time):; bit.bio. **L. Foulser:** A. Employment/Salary (full or part-time):; bit.bio. **S. Milde:** A. Employment/Salary (full or part-time):; bit.bio. **C. Aruthan:** A. Employment/Salary (full or part-time):; bit.bio. **G. Belli Valletta:** A. Employment/Salary (full or part-time):; bit.bio. **J. Hundling:** A. Employment/Salary (full or part-time):; bit.bio. **V. Yianni:** A. Employment/Salary (full or part-time):; bit.bio. **B. Haugen:** A. Employment/Salary (full or part-time):; bit.bio. **I. Ferreira:** A. Employment/Salary (full or part-time):; bit.bio. **B. Newman:** A. Employment/Salary (full or part-time):; bit.bio. **T. Oosterveen:** A. Employment/Salary (full or part-time):; bit.bio. **G. Mastrogiovanni:** A. Employment/Salary (full or part-time):; bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time):; bit.bio. **E. Metzakopian:** A. Employment/Salary (full or part-time):; bit.bio. **M. Kotter:** A. Employment/Salary (full or part-time):; bit.bio.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.016/LBA16

Topic: A.03. Stem Cells and Reprogramming

Support: AMED JP20gm1410001
Kakenhi 20K20643, 20H05786, 24H02307

Title: Network modifications and enhanced output segregation in connected organoids following repetitive spatiotemporal stimulation

Authors: ***S. A. CHOW**[1], H. HU[1,2], T. DUENKI[1,2], T. ASAKURA[3], S. SUGIMURA[3], Y. IKEUCHI[1,2];
[1]Inst. of Industrial Sci., [2]Chem. and Biotech., The Univ. of Tokyo, Tokyo, Japan; [3]Res. Inst. of Advanced Technol., Softbank Corp., Tokyo, Japan

Abstract: Neural circuits are the fundamental basis underlying brain functions. The complex three-dimensional structure of organoids provides an intrinsically complex neural network, however, it lacks the hierarchical macroscopic circuit structures. We have previously demonstrated that compared to single organoids, connected organoids produce more complex activity and demonstrated short-term plasticity following optogenetic stimulation. In this research, we cultured connected organoids on high-density multielectrode arrays. With time, axons grew from the organoids and connected with each other to form a neural circuit with synchronized activity. We repetitively stimulated and recorded the connected organoids using two distinct spatiotemporal patterns to monitor the changes in response to the two stimulations over an extended period of time. To investigate output signal segregation, multiple machine learning algorithms were tested. We found that the connected organoids showed different response to stimulation compared to the non-connected organoids. Network analyses before,

during and after stimulation showed network alterations following long-term stimulation of the organoids. This result highlights the importance of circuitry in functionality of organoids and demonstrated the potential of connected organoids in future applications.

Disclosures: S.A. Chow: None. **H. Hu:** None. **T. Duenki:** None. **T. Asakura:** None. **S. Sugimura:** None. **Y. Ikeuchi:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.017/LBA17

Topic: A.03. Stem Cells and Reprogramming

Title: Driving experimental reproducibility and lot-to-lot biological consistency in human iPSC-derived cells enabled by opti-ox technology

Authors: B. NEWMAN, H. GARNETT, R. O'REILLY, N. JAMES, S. POKORNY, J. HUNDLING, B. TALSANIA, L. KOWALSKI, V. YIANNI, R. HICKMAN, S. MILDE, *I. FERREIRA, **R. NORTHEAST**, G. MASTROGIOVANNI, T. OOSTERVEEN, A. WILCZYNSKA, W. BERNARD, F. PATELL-SOCHA, E. METZAKOPIAN, K. GOLDEN, M. KOTTER;
bit.bio, Cambridge, United Kingdom

Abstract: Transcription factor (TF)-mediated cellular reprogramming has introduced a novel paradigm in developmental biology, challenging traditional methods and facilitating scientific innovation.
Due to a lack of standardised, easy-to-use, and readily accessible human cell models, scientists often rely on animal models, primary cells, and/or cell lines that considerably differ from human biology. Induced pluripotent stem cell (iPSC)-derived cells are an alternative to these, offering a human model for disease research. Directed differentiation to generate the desired cell types from iPSCs through signalling with growth factors and small molecules involves lengthy, complex protocols that are challenging to reproduce, difficult to scale, and lead to heterogeneous populations. Moreover, despite the benefits of forward programming, several challenges remain associated with conventional vector-based methods of transgene expression impacting the efficiency, consistency and purity of the resulting cell populations, as the random integration of TFs can result in gene silencing.
The use of these models makes it difficult to generate consistent data from a scalable source of cells, with experimental variability often preventing scientists from being able to reproduce results over time or replicate other scientists' experiments.
Genomic safe harbour (GSH)-mediated optimised inducible overexpression (opti-ox) of cell type-specific TFs enables highly controlled, consistent and scalable manufacturing of human

iPSC-derived cells, addressing these challenges. This technology has been used to deterministically cell program iPSCs into different cell types, including ioGlutamatergic Neurons, ioGABAergic Neurons, ioMotor Neurons, ioSensory Neurons, ioMicroglia, ioOligodendrocyte-like cells, and ioAstrocytes. The resulting cell types are highly defined and consist of homogeneous populations, confirmed by ICC and RT-qPCR. Moreover, whole transcriptome analysis reveals consistent expression profiles across manufactured lots, demonstrating consistency of the cells.
The availability of consistent lots of human iPSC-derived cells has the potential to address the lack of experimental reproducibility seen across research, allowing scientists to accelerate their studies and enhance the reliability of their findings.

Disclosures: **B. Newman:** A. Employment/Salary (full or part-time):; bit.bio. **H. Garnett:** A. Employment/Salary (full or part-time):; bit.bio. **R. O'Reilly:** A. Employment/Salary (full or part-time):; bit.bio. **N. James:** A. Employment/Salary (full or part-time):; bit.bio. **S. Pokorny:** A. Employment/Salary (full or part-time):; bit.bio. **J. Hundling:** A. Employment/Salary (full or part-time):; bit.bio. **B. Talsania:** A. Employment/Salary (full or part-time):; bit.bio. **L. Kowalski:** A. Employment/Salary (full or part-time):; bit.bio. **V. Yianni:** A. Employment/Salary (full or part-time):; bit.bio. **R. Hickman:** A. Employment/Salary (full or part-time):; bit.bio. **S. Milde:** A. Employment/Salary (full or part-time):; bit.bio. **I. Ferreira:** A. Employment/Salary (full or part-time):; bit.bio. **R. Northeast:** A. Employment/Salary (full or part-time):; bit.bio. **G. Mastrogiovanni:** A. Employment/Salary (full or part-time):; bit.bio. **T. Oosterveen:** A. Employment/Salary (full or part-time):; bit.bio. **A. Wilczynska:** A. Employment/Salary (full or part-time):; bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time):; bit.bio. **F. Patell-Socha:** A. Employment/Salary (full or part-time):; bit.bio. **E. Metzakopian:** A. Employment/Salary (full or part-time):; bit.bio. **K. Golden:** A. Employment/Salary (full or part-time):; bit.bio. **M. Kotter:** A. Employment/Salary (full or part-time):; bit.bio.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.018/Web Only

Topic: A.04. Transplantation and Regeneration

Support: PROSNII 277086

Title: Transplantation of Olfactory Ensheathing Cells into the retrosplenial cortex of CD1 mice

Authors: ***F. PANTOJA**[1], N. CARRILLO-GONZÁLEZ[1], L. VÁZQUEZ MURO[1], G. GALINDO SILLER[2], G. ESCOBAR CAMBEROS[1], J. BURITICÁ[2], G. GUDIÑO-CABRERA[1], T. CAMPOS ORDONEZ[1];

[1]Biología Celular y Mol., [2]Ctr. de Estudios e Investigaciones en Comportamiento, Univ. of Guadalajara, Guadalajara, Mexico

Abstract: Olfactory Ensheathing Cells (OECs) are proposed as a potential therapeutic strategy for invasive lesions; these cells share properties with Schwann cells and astrocytes. OECs express the p75 neurotrophic receptor (p75NTR) and glial fibrillary acidic protein (GFAP). They modulate the local environment and support repairing neural connections by forming permissive glial bridges in the injured area when transplanted into a spinal cord injury. However, their role after transplantation into the retrosplenial cortex is unknown. This preliminary study analyzes the safety of OEC transplantation on a brain area. Our objective was to investigate the effects of OEC transplantation into the retrosplenial cortex on the mobility of mice after 21 days post-surgery. We used adult CD1 mice as donors of olfactory bulbs; this tissue was processed by cell culture to generate the OEC transplant (n=3). Adult mice were injected into the retrosplenial cortex with the OEC transplant (n=8). Sham received an injection of a vehicle (n=8). After 21 days post-surgery, mice did an open field test (OFT) to measure traveled distance, immobility, velocity, and time in the center and periphery. Post-surgery follow-up included daily visual inspections to observe the absence of infection, bleeding, or naso-oral secretions. No subjects were excluded, and no deaths were related to the procedure. Neither group exhibited aggression, seizures, or breathing problems. Our data suggest that OEC transplantation into the retrosplenial cortex did not affect any variable of OFT. Future studies need to analyze glial scar extension, pro- and anti-inflammatory cytokines expression, neurite outgrowth, and myelination. Developing new treatments that promote and accelerate the regeneration process in brain regions such as the retrosplenial cortex is essential for advancing biomedical research.

Disclosures: F. Pantoja: None. **N. Carrillo-González:** None. **L. Vázquez Muro:** None. **G. Galindo Siller:** None. **G. Escobar Camberos:** None. **J. Buriticá:** None. **G. Gudiño-Cabrera:** None. **T. Campos Ordonez:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.019/LBA18

Topic: A.04. Transplantation and Regeneration

Title: Specific integration of grafted human pluripotent stem cell-derived A10 dopaminergic neurons into host neural circuits to relieve depression

Authors: *W. YAN[1,2], Y. CHEN[1,2];
[1]Inst. of Neuroscience, Chinese Acad. of Sci., SHANGHAI, China; [2]CAS Ctr. for Excellence in Brain Sci. and Intelligence Technol., Shanghai, China

Abstract: Transplantation of human pluripotent stem cell (hPSC)-derived neurons to replace lost neurons and repair neural circuits has proven to be a valuable avenue for treating neurological disorders including Parkinson’s disease, Alzheimer's disease, Huntington's disease, which are characterized by neuronal loss. However, it is still not known whether the engrafted cells can integrate into endogenous neural networks and be used to treat the neuropsychiatric disorders, like Major depressive disorder, which are associated with neural dysfunction instead of neuronal loss. Here we report an efficient differentiation paradigm for hPSCs to generate VTA A10-like mDA neurons and found that post-mitotic patterning by Notch inhibitor, GDNF and AA induced the specification of A10 subtype. These hPSC-derived mDA neurons exhibited important characteristics of A10 subtype mDA neurons including expression profiles and electrophysiological properties. Moreover, grafted A10-like mDA neurons specifically project axons to endogenous-A10-target brain regions such as nucleus accumbens, olfactory tubercle and amygdala. The grafted A10-like mDA neurons were able to reconstruct mesolimbic dopamine pathway and induced the anxiolytic phenotype in transplanted normal mice or antidepressant-like phenotypes in transplanted depression mice model. These results indicate the grafted A10-like mDA neurons reconstructed specific circuit similar with the endogenous neural networks and restore the function of dysfunctional circuit, highlighting the promising application of hPSC-derived neuron subtypes in treatment of neuropsychiatric disorders.

Disclosures: W. Yan: None. **Y. Chen:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.020/LBA19

Topic: A.05. Axon and Dendrite Development

Support: NIH-NIDCD DC105748
DC107618
DC115824

Title: Calretinin as a marker to track developing olfactory tracts

Authors: *N. SPENCE[1,2], E. MARTÍN LÓPEZ[2], B. BRENNAN[2], N. LANGE[2];
[1]Yale Univ., New Haven, CT; [2]Neurosurg., Yale Sch. of Med., New Haven, CT

Abstract: The olfactory system is interconnected by projection neurons through an intricate circuit of axonal pathways. From the periphery in the olfactory epithelium (OE), the olfactory sensory neurons (OSNs) send their axons to the olfactory bulb (OB) via the olfactory nerve (ON) where they synapse with mitral and tufted cells (M/Tc) who project their axons to different olfactory cortical areas via the lateral olfactory tract (LOT). Some subpopulations of OSNs and

M/Tc express calretinin (CR), allowing us to use this marker as a proxy to tract the development of these pathways in the OB and piriform cortex (PC). To label CR, we cross-mated Calb2-Cre-ERT2 x Ai14 mice where CR^+ cells express tdTomato after induction with 4-hydroxy-tamoxifen (4OH-Tx) at the embryonic day 11 (E11). In the OE, the first evidence of CR^+ cells was seen at E14 around the septum, where some ON axons were visible. From E16 onwards, an increase in both the number and amount of CR was evident in the OSNs that were observed extending axons towards the OB to synapse with M/Tc in the glomeruli. Additionally, we used electron microscopy to follow synaptogenesis of LOT axons as they reach the PC along the anterior to posterior axis. The number of LOT-CR^+ axons innervating the PC increased gradually as the embryonic development progressed in an anterior to posterior gradient. This increase in axonal directions matched the number of synapses occurring in layer 1 of PC. Interestingly, most CR+ axons run in the inner part of the LOT, separated from the surface. Collectively, these findings help to better understand the development of the cortical olfactory circuitry at embryonic stages.

Disclosures: N. Spence: None. **E. Martín López:** None. **B. Brennan:** None. **N. Lange:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.021/LBA20

Topic: A.05. Axon and Dendrite Development

Support: NIDCD 1R01DC021456

Title: Isl1 controls axon pathfinding of retinal ganglion cells in the binocular visual pathway

Authors: *S. BISWAS[1], S. LI[2], X. XIE[3], L. GAN[3];
[2]Dept. of Neurosci. & Regenerative Med., [3]Dept. of Neurosci. and Regenerative Med., [1]Augusta Univ., Augusta, GA

Abstract: A critical regulator of binocular vision is the establishment of the proper ratio of retinal ganglion cells (RGCs) that cross the midline (contralateral RGCs) in the brain, and ones that do not (ipsilateral RGCs).
We show that in the absence of the LIM-homeodomain transcription factor, ISL1, there is an expansion of the ipsilateral RGC domain in the retina. In *Isl1-null* mice, there is a central expansion of Zic2 expression, which is normally restricted to the ventrotemporal crescent (VTC) of the retina. In addition, the expression of Isl2, a transcription factor required for contralateral RGC axon guidance, is markedly down regulated. Results from retrograde DiI labeling of RGCs from the superior colliculi show that RGCs in the contralateral domain of the *Isl1-null* retina project ipsilaterally at the optic chasm. Interestingly, whole eye injection of cholera toxin subunit B (CTB) shows that ipsilaterally projecting RGCs from the contralateral domain of the retina in

Isl1-null mice nonetheless project to regions of the dorsal lateral geniculate nucleus and superior colliculus that are targeted by contralateral projections in wild type mice.
The expression of genes in the diencephalic midline that play a role in correct guidance of the ipsilateral and contralateral optic tract such as EphrinB2 and Nrcam, are unchanged in *Isl1-null* mice. RNA sequencing as well as gene expression analyses demonstrate significant changes in the expression of genes involved in RGC axon pathfinding in *Isl1-null* retinas relative to controls. We propose that Isl1 acts upstream of Isl2 and Zic2 in specifying contralateral versus ipsilateral RGC domains in the retina.
Please note: Data was obtained from male and female embryonic and neonatal (P0) mice.

Disclosures: S. Biswas: None. **S. Li:** None. **X. Xie:** None. **L. Gan:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.022/LBA21

Topic: A.05. Axon and Dendrite Development

Support: NIH R35 NS122073
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Scribble clusters Kv1 potassium channels at the axon initial segment

Authors: *W. ZHANG, V. PALFINI, M. N. RASBAND;
Baylor Col. of Med., Houston, TX

Abstract: Axon initial segments (AISs) initiate neuronal action potentials. Voltage-gated Kv1 potassium channels (Kv1) are highly enriched at the AIS and regulate the repolarization phase of the action potential. However, the mechanisms responsible for the AIS clustering of Kv1 channels and its associated proteins (e.g. PSD93 and ADAM22) remain poorly understood. Here, based on a proteomic dissection of the AIS that we performed, we screened potential AIS Kv1 channel binding proteins. We identified the PDZ-domain containing scaffolding protein SCRIB at the AIS and found that it maintains AIS Kv1 channel clustering. Using a variety of experimental approaches including knock-out, cell surface clustering and co-immunoprecipitation, we show that SCRIB both directly clusters AIS Kv1 channels and links AnkG and the AIS Kv1 channel protein complex. Together, these results define a new AnkG-dependent scaffolding protein complex that functions to cluster AIS Kv1 channels, ADAM22, PSD93, and other components of the AIS Kv1 channel protein complex.

Disclosures: W. Zhang: None. **V. Palfini:** None. **M.N. Rasband:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.023/LBA22

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant NS114247
NIH Gran NS112504

Title: Map7 coordinates motor recruitment to regulate transport selectivity at branch junctions

Authors: *E. MOESE[1], S. TYMANSKYJ[2], L. MA[2];
[2]Neurosci., [1]Thomas Jefferson Univ., Philadelphia, PA

Abstract: Proper development and function of neurons requires tightly regulated microtubule (MT) -based transport of various cargo from cell bodies to synaptic terminals. Improper transport is implicated in various neurological diseases. Neurons have elaborately branched axons creating complex connections. Intracellular transport at axon branch junctions requires tight regulation of cargos, as suggested by recent discovery of selective transport in cultured dorsal root ganglion (DRG) neurons. Anterograde transport of lysosomes displayed preference for longer branches or branches with a dynamic growth cone. Furthermore, this selectivity is differentially regulated for various cargos and mediated by kinesin-3 motors. However, it is unknown what local mechanisms at branch junctions are mediating selectivity. Interestingly, MAP7 is a MT associated protein enriched at branch junctions in embryonic DRG neurons. *In vitro*, MAP7 recruits kinesin-1 to MTs but inhibits kinesin-3 from MT binding. Transport of cargos such as lysosomes when MAP7 is overexpressed displayed increased run time but decreased velocity indicating kinesin-3 MT binding is blocked. Therefore, we hypothesize that MAP7 coordinates motor recruitment and transport selectivity at branch junctions via phosphoregulation. To test this hypothesis, we first examined MAP7 knockout neurons. Preliminary data showed an increase in the anterograde transport velocity of lysosomes, consistent with the idea that MAP7 normally inhibits kinesin-3 but favors kinesin-1 transport. Currently, we are using these neurons to determine the requirement of MAP7 on transport selectivity. Next, we examined the role of MAP7 phosphorylation by mutating 13 SP/TP sites in the P-domain, a highly unstructured region that is involved in MT binding and axonal localization. Based on fluorescence recovery after photobleaching (FRAP) analysis, we found that that the phospho-mimetic mutant displays decreased MT binding compared to the phospho-null mutant. Intriguingly, the phospho-mimetic mutant is not localized to the branch junctions as the wildtype or the phospho-null mutant, instead it appears in the distal axons as well as the growth cones, which are normally avoided by MAP7. These data suggest phosphorylated MAP7 is readily removed from MTs, which could in turn increases kinesin-3-mediated transport at branch junctions. To test this possible mechanism, we are currently testing the role of the phosphomutants on selective transport. By parsing out the

relationship between the regulation of MAPs and intracellular transport we will begin to understand how regulated transport supports axon development and maintenance.

Disclosures: E. Moese: None. **S. Tymanskyj:** None. **L. Ma:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.024/LBA23

Topic: A.05. Axon and Dendrite Development

Title: Genetic dissection of motor proteins mediating dense core vesicle axonal trafficking in Drosophila

Authors: *A. DERMADY[1,2], J. YIN[2], H.-L. CHEN[2], Q. YUAN[2];
[1]Brown Univ., Providence, RI; [2]Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD

Abstract: Neuropeptides are known to act as modulators of development and a variety of behaviors, but the mechanisms and events controlling their release are not as well understood. One such key event is the bidirectional transport of neuropeptide-containing dense core vesicles (DCVs) along the axon tract. While many studies of DCV transport in *Drosophila* have been conducted in motor neurons, here we use the pigment dispersing factor (PDF)-releasing peptidergic lateral ventral neurons (LNvs) as a model system to study the regulation of axonal DCV transport. Using fixed staining, live imaging, and behavioral analysis, we found that, as shown previously in other peptidergic neurons, Unc-104 and Dhc64c, are required for anterograde and retrograde transport of PDF, respectively. However, we also found additional motors that may play a role in DCV transport in the LNvs, such as the kinesins Klp68D and Khc-73, and most interestingly, the axonemal dynein subunits CG9313 and Dhc93AB. While axonemal dyneins typically do not contribute to cytoplasmic transport, we hypothesize that these subunits may nevertheless act as regulators of axonal DCV transport in the LNvs. These findings may further our knowledge of mechanisms regulating axonal transport, particularly of neuropeptides.

Disclosures: A. Dermady: None. **J. Yin:** None. **H. Chen:** None. **Q. Yuan:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.025/LBA24

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: R01EY025437 (NEI)
Picower Institute Innovation Fund

Title: Somatostatin innervation and synapse formation in the developing mouse visual cortex

Authors: *J. R. BOIVIN[1], B. SCHMERL[1], K. BURNELL[1], C.-F. LEE[2], J. LEE[1], E. NEDIVI[1]; [1]MIT, Cambridge, MA; [2]Neurobio., Duke Univ., Durham, NC

Abstract: Despite the importance of inhibition for regulating developmental plasticity, the emergence of inhibitory neocortical innervation and synapse formation have not been well characterized. Inhibitory somatostatin (SST) neurons, which innervate pyramidal dendrites, play a key role in cortical signal processing but are particularly understudied in the context of developmental plasticity. While it is known that cortical excitatory neurons follow a deep to shallow developmental progression, and that excitatory synapses show exuberant postnatal synaptogenesis followed by pruning, it is unknown whether inhibitory innervation follows the same developmental trajectories. Here, we use a genetic labeling strategy to visualize SST boutons and their resident synapses in the mouse visual cortex, beginning before eye opening and continuing into adulthood. We show that robust depth differences in SST innervation density as reflected by bouton formation emerge during development, with the highest density in Layer 1 and the lowest density in Layer 6. SST innervation fills in across all cortical layers simultaneously, with the sharpest increase occurring after eye opening and during the opening of the cortical critical period for ocular dominance plasticity. Surprisingly, SST bouton density is unaffected by dark-rearing, suggesting that SST bouton formation and maintenance do not require visual experience. We further investigated whether bouton formation indeed goes hand in hand with synapse formation, using epitope-preserving Magnified Analysis of Proteome (eMAP) to visualize individual synapses on each SST bouton. We found that before eye opening, many boutons are present without resident inhibitory synapses, and the number of synapses per bouton increases across development. These eMAP results indicate that early in development, boutons may be structurally present without their full complement of synaptic proteins, and that there is then a steady developmental increase in both bouton density and synapse number per bouton. Our results show that in contrast to the developmental trajectory of excitatory circuitry, which follows a deep to shallow progression and goes through an exuberant growth phase followed by pruning, inhibitory innervation emerges concurrently across layers and progresses steadily without subsequent pruning. Further, unlike excitatory circuit development, inhibitory SST innervation and synapse formation appear independent of visual experience. These findings suggest that inhibitory innervation follows fundamentally different rules than excitatory innervation during development.

Disclosures: J.R. Boivin: None. **B. Schmerl:** None. **K. Burnell:** None. **C. Lee:** None. **J. Lee:** None. **E. Nedivi:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.026/LBA25

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Midwestern University Start Up Funding
Midwestern University Biomedical Sciences

Title: Maternal Diet-induced Obesity Alters the Offspring Neuromuscular Synapse

Authors: J. HUNTER, K. DINOVO, ***I. MARTINEZ-PENA Y VALENZUELA**;
Midwestern Univ., Downers Grove, IL

Abstract: INTRODUCTION Maternal obesity is a growing public health concern and poses significant health risks to offspring later in life. The perinatal period is a vulnerable stage in the nervous system's development because neuronal connections are extensively refined and may be influenced by the intrauterine environment during fetal programming. Several studies have found that feeding female mice with obesogenic diets is associated with offspring's central nervous system impairment. However, little is known about how maternal high-fat diet (HFD) affects the stability of peripheral synapses during development, specifically, the neuromuscular junction (NMJ), a vital synapse. In this study, we investigate the role of maternal HFD on the structure and function of the offspring's NMJ. **METHODS** We used Non-Swiss Albino mice (CF1), from postnatal day 0 (P0) to P21. We used females fed with an HFD during pregnancy and lactation. We used a battery of behavioral tests to evaluate whether maternal HFD affects postnatal motor function. To analyze the effect of maternal HFD on the NMJ postsynaptic structure, we used fluorescent labeling techniques to assess the distribution, density, and dynamics of acetylcholine receptors (nAChRs) at various postnatal ages. To investigate the effect of maternal HFD on the NMJ presynaptic components, we analyzed the motor neuron and the Schwann cell. We visualized offspring muscles in both upright and confocal microscopes. We performed transmission electron microscopy to visualize subcellular structures in postnatal muscles. **RESULTS** In the motor skills tests, we found that neonatal mice exposed to HFD performed significantly worse than their age-matched SD pups at any postnatal day tested (from P2 to P13). Perinatal exposure to an HFD suggests behavioral disturbances in the offspring such as increased limb clasping behaviors, higher muscle weakness, lower motor coordination, and lower trunk control than the SD group. Furthermore, maternal HFD affects the distribution, density, and dynamics of nAChRs in the postsynaptic apparatus, and affects the innervation of the NMJs. Analysis of the electron micrographs of skeletal muscle from the HFD group revealed a higher number of intramyocellular lipid droplets compared to the SD group, and the HFD group showed disrupted peri-droplet mitochondria in the first and second postnatal week. **CONCLUSIONS** These results suggest that perinatal exposure to an HFD correlates to motor deficits in the

offspring and that developmental milestones may be delayed in pups exposed to maternal HFD. Maternal HFD affects both presynaptic and postsynaptic components of the offspring NMJs.

Disclosures: J. Hunter: None. **K. DiNovo:** None. **I. Martinez-Pena y Valenzuela:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.027/Web Only

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: FRGS/1/2021/SKK0/UITM/02/5

Title: Attenuation of Syn I and PSD-95 Protein Levels in Prenatal BPA-induced Attention and Working Memory Impairment of Prefrontal Cortex Adolescent Male Sprague Dawley rats

Authors: N. SALEHHUDDIN, A. HUSIN, ***R. SIRAN**;
Universiti Teknologi MARA, Sungai Buloh, Malaysia

Abstract: Introduction: Bisphenol A (BPA) is an environmental xenoestrogen compound associated with attention and memory impairments. According to previous studies, BPA exposure during gestation and lactation impacted neurodevelopment more than other stages, as this phase is considered a critical brain developmental window with high synaptic plasticity. **Methods:** This study investigates the effects of prenatal BPA exposure on the synaptic markers (synapsin I and PSD-95) level in the prefrontal cortex of male adult Sprague Dawley and the neurobehavioral outcomes. The pregnant rats were given a daily oral dose of 5 mg/kg of BPA with 0.1% Tween 80 (n=3), starting from pregnancy day 1 until 21. The control group was treated the same, except the daily oral dose was 0.1% Tween 80 (n=3). The mothers were observed daily until the spontaneous delivery. The male foetuses (n=4) were identified and assessed with neurobehavioral tests to evaluate the attention and working memory function when reaching adolescent age, postnatal day 40 (PND40). Then, the male rats were sacrificed to collect the prefrontal cortex of the brain. The expression of synaptic markers, synapsin I (Syn I) and Postsynaptic Density-95 (PSD-95) were determined by ELISA. **Results:** The findings showed that prenatal BPA exposure at 5 mg/kg/day significantly reduces the level of Syn I and PSD-95 in the prefrontal cortex of the male SD rats at PND40. Consequently, the rats manifested attention and working memory impairments when reaching PND40. **Conclusion:** The findings suggested that prenatal BPA exposure reduced the Syn I and PSD-95 levels in male rats' prefrontal cortex, leading to attention and working memory deficits when reaching adolescence.

Disclosures: N. Salehhuddin: None. **A. Husin:** None. **R. Siran:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.028/LBA26

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant NS123710
NIH Grant NS115543
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NIH Grant DC014701
Paul and Lilah Newton Brain Science Award
Simons Center for the Social Brain Equipment Grant
Brain Research Foundation Seed Grant
Human Frontier Science Program long-term fellowship LT000479/2016-L

Title: Devatlas: a reporter system for mapping of circuit maturation in the developing brain

Authors: *J. XUE[1], A. BRAWNER[3], J. K. LIWANG[4], J. THOMPSON[3], T. D. YELHEKAR[2], H.-J. PI[5], K. T. NEWMASTER[6], Q. QIU[7], Y. KIM[8], Y. LIN[2];
[1]UTSW Med. Ctr., DALLAS, TX; [2]UTSW Med. Ctr., Dallas, TX; [3]Upstate Med. Univ., Syracuse, NY; [4]Neural & Behavioral Sci., Penn State Col. of Med., Hershey, PA; [5]The Pennsylvania State Univ., Hershey, PA; [6]Pennstate Col. of Med., Hershey, PA; [7]Stowers Inst. Med., Kansas City, MO; [8]Neural and Behavioral Sci., Penn State Univ., Hershey, PA

Abstract: Brain development is a highly dynamic and asynchronous, marked by the sequential maturation of functional circuits across the brain. This process is highly influenced by neuronal activity. However, the timing and mechanisms driving circuit maturation remain elusive due to an inability to identify and map neuronal populations as they mature. Importantly, while impaired circuit maturation is often the leading cause in many neurodevelopmental disorders (NDDs), it is still challenging to pinpoint when and where circuit maturation is affected by the genetic and environmental factors in NDDs. To address these challenges, we have created a reporter system, DevATLAS (Developmental Activation Timing-based Longitudinal Acquisition System), which is based on the activation of an immediate early gene (IEG), *Npas4*, to capture neurons undergoing activity-dependent circuit maturation. Npas4 is known to be selectively and robustly induced by neuronal activity and functionally involved in establishing circuit E/I balance, a critical step during activity-dependent circuit maturation. Neurons are permanently labeled by tdTomato when they are activated to express Npas4 for the first time during early development to initiate activity-dependent circuit maturation. Using an established whole-brain imaging and analysis pipeline, we have constructed the first longitudinal, spatiotemporal map of whole-brain circuit maturation during development. Furthermore, DevATLAS can be used to uncover mechanisms that drive circuit maturation *in* vivo. We have identified a cellular mechanism by which early experiences accelerate the development of hippocampus-dependent learning by amassing synaptically mature granule cells in the dentate gyrus. Additionally,

convergent molecular pathways driving synaptic maturation in multiple circuits *in vivo* have been identified, facilitated by DevATLAS. Most importantly, DevATLAS proves to be a powerful high-throughput to pinpoint when and where circuit maturation is disrupted in mouse models of NDDs. Finally, we have established a web-based open resource to share our existing and future whole-brain imaging datasets with the neuroscience community freely. In summary, DevATLAS will have a wide impact on our understanding of *in vivo* circuit maturation during early brain development, by (1) providing a systematic blueprint of whole-brain circuit development, a much-needed resource for the neuroscience research community; (2) facilitating the identification of fundamental mechanisms underlying *in vivo* circuit maturation; and (3) accelerating the discovery of disease etiologies of many neurological disorders such as NDDs.

Disclosures: J. Xue: None. **A. Brawner:** None. **J.K. Liwang:** None. **J. Thompson:** None. **T.D. Yelhekar:** None. **H. Pi:** None. **K.T. Newmaster:** None. **Q. Qiu:** None. **Y. Kim:** None. **Y. Lin:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.029/LBA27

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: 1K01MH131895-01A1

Title: Serotonin Signaling During Development: Impact on Response to Threat Across Species

Authors: *G. ZANNI;
Columbia Univ., New york, NY

Abstract: Fear is the emotion that is elicited when danger or threat are perceived or recognized. Maladaptive fear is common in anxiety disorders. Fear responses are orchestrated by the activation of stimulus-specific neural circuits that converge in the periaqueductal gray (PAG). A risk factor for increased fear is increased 5-HT in early life, for example due to SSRIs use in pregnancy. In rodent postnatal day 2 to 11 (P2-11) fluoxetine causes enduring changes in 5-HT function and increased anxiety. Yet, it remains unknown if changes in developmental 5-HT signaling alters adult 5HT PAG circuit function to increase innate fear. We adopted a cross-species approach to show how increased developmental 5HT signaling impacts innate fear behavior and underlying neural circuits including the PAG. We adopted a cross-species approach: 1) we used chemogenetic (Pet1Cre::Hm3d) or pharmacologic (fluoxetine, 10mg/kg) to increase 5-HT signaling during P2-11 in mice, 2) we used in utero SSRIs exposed or unexposed individuals from the ABCD study, and 3) we used fiber photometry (FP) to measure 5-HT (iSeroSnFR) input onto GABAergic (JRGeco1a) output in VgatCre mice injected with fluoxetine

or saline during P2-11. We investigated fMRI imaging and innate fear responses during predator odor exposure in mice and BOLD response to fearful compared to neutral faces as well as CBLC scores in humans. Using projection-specific excitatory and inhibitory optogenetics (Pet1Cre::Ai32 or Ai39) we explored the necessity of adult dlPAG input that impacts innate fear responses in mice. Using FP we established a direct relationship of 5-HT in controlling GABA signaling during fear responses. In mice, increased developmental 5-HT signaling exacerbated innate fear responses and activation of fear brain regions (i.e., amygdala and PAG). Human adolescents exposed to SSRIs in utero showed hyper activation of fear brain structures (i.e., amygdala, thalamus) and exhibited higher anxiety symptoms than unexposed adolescents. In adult mice 5-HT in dlPAG is pivotal for disinhibiting innate fear responses via increased GABA signaling. Increased 5HT levels, i.e. SSRI, in early life enhances innate fear responses and fear brain circuit activation that are conserved across species. Understanding the modulation of PAG by 5-HT will provide insight into pathophysiology and etiology of anxiety disorders.

Disclosures: G. Zanni: None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.030/LBA28

Topic: A.07. Developmental Disorders

Support: NIH Grant K01NS107723

Title: Delayed neurodevelopmental milestones in conditional Itgb3 KO mice

Authors: A. R. KALINOWSKI[1], C. J. DENZLER[1], E. C. VINSON[1], K. A. JEWELER[1], N. G. RUSAK[1], *G. VIDAL[2];
[1]Biol., [2]James Madison Univ., Harrisonburg, VA

Abstract: Integrin β3 (Itgb3) mutations are associated with autism spectrum disorder. Itgb3 is required in forebrain excitatory neurons and astrocytes for normal social and grooming behaviors in adult mice. Recent evidence from our lab shows that postnatal Itgb3 expression is highest in cortical layer 5 and that it is developmentally regulated. Specifically, layer 5 Itgb3 expression is strongest in the motor and somatosensory cortex between P0-P21, peaking around P7-P14. The early developmental regulation of Itgb3 in the motor and somatosensory cortex led us to hypothesize that Itgb3 is required for the normal development of early somatomotor behaviors. We tested conditional Itgb3 KO mice (floxed Itgb3 line crossed with the Emx1-Cre driver line) and control mice (floxed Itgb3 line) every day from P1-P21, utilizing a battery of sensorimotor and other behavioral tests. Both mouse lines were confirmed to have the same C57BL6/J genetic background via SNP-based genetic monitoring assays. Experimenters were blinded to the

genotype of the mice. Individual mice within litters were identified by microtattoo. Behaviors were quantified and analyzed via statistical testing that accounted for litter-to-litter variations. Almost all behaviors tested were validated in controls, and the onset of most sensorimotor behaviors occurred between P7-P15. Conditional Itgb3 KO were highly delayed in the onset of somatomotor behaviors such as body and air righting (~4 d delay), cliff avoidance and vibrissa-induced forelimb placing (~2 d delay), and whisking (~1 d delay). Although the onset of forelimb grasping was similar between the two groups (~P10), within a week, control mice were able to maintain their grip for approximately 6 times longer than conditional Itgb3 KO mice. The weight of both groups was similar in the first two weeks of postnatal life, but at P16-P21, conditional Itgb3 KO mice were ~15% heavier than control mice. Other developmental milestones, such as eye opening and auditory startle reflex, were not delayed in conditional Itgb3 KO. We conclude that forebrain Itgb3 is required for the normal development of early somatomotor behaviors.

Disclosures: A.R. Kalinowski: None. **C.J. Denzler:** None. **E.C. Vinson:** None. **K.A. Jeweler:** None. **N.G. Rusak:** None. **G. Vidal:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.031/LBA29

Topic: A.07. Developmental Disorders

Support: Southern Methodist University
UT Southwestern Medical Center

Title: Effective Connectivity in Episodic Memory Networks

Authors: *S. ZAFARMANDI ARDABILI[1], C. E. DAVILA[1], B. C. LEGA[2];
[1]Southern Methodist Univ., Dallas, TX; [2]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX

Abstract: Episodic memory networks involve interactions between the hippocampus regions. This study employed Dynamic Causal Modeling (DCM) using intracranial EEG (iEEG) data acquired during episodic encoding to examine the directed influences within hippocampal networks. We focus on effective connectivity estimates between the left anterior hippocampus (LAH) and the left posterior hippocampus (LPH) during successful vs unsuccessful encoding events. Using DCM, we explored how connectivity patterns between these hippocampal regions are modulated during memory encoding and further predict success. DCM for induced responses was investigated, revealing significant cross and intra-frequency directed coupling (effective connectivity). We also report which coupled frequencies are modulated by successful vs unsuccessful encoding. Bayesian inversion techniques enabled the inference of model parameters

and the comparison of different hypotheses regarding connectivity patterns. These insights into hippocampal connectivity provide a deeper understanding of the neural mechanisms underlying successful memory encoding using a novel application of DCM to intracranial EEG data.
Keywords: Intracranial EEG, Dynamic Causal Modeling, Episodic Memory, Hippocampus, Induced Responses

Disclosures: S. Zafarmandi Ardabili: None. **C.E. Davila:** None. **B.C. Lega:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.032/LBA30

Topic: A.07. Developmental Disorders

Support: Simons Foundation Autism Research Initiative (Pilot Award)

Title: Sensory sensitivity differences across sexes in autistic adults with sleep disturbances

Authors: *I. CULLEN[1], M. BUCAN[2], E. S. BRODKIN[3];
[1]Neurosci. Grad. Group, [2]Dept. of Genet., Univ. of Pennsylvania, Philadelphia, PA; [3]Psychiatry, Univ. of PA Sch. of Med., Philadelphia, PA

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication, as well as restricted, repetitive patterns of behaviors and interests. (5th ed.; DSM–5; American Psychiatric Association, 2013) Moreover, autistic individuals commonly suffer from hypersensitivity or hyposensitivity to sensory stimuli – a diagnostic criterion of ASD -- as well as various types of sleep disturbances. (Ben-Sasson et al. 2019, Weissenkampen et al. 2024) Sex differences in sensory sensitivities (female vs. male assigned at birth) have been understudied. In a sample of 252 autistic adults (94 male, 158 female), many of whom had various sleep difficulties, we assessed sensory hypersensitivity and hyposensitivity using the Glasgow Sensory Questionnaire (GSQ), a 42-question survey evaluating valence of 7 different sensory domains. (Robertson and Simmons, 2013) Through analysis of GSQ scores using two-sample t-tests, we found that females reported higher levels of sensory sensitivities than males (F: 78.5 ± 24.9, M: 62.5± 27.9, $p < 0.001$, t-value: 4.70) and reported more sensitivities in all domains than males (auditory, visual, gustation, olfaction, vestibular, and tactile). These results highlight another understudied sex difference in ASD behavioral phenotypes. In future studies, we will study underlying mechanisms of this sex difference and test for relationships between sensory sensitivities and sleep / wake / activity disturbances.

Disclosures: I. Cullen: None. **M. Bucan:** None. **E.S. Brodkin:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.033/LBA31

Topic: A.07. Developmental Disorders

Support: ZonMW, MKMD project 114024186

Title: Differential regulation of the mTOR pathway across genetic and environmental animal models of Autism Spectrum Disorder: a meta-analysis

Authors: *C. M. DRION, A. ABROMEIT, C. LEMAOULT, M. J. H. KAS;
Neurobio., Groningen Inst. for Evolutionary Life Sciences, Univ. of Groningen, Groningen, Netherlands

Abstract: Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental disorder of which the etiology is unknown. ASD is thought to result from altered brain development caused by genetic and/or environmental factors. As such, many different factors have been identified and consequently studied in a variety of genetic and environmental animal models. Recently, the mammalian target of rapamycin (mTOR) pathway has been implicated in synaptic remodeling, a process strongly associated with ASD. To investigate whether differentially regulated mTOR signaling is a shared mechanism in this heterogeneous neurodevelopmental disorder, we performed a systematic review and meta-analysis of 156 studies that investigated this pathway in a large variety of genetic and/or environmental animal models for ASD. Using a random-effects model we found that, compared to controls, expression of several mTOR pathway-related proteins was consistently increased or decreased across ASD models. Using subgroup analyses, we further specified the results and found that expression of other mTOR pathway-related proteins varied depending on species, sex, age, or brain region. Our results support involvement of mTOR pathway-related proteins in ASD, but also demonstrate a high degree of variability in mTOR regulation across animal models. These findings contribute to our understanding of common mechanisms in ASD development that will require further investigation.

Disclosures: C.M. Drion: None. **A. Abromeit:** None. **C. LeMaoult:** None. **M.J.H. Kas:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.034/LBA32

Topic: A.07. Developmental Disorders

Title: Opposite fine disorganization of the neocortex associated with Down syndrome and autism spectrum disorder

Authors: *S. HU[1], B. LI[1], S. LI[1], J. MA[1], X. LYU[2], S.-H. SHI[1];
[1]Tsinghua Univ., Beijing, China; [2]Nankai Univ., Tianjing, China

Abstract: Down syndrome (DS) and autism spectrum disorder (ASD) are two common neurodevelopmental disorders with some similarities as well as characteristic differences in symptoms. While abnormal neocortical development and organization have been implicated in DS and ASD, the exact nature and origin of the defects remain largely elusive. Here we show that opposite dysregulation of the fine structural and functional organization of neocortical excitatory neurons are associated with these two disorders. In *Ts65Dn* mice, a commonly used DS model, clonally related excitatory neurons originated from the same radial glial progenitor (RGP) become laterally compact with an elevated synaptic connectivity. In contrast, in three well-characterized mouse models of unrelated ASD high-risk genes, including *Chd8*, *Fmr1*, and *Dyrk1a*, clonally related excitatory neurons originated from individual RGPs become laterally dispersed with a reduced synaptic connectivity. Interestingly, in concordance with these defects, the expression of *clustered protocadherins* (*cPcdhs*) is oppositely affected in DS and ASD models, restoration of which rescues the defects. Together, these results suggest that exquisite organization of neocortical excitatory neurons is a crucial converging point of neurodevelopmental disorders.

Disclosures: S. Hu: None. **B. Li:** None. **S. Li:** None. **J. Ma:** None. **X. Lyu:** None. **S. Shi:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.035/LBA33

Topic: A.07. Developmental Disorders

Title: Modeling brain overgrowth in autism using patient-derived induced pluripotent stem cells

Authors: *S. CHEN[1], I. CHEN[2], S. CHETTY[3];
[1]Ctr. for Regenerative Med., Massachusetts Gen. Hosp., Boston, MA; [2]Harvard Col., Yorba Linda, CA; [3]Psychiatry, Massachusetts Gen. Hospital/Harvard Med. Sch., Boston, MA

Abstract: Autism spectrum disorder (ASD) affects approximately 1 in every 36 children in the United States and can influence social interaction and daily functioning. Within autism's broad range of symptoms, disproportionate megalencephaly—a condition characterized by abnormal brain overgrowth—is a commonly cited characteristic of autism and has been shown to be

associated with increased intellectual disability and cognitive impairment in autistic individuals. Clinically, disproportionate megalencephaly often serves as an early indicator of ASD, highlighting the critical need to understand the underlying mechanisms of brain overgrowth to develop targeted interventions. However, few studies have been conducted to elucidate the cellular mechanisms underlying disproportionate megalencephaly, likely due to challenges in accessing developing human brain tissue. Our work uses human induced pluripotent stem cells (iPSCs) to generate neural progenitor cells (NPCs) from individuals with autism who exhibit disproportionate megalencephaly (ASD-DM), individuals with autism who have normal brain size (ASD-N), and neurotypical individuals with normal brain size as the control group (TD-N) to investigate the mechanisms contributing to disproportionate megalencephaly. Our results indicate increased cell viability and reduced apoptosis in ASD-DM NPCs compared to ASD-N and TD-N NPCs, prompting further investigation into cellular pathways associated with cell survival and apoptosis. The findings in this study underscore the promising potential of iPSC research in advancing our understanding of DM in autistic individuals and shed light on potential therapeutic targets.

Disclosures: S. Chen: None. **I. Chen:** None. **S. Chetty:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.036/LBA34

Topic: A.07. Developmental Disorders

Support: Swiss National Science Foundation project 205320_188910/1
ERC Advanced Grant 694829 neuroXscales

Title: Studying the interplay between network activity and connectivity in ASD mouse models

Authors: *T. GÄNSWEIN[1], H. ULUSAN[2,1], F. CARDES[1], A. HIERLEMANN[1], S. S. KUMAR[1], J. BARTRAM[1];
[1]Swiss Federal Inst. of Technol. Zurich, Basel, Switzerland; [2]Middle East Tech. Univ., Ankara, Turkey

Abstract: Neurodevelopmental disorders often cause severe lifelong impairments and can lead to a reduced lifespan. With a prevalence of about 1%, autism spectrum disorder (ASD) is one of the most common neurodevelopmental disorders. It has previously been shown that the excitation/inhibition (E/I) balance in cortical networks may be altered in autism. In addition, dysregulations in the assembly of the earliest circuits of the cerebral cortex have been reported in ASD model systems. However, ASD is a complex polygenic disorder so that it remains challenging to find convergent abnormalities. Further complicating investigations of ASD's

pathophysiological mechanisms is the fact that circuit structure and activity influence each other during development and should be investigated in parallel. Therefore, we studied the interplay between network activity and circuit topology during development to identify shared circuit abnormalities in multiple mouse models of ASD. We used acute brain slices of common ASD mouse models at different neurodevelopmental time points. In such ex-vivo preparations, the local to mid-range neuronal circuitry is mostly preserved. This preservation allows for a comprehensive investigation of network activity and mesoscale circuitry with high-precision tools, such as high-density microelectrode arrays (HD-MEAs).
To assess alterations in network spiking dynamics, circuit topology, and E/I balance, we combined patch clamping with our in-house-developed state-of-the-art HD-MEA. The complementary-metal-oxide-semiconductor (CMOS)-based HD-MEA features 59'760 electrodes and 2'048 channels for simultaneous read-out at 20 kHz sampling rate. The large sensing area of 4.5 x 2.4 mm^2 and the small electrode pitch of 13.5 µm enables a detailed study of neuronal networks across scales - from subcellular compartments through single cells to full networks. The combination with patch-clamp recordings, which allow for detection of sub-threshold events, enables a comprehensive network characterization.
Here, we introduce our new platform and report first results characterizing (i) the development of connectivity motifs within S1, focusing on cortical layer 5, (ii) cell-type specific changes in spiking dynamics across all cortical layers, and (iii) the evolution of the E/I ratio during development in multiple autism mouse models in comparison to wild-type animals.

Disclosures: T. Gänswein: None. **H. Ulusan:** None. **F. Cardes:** None. **A. Hierlemann:** None. **S.S. Kumar:** None. **J. Bartram:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.037/LBA35

Topic: A.07. Developmental Disorders

Support: NS116828-04

Title: Elevated perinatal interleukin6 modifies hippocampal physiology and produces cognitive and behavioral changes.

Authors: *R. HOUBEIKA[1], S. ALI[1], N. MARCELINO[1], F. JANCZUR VELLOSO[2], O. BOZDAGI GUNAL[3], S. W. LEVISON[2];
[2]Pharmacology, Physiol. & Neurosci., [3]Psychiatry, [1]Rutgers Univ., Newark, NJ

Abstract: Elevated perinatal interleukin-6 modifies hippocampal physiology and produces cognitive and behavioral changes. *Rouba Y. Houbeika, Sidra Ali, Naia Marcelino, Fernando*

Janczur Velloso, Ozlem Gunal and Steven W. Levison
Autism (ASD) spectrum disorder is a neurodevelopmental disorder characterized by difficulties in communicating and interacting with other people. Successful social interaction requires acquiring information and reconstructing those memories to behave accordingly, highlighting the importance of the hippocampus. Epidemiologic studies have demonstrated that maternal infections stimulate the production of interleukin-6 (IL-6), which can cross the placenta and fetal blood brain barrier to alter brain development. To model the effects of increased levels of IL-6 at the end of the second trimester of human development which hasn't been studied before we have injected male and female mice with PBS or with 75 ng IL-6 twice daily, from post-natal day 3 until post-natal day 6. Our published studies have shown that this IL-6 treatment paradigm alters patterns of ultrasonic vocalizations, reduces social interactions and increases self-grooming in male mice. Since many individuals with ASD have intellectual disabilities, the goal of this study was to evaluate performance on a memory test and evaluate the changes in hippocampal physiology. Here we show that contrary to our expectations, when tested at 5 weeks of age, the IL-6 treated males spent more time exploring the object at the new location as compared to the controls while the IL-6 treated females spent the same amount of time exploring the object at the old and novel location. Correspondingly, after inducing LTP in the CA1 with 2 sets of 4 trains of tetanic stimulation (100 Hz) with 20s intervals male mice showed a 30.4 % increase in the acquisition of LTP induction. The male mice also showed larger depression of the field EPSP by 26.04 % after LTD was induced by 900 pulses at 1 Hz for 15 min. By contrast, female mice showed no significant changes in LTP. While total apical dendritic spines were reduced by 25 % in the CA1 region of the IL-6 treated males there was a 69% increase in thin spines. Western blot analysis of the NMDA and AMPA receptor subunits, GluN2A, GluA1 and GluA2 at 6 weeks of age showed no changes in hippocampal homogenates of IL-6 vs control mice. Taken altogether, these data show that a short increase in circulating IL-6 is sufficient to causing lasting changes in hippocampal synaptic plasticity and function. Supported by NS116828-04 awarded to SWL.

Disclosures: R. Houbeika: None. **S. Ali:** None. **N. Marcelino:** None. **F. Janczur Velloso:** None. **O. Bozdagi Gunal:** None. **S.W. Levison:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.038/LBA36

Topic: A.07. Developmental Disorders

Support: Simons Foundation Autism Research Initiative Grant
Israel Science Foundation Grant 1150/20

Title: Simons Sleep Project: An open science resource for accelerating scalable digital phenotyping research in autism and other psychiatric conditions

Authors: *I. DINSTEIN[1], **M. HACOHEN**[2];
[1]Psychology, Ben Gurion Univ., Beer Sheva, Israel; [2]Cognitive and Brain Sci., Ben-Gurion Univ., Beer Sheva, Israel

Abstract: Sleep disturbances and their underlying neurophysiology are of high interest in autism research given their reported high prevalence and deleterious clinical impact. Previous studies utilizing questionnaires, actigraphy, or polysomnography (PSG) have demonstrated large heterogeneity across autistic individuals who exhibit different sleep disturbances and alterations in neurophysiology. The goal of the SSP was to establish a comprehensive open science resource for studying mechanisms of sleep in autism using multiple digital phenotyping techniques and for assessing their relationship with parent reported core autism symptoms and common co-occurring symptoms (e.g., sensory problems and irritability).
Data was collected from 99 families recruited from the Simons Powering Autism Research (SPARK) cohort. Each family had an autistic child and non-autistic sibling, both 10-17 years old, who had previously completed whole exome sequencing that did not reveal any clinical findings (i.e., idiopathic autism). Parents completed multiple questionnaires and received a Dreem3 EEG headband (Beacon Biosignals Inc.), EmbracePlus smartwatch (Empatica Inc.), and Withings Sleep mat (Withings Inc.). Simultaneous data was collected from all devices along with a sleep diary for 2-3 weeks from each child. In total, over 3200 nights of data were recorded. Raw EEG and actigraphy data from the Dreem3 were harmonized with raw actigraphy, electrodermal activity, skin temperature, and photoplethysmography data from the EmbracePlus, and pressure data from the Withings mattress sensor.
We describe the data repository along with preliminary analyses of the EEG data that were processed using automated algorithms to identify participants with at least five nights of high-quality sleep data that contained at least three hours of sleep per night. Sleep staging analyses with the POPS, YASA, and Dreem algorithms revealed that, contrary to previous reports from single night PSG studies, there were no significant differences across autism and sibling groups in percentage of sleep in any sleep stage (N1, N2, N3, or REM), apart from the YASA algorithm, where REM sleep was longer in the autism group ($t(170)=3.17$, $p=0.006$).
SSP data will be openly available from the Simons Foundation Autism Research Initiative (SFARI) starting October 2024 and offer an unprecedented opportunity for the research community to study sleep and other aspects of autism with objective digital phenotyping techniques.

Disclosures: I. Dinstein: None. **M. Hacohen:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.039/LBA37

Topic: A.07. Developmental Disorders

Support: SFARI Grant

Title: 27- & 40-hz auditory entrainment delay in children with autism spectrum disorder

Authors: *M. DARRELL[1], T. VANNEAU[2], D. CREGIN[2], T. LECAJ[2], J. J. FOXE[4], S. MOLHOLM[3];
[1]Neurosci., [2]Albert Einstein Col. of Med., Bronx, NY; [3]Pediatrics, Albert Einstein Col. of Med., New York, NY; [4]Neurosci., Univ. of Rochester, Bronx, NY

Abstract: Motivation Alterations in auditory and speech processing have been widely described in autism spectrum disorder (ASD), which may contribute to social and attentional impairments. In this work, we utilized brief auditory stimuli at a repetitive frequency to evoke an auditory steady state response (ASSR), to evaluate the neurophysiology of auditory entrainment in ASD compared to typically developing (TD) children. ASSR in ASD has largely been studied using MEG and yielded conflicting results. Here, we evaluated ASSR in a relatively large sample of ASD and unaffected siblings using more accessible EEG techniques. This work aims to provide insight into the mechanisms behind altered auditory processing and entrainment in ASD. **Methods** Participants were 8-12 years, with full-IQ >80. Mean age and percent females (F) by group are as follows: ASD (n=46): 10.8 years, 16% F; TD (n=26): 10.2 years, 46% F; unaffected siblings (n=23): 10.5 years, 59% F. Stimuli were 500 ms trains of binaural clicks at either 27 or 40 Hz. EEG recordings were collected from 70 active BioSemi channels. Dependent measures included: ASSR power at stimulation frequency during the steady-state response (from 200-500 ms); the broad-band response leading into the steady-state response (BB); and PLA, the difference in phase angle from the expected angle (TD mean). Group differences in BB and ASSR power were assessed by ANOVA; PLA was assessed by Watson-Williams test. **Results** ASD demonstrated a delayed BB response compared to TD in the early negative window (180-250 ms) for 40-Hz (R-side only) and 27-Hz stimulation, which negatively correlated with IQ. Spectro-temporal analysis suggested this reflected low frequency neural activity, as group differences in BB amplitude held true after low-pass filtering to include only delta and theta bands (0.5-8 Hz). There were no significant group differences in ASSR power or PLA. Siblings did not significantly differ from either ASD or TD in any measure. **Discussion** Group differences (ASD vs. TD) in ASSR response predominate in the negative slope of the BB, which may reflect reduced efficiency in the initial auditory cortical entrainment to an external stimulus. We identified the BB delay in ASD for both 27/40 Hz stimulation, suggesting the deficit is likely not specific to rate coding, as previously theorized, but may reflect a broader impairment in instantiation of steady state entrainment. Failure to identify differences in BB amplitude between siblings and either ASD/TD group is consistent with an intermediate response, which would suggest that the BB response is endophenotypic, although this requires further investigation.

Disclosures: M. Darrell: None. **T. Vanneau:** None. **D. Cregin:** None. **T. Lecaj:** None. **J.J. Foxe:** None. **S. Molholm:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.040/LBA38

Topic: A.07. Developmental Disorders

Support: FRAXA Fellowship
NIH Grant 5R01MH106490

Title: Human FMR1 isoform-specific regulation of translation and behavior in novel humanized mouse models

Authors: *K. E. REYNOLDS[1], M. MAJID[2], K. KEUM[1], S. SANDOVAL[3], X. ZHAO[3], Y. YANG[1];
[1]Dept. of Neurosci., [2]Tufts Univ. Sch. of Med., Boston, MA; [3]Neurosci., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Encoded by the FMR1 gene, the FMRP protein is one of the most crucial RNA-binding proteins in the developing brain as it regulates the translation of hundreds of mRNAs, many associated with synaptic function. FMRP contains three main RNA-binding motifs: K-homology (KH) domains KH1 and KH2, and an RGG box. Human FMR1 (hFMR1) mRNA undergoes alternative splicing to produce over 20 unique isoforms. It is unknown whether these isoforms have distinct functions; however, alternative splicing of exons associated with RNA-binding regions suggests possible differences in RNA-binding affinity and/or specificity between isoforms. The largest alternatively spliced region directly linked to an FMRP RNA-binding domain is exon 12, which encodes the KH2 domain variable loop. Exon 12 is absent in nearly ¼ of known protein-coding isoforms of hFMR1. Given the KH2 domain's role in translational regulation, we hypothesize that the presence vs. absence of exon 12 leads to differential FMRP-RNA binding interactions, resulting in distinct roles for exon 12-containing and exon 12-lacking isoforms. To investigate this, we first compared the ratio of exon 12-containing FMR1 isoforms to total FMR1 isoforms throughout development in control organoids and human cortex (age 0-45+, both sexes) using exon 12-specific qPCR primers. Exon 12-containing isoforms were most abundant during development and were considerably reduced with age. We then utilized known exon 12-containing hFMR1 ISO13 and exon 12-lacking hFMR1 ISO17 sequences to generate two new humanized, inducible mouse lines that allow us to further investigate the role of exon 12 in the developing brain. Our novel hFMR1-ISO13^{flox} and hFMR1-ISO17^{flox} mice differ solely in their inclusion vs. exclusion of exon 12, allowing the function of the KH2 variable loop region to be directly studied. Both lines were crossed with B-actin-Cre^{+} mice to induce Cre-mediated recombination during embryogenesis. Human FMRP was detectable in the cortex of both hFMR1-ISO13$^{f/y}$/B-actin-Cre^{+} and hFMR1-ISO17$^{f/y}$/B-actin-Cre^{+} mice as early as E15, while endogenous mouse FMRP was absent. Both isoforms normalized the *Fmr1* KO hyperactivity phenotype in male ~P40 mice; however, only ISO13 rescued *Fmr1* KO deficits in fear-

conditioned memory acquisition at ~P80, indicating that these isoforms may serve overlapping yet distinct roles during brain development and maturation. Further analysis of RNA binding specificity will determine whether the presence vs. absence of exon 12 allows FMRP to regulate a distinct population of RNAs. Importantly, these new tools will also enable the study of specific FMRP isoforms in a more human-relevant context.

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Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.041/LBA39

Topic: A.07. Developmental Disorders

Support: NIH NICHD INCLUDE R01HD104640-01A1

Title: Hypoglossal nucleus phenotypes of the juvenile Ts65Dn mouse model of Down syndrome

Authors: L. VUE, K. K. HANG, N. P. CONNOR, ***T. J. GLASS**;
Surgery, Univ. of Wisconsin Madison, Madison, WI

Abstract: Down syndrome (DS) is a developmental disorder in which atypical tongue movement contributes to impairments of speech, breathing, feeding, and swallowing. Our previous work found that the Ts65Dn mouse model of DS at postnatal days of age 35-36 (p35-36) demonstrated significant behavioral deglutition phenotypes consistent with reduced efficiency in eating, coinciding with significant alterations in tongue muscle microanatomy. While loss of cholinergic neurons has been reported to occur in Ts65Dn, it is unknown whether cholinergic motor neurons that direct movement of the tongue muscles are impacted in Ts65Dn. Therefore, this study tested the hypothesis that the Ts65Dn mouse model of DS demonstrates significant biological differences of the cholinergic motor neurons of the hypoglossal nucleus at p35-36, relative to euploid sibling controls. Methods: Ts65Dn and euploid sibling controls (n =4-5 male and 5-6 female mice per group) were euthanized at p35-36 and brains were frozen on dry ice. Serial cross sections extending throughout the entirety of the hypoglossal nucleus were stained through immunofluorescence to permit identification of hypoglossal nucleus cholinergic motor neurons, expressing both neuronal nuclei (NeuN) and choline acetyltransferase (ChAT). A semi-automated image analysis protocol was created and used to quantify hypoglossal motor neurons in de-identified images of serial tissue sections. Dependent variables included motor neuron cell count (#) and density (# cells / mm^2). Data were analyzed by 2-way ANOVA to detect significant effects of sex and genotype, as well as significant interactions between sex and genotype. Results: Ts65Dn show significantly fewer hypoglossal motor neurons than euploid

sibling controls, as indicated through two different anatomical measures. Ts65Dn have fewer hypoglossal motor neurons than euploid siblings [$F(1,16)=9.22$, $p=.008$] as evaluated through total numbers of hypoglossal motor neurons present, and also have significantly reduced density of hypoglossal motor neurons [$F(1,16)=7.70$, $p=.014$] as determined by the number of motor neurons per mm^2 of hypoglossal nucleus. Conclusions: While expansion of this study is on-going, these early results suggest that significant phenotypes of the hypoglossal motor nucleus coincide with alterations of tongue muscle microanatomy and functional deglutition phenotypes in the Ts65Dn model of DS. The use of mouse models to clarify hypoglossal nucleus phenotypes associated with DS will guide future research to ensure that therapies targeting tongue movement disorders are as biologically informed for patients with DS as they are for the general population.

Disclosures: L. Vue: None. **K.K. Hang:** None. **N.P. Connor:** None. **T.J. Glass:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.042/LBA40

Topic: A.07. Developmental Disorders

Title: Characterizing neural rosette formation in a dorsal forebrain spheroid model of Down syndrome

Authors: *A. AYOUB[1,2], T. F. HAYDAR[3,2];
[1]Children's Natl. Hosp., Washington, DC; [2]Integrated Biomed. Sci., George Washington Univ. Sch. of Med. and Hlth. Sci., Washington, DC; [3]Children's Natl. Hosp., Washington, DC

Abstract: Down syndrome (DS) is characterized by microcephaly, altered cortical lamination and intellectual disability (ID). Early alterations in neural precursor cell (NPC) populations during corticogenesis may contribute to the neuroanatomical and cognitive impairments associated with ID. Data sets examining 3D culture models of trisomy 21 at differentiation day (D) 30 and later have demonstrated impaired NPC proliferation, reduced neurogenesis, and a concomitant decrease in organoid size. Clusters of NPCs within organoids form proliferative, morphogenic centers known as neural rosettes. Direct comprehensive characterization of neural rosette formation and expansion during early organoid development in DS has not been done. Here we present an exploratory analysis of these structures during very early development, <D30 in culture. We conducted three technical replicates to differentiate one isogenic line of induced pluripotent stem cells derived from a 25-year-old woman with DS into human cortical spheroids with dorsal forebrain characteristics. We performed high-resolution 3D imaging of entire cleared spheroids using a 2-photon laser-scanner and a combination of immunohistochemical markers to characterize the architectonic features, size, and cellular composition of neural rosettes. EdU proliferative assays and co-immunostaining were performed to characterize the cell cycle phase

duration and proliferation rate of NPCs within rosettes. We find that spheroid growth is consistent between genotypes until day 18, in which trisomic spheroids grow at a slower rate and display smaller size compared to isogenic euploid controls (n = 24 per genotype and timepoint). We have observed differences in the density, size and composition of each rosette between genotypes. Specifically, euploid spheroids have a greater density of medium- to large-sized rosettes, determined by luminal area. While trisomic spheroids have fewer and less coherent rosettes, indicating disordered development. We expect to find delayed cell cycle progression and impaired proliferation in trisomic spheroids, indicated by increased total cell-cycle length, prolonged s- to m-phase duration, and fewer mitotic figures. By characterizing differences in rosette formation and NPC dynamics in trisomic spheroids, we start to elucidate the cellular underpinnings of the neuroanatomical deficits occurring during early development in DS.

Disclosures: A. Ayoub: None. **T.F. Haydar:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.043/LBA41

Topic: A.07. Developmental Disorders

Support: NIAAA 5R01AA029114
Developmental Exposure Alcohol Research Center, Binghamton, NY

Title: Acute Ethanol Exposure Triggers Src Family Kinase Hyperactivity in Human Cerebral Organoids

Authors: *J. DOUPE[1,2], M. ANAM[2], B. HOWELL[2], E. C. OLSON[3];
[1]Upstate Med. Univ., Syracuse, NY; [2]Neurosci., [3]Neurosci. and Physiol., SUNY Upstate Med. Univ., Syracuse, NY

Abstract: Fetal alcohol syndrome (FAS) is a major cause of intellectual disability in humans and is characterized by disrupted brain development and postnatal cognitive impairments. The pathology of FAS is complex and includes disruptions of signaling pathways involved in neuronal proliferation, migration, differentiation, and apoptosis. However, it is unclear whether there are common biochemical mechanisms that initiate this diverse pathology. Prior work from our laboratory established that acute ethanol exposure in doses ranging from 100 to 400mg/dl causes a rapid (<15 minute) increase in tyrosine phosphorylation of multiple proteins, both in cultured mouse neurons and in the fetal mouse brain after maternal dosing (400mg/dl). Pharmacological intervention revealed that Src Family Kinase (SFK), likely Src itself, was critical for the hyperphosphorylation. Immunoprecipitation and phosphoantibody array data revealed phosphorylation targets in several critical neurodevelopmental signaling pathways

including the Reelin signaling pathway, involved in migration and dendritogenesis, the Erb2 pathway involved in neuronal proliferation and the EphA3 pathway involved in axonal outgrowth. This suggests that multiple cellular pathologies could be initiated by this SFK mediated hyperphosphorylation. To determine whether this SFK activation mechanisms could contribute to FAS we asked whether ethanol can trigger a similar response in human embryonic cortical neurons. Using cultured cerebral organoids, generated from human iPSCs (Kolf2.1/J), we find that 15 minute exposure to 400 mg/dl ethanol causes a ~2.5 fold increase in phosphotyrosine immunosignal in 50 DIV and older organoids. The highest response is observed in regions of the organoids enriched in Dcx+ and Tbr1+ immature neurons. The phosphorylation response is completely blocked with PP2, a selective inhibitor of SFKs but not with the inactive control compound PP3. These initial results suggest that human cortical neurons, like mouse cortical neurons, are vulnerable to ethanol induced SFK hyperactivation and likely, the consequent disruption of multiple developmentally important signaling pathways.

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Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.044/LBA42

Topic: A.07. Developmental Disorders

Title: Preclinical gene therapy trial for FRRS1L epileptic encephalopathy

Authors: *M. SHEIBANI[1], S. KASIRI[2], J. WU[2], J. SCHWENK[3], B. FAKLER[4], B. MINASSIAN[2];
[1]Pediatric Neurol., UT Southwestern Med. center, dallas, TX; [2]Pediatric Neurol., UT Southwestern Med. Ctr., Dallas, TX; [3]Inst. of Physiol., [4]Inst. of physiology, Univ. of Freiburg, Freiburg, Germany

Abstract: Gene therapy offers a unique therapeutic potential for treating rare genetic disorders, such as epileptic-dyskinetic encephalopathy related to Ferric Chelate Reductase 1 Like (FRRS1L), a severe pediatric neurodevelopmental disorder caused by homozygous mutations in the *FRRS1L* gene. The disease presents with intellectual and developmental delay, epilepsy, chorea and other progressive and debilitating motor impairments. There is currently no treatment available for this disease. *FRRS1L* is a key determinant in the biogenesis of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the brain, essential to their maturation and recruitment into synaptic membranes. In the absence of *FRRS1L*, AMPA receptors assembly line is compromised, causing impaired

excitatory neurotransmission in the central nervous system (CNS) and a range of other neurological deficits. To counter this, we developed a novel adeno-associated virus stereotype 9 (AAV9) vector utilizing a JeT promoter to drive the expression of human *FRRS1L* gene. This vector was administered via intrathecal injections at postnatal day 10-14 in low and high doses to *FRRS1L*-Knockout (KO) mice, which share multiple phenotypic traits with affected patients. Virus injected KO-mice were examined and compared with phosphate buffered saline (PBS) injected KO and Wild-type (WT) controls, assessing the safety and efficacy of this approach. Initial observations (N= 8-11 per group) showed that both doses are well tolerated, followed by promising levels of FRRS1L gene and protein detection in the CNS. Our ongoing preclinical trial further investigates possible functional restoration of AMPA receptors and subsequent neurological improvements through comprehensive biochemical and behavioral evaluations. Preliminary results indicate a dose-dependent increase of AMPA receptors on synaptic membranes as well as improvements in the treated KOs (N=7-9 per dose) compared to untreated ones, in multiple behavioral tests including rotarod, grip strength, and fear-conditioning. While studies are ongoing to confirm these findings and explore long-term outcomes, our results suggest the potential of gene replacement as a promising treatment for children suffering this severe epileptic encephalopathy.

Disclosures: M. Sheibani: None. **S. Kasiri:** None. **J. Wu:** None. **J. Schwenk:** None. **B. Fakler:** None. **B. Minassian:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.045/LBA43

Topic: A.07. Developmental Disorders

Support: R01AG075000/AG/NIA NIH

Title: Multidimensional Age-Related Associations of Locus Coeruleus with Attention Behavior: Insights from Structural and Functional MRI Data

Authors: *J. NEAL[1], S. KIM[4], I. KIM[5], B. KATZ[2], T.-H. LEE[3];
[1]Virginia Tech., Blacksburg, VA; [2]Human Develop., Virginia Tech., Averill Park, NY;
[3]Psychology, Virginia Tech., Blacksburg, VA; [4]Univ. of North Carolina, Chapel Hill, NC;
[5]Psychiatry and Behavioral Sci., Duke Med. Ctr., Durham, NC

Abstract: The Locus Coeruleus (LC) has been previously identified as pertaining to broad arousal in the nervous system, especially in terms of norepinephrine production. Various measures of LC integrity & activity have been associated with neurodegenerative disorders and

task performance in older adults, but has limited study in youth populations. 201 participants (62 children: 8-17yrs; 79 young adults: 18-30yrs; 60 adults: 33-54yrs) completed either the BAARS IV or the Vanderbilt Parental Rating scale, both commonly used to evaluate attentional behaviors for ADHD diagnosis. Participants also underwent MRI scans. For structural images, we estimated the neuromelanin contrast ratio (CNR) by manually selecting neuromelanin-intensive voxels at the LC location using T1-FSE images and LC volume size using T1-anatomical images. For functional images, we calculated functional signal variability (MSSD) by extracting individuals' resting-state BOLD signal of LC using a probability atlas, created by the majority vote process with individuals' T1-FSE images. One-way ANOVA analyses revealed a significant age-group difference for the left LC MSSD ($p = .037$), left and right CNR ($p < .001$), and total attention score ($p<.001$). In children, significant predictive effects were found for right LC MSSD ($p = .044$) and marginal effect of right LC volume ($p = .054$) on *total attention score*. For attention subscores, right LC-MSSD significantly predicted *inattentiveness* ($p = .044$), left LC volume predicted hyperactivity ($p = .040$), and right LC CNR significantly predicted *impulsivity* ($p = .009$). In young adults, there were marginal effects of right LC CNR ($p = .076$) and LC volume ($p = .056$) for total attention score, a significant effect of right LC volume ($p = .013$) for *inattentiveness*, significant effects of right LC CNR ($p = .024$), and marginal effects of left LC CNR ($\beta = .255$, $p = .057$) and right LC volume ($p = .091$) for *hyperactivity*. In adults, a marginal effect of right LC volume ($p = .067$) was found for *total attention score*, a significant effect of right LC volume ($p = .005$) for *inattentiveness*, and a significant effect of left LC volume ($p = .011$) for *impulsivity*. Significant age-related differences were observed across multiple dimensions of the LC, suggesting important aspects of neurodevelopment occurring there. In relation to behavior, BOLD signal variability, volume size, and CNR integrity of the right LC were found to exhibit significant relationships for the overall attention score and subscores. Findings of lateralized differences in the LC replicate previous findings, and together with the age-related differences suggest the utility of refined neurodevelopmental LC study.

Disclosures: J. Neal: None. **S. Kim:** None. **I. Kim:** None. **B. Katz:** None. **T. Lee:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.046/LBA44

Topic: A.07. Developmental Disorders

Title: Neuronal migration defect and neocortical heterotopia formation in mice with patient-specific mutation of Dync1h1

Authors: B. SHAFIT-ZAGARDO[1], R. F. STOUT, Jr.[2], ***R. RAMOS**[2];
[1]Albert Einstein Col. of Med., Bronx, NY; [2]New York Inst. of Technol. Col. of Osteo. Med., Old Westbury, NY

Abstract: In humans, mutations of DYNC1H1 result in diverse neurological presentations including intellectual disabilitie, brain malformation, cognitive delay, and motor deficits. Cytoplasmic dynein heavy chain (DYNC1H1) is a multi-subunit protein complex that provides motor force for movement of cargo on microtubules back to the soma. The aim of the study was to characterize the neuroanatomy of a mouse generated to superficially model a newly identified de novo heterozygous DYNC1H1 mutation present in a child with motor deficits, intellectual disability, and on the autism spectrum. After crossing with YFP reporter mice to label neocortical neurons, we show several indicators of neuronal migration defects in our model. First, in the dorsal neocortex, we observe focal heterotopia in layer I characterized by collections of neurons normally destined for all neocortical layers. Second, in the dorsal neocortex, we also observe a general increase in the number of neurons in layer I, which reflects a general smearing of layer II/III. Third, we observe that many YFP labeled neurons in layer I exhibit a loss of dendritic orientation and are frequently pointing straight down towards the white matter. Finally, in the lateral neocortex adjacent to the rhinal sulcus, we observe multiple heterotopia of neurons in layer I which produces a sawtooth cytoarchitecture. Dendritic bundles from deeper layer neurons are observed in between heterotopia. Our results are discussed in relation to other Dync1h1 mouse models and in the context of diverse mutations and clinical presentations seen in humans.

Disclosures: B. Shafit-Zagardo: None. **R.F. Stout:** None. **R. Ramos:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.047/LBA45

Topic: A.07. Developmental Disorders

Support: NIH/NIGMS P20GM139760

Title: Astrocyte morphology and metabolism in a mouse model of developmental stuttering

Authors: *N. GUARINO, D. CHUGANI, A. DUTTA, H. CHOW;
Univ. of Delaware, Newark, DE

Abstract: Developmental stuttering is a neurodevelopmental disorder with a strong genetic component. One of the most commonly occurring genes discovered was *GNPTAB*, which encodes a protein that helps traffic newly synthesized lysosomal hydrolase precursors. A transgenic mouse *Gnptab* E1179K model was created. These mice recapitulate atypical vocal behaviors including reduced frequency and increased pauses. Furthermore, these mice were found to have altered astrocytic morphology in the corpus callosum (CC) in a specific subset of GFAP positive astrocytes. The purpose of this study was to assess morphological mutant *Gnptab*

astrocytic changes in brain tissue and in culture; and to assess altered astrocytic energy metabolism. We performed immunofluorescence for GFAP on brain tissue slices taken from 8-week old wild-type (n=3) or mutant (n=3) male mice in CC, striatum, and hippocampus (control). Cortical astrocytes from p1-p3 wild-type (n=14) or mutant (n=9) pups were cultured to investigate morphology in culture using GFAP immunofluorescence, as well as metabolic changes using Seahorse analysis, and lactate and ATP assays (n=3/genotype). We find that in addition to the previously documented changes in CC ($p < 0.01$), the striatum also showed decreased GFAP staining area in mutant mice ($p < 0.01$). Mutant cortical astrocyte cultures show similar decreases in GFAP staining area as tissue. Furthermore, cultured astrocytes showed an altered metabolic phenotype compared to wild-types. Oxygen consumption rate was increased overall in mutant astrocytes ($p < 0.001$), as was basal mitochondrial O_2 consumption ($p< 0.01$), non-mitochondrial O_2 consumption ($p < 0.01$), proton leak ($p < 0.05$), and projected ATP production ($p < 0.05$). Extracellular acidification rate, a proxy for glycolysis, was also increased in mutant astrocytes ($p < 0.001$), indicating a higher metabolic profile in general. Lactate studies showed that there was no difference in intracellular lactate ($p > 0.05$); however, extracellular lactate was increased in mutant astrocytes ($p < 0.01$), confirming an increase in glycolysis. Lastly, intracellular ATP measurements taken from lysed cells show a reduced amount of ATP present in mutant astrocytes compared to wild-type ($p < 0.01$), which may denote higher ATP usage in the mutant cells. (All p values obtained using Student's t test). Together these data show that there are underlying metabolic alterations in mutant *Gnptab* astrocytes concomitant with morphological changes, that may represent compensational responses to altered lysosomal function or alternatively may offer druggable targets for interventions in developmental stuttering.

Disclosures: N. Guarino: None. **D. Chugani:** None. **A. Dutta:** None. **H. Chow:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.048/LBA46

Topic: A.07. Developmental Disorders

Support: NIH Grant OD021324
NIH Grant OD011104
NIH Grant OD010568
NIH Grant OD024282

Title: Agnathia-otocephaly complex in rhesus macaques

Authors: *E. J. VALLENDER[1,3], Y. TOUISSI[2], A. A. SAIED[3], K. J. VAIL[3], A. K. MYERS[3], L. A. DOYLE-MEYERS[3];

[1]Univ. of Mississippi Med. Ctr., JACKSON, MS; [2]Univ. of Mississippi Med. Ctr., Jackson, MS; [3]Tulane Natl. Primate Res. Ctr., Covington, LA

Abstract: Agnathia-otocephaly complex is a rare lethal congenital malformation characterized by mandibular hypoplasia and auricular malposition. It is caused by defects in neural crest cell migration that result in abnormalities in development derived from the first branchial arch. In more extreme cases, it results in other midline craniofacial and forebrain deficits. Recently, three rhesus macaques from a single breeding group presented with features consistent with agnathia-otocephaly complex. All animals displayed synotia, microstomia, agnathia, and aglossia/hypoglossia with one animal showing a more severe pathology with cyclopia and a proboscis. While the brain of one animal was grossly normal, another had marked hydrocephalus and lissencephaly, and the more severely affected animal had severe alobar holoprosencephaly. Whole genome sequencing from the animals identified a recessive mutation in the *TWSG1*, p.His197Arg, derived from separate half-avuncular matings. The mutation has only been observed in relatives of the affected individuals (minor allele frequency less than 0.05%) and shows perfect conservation across all available vertebrate reference genomes. While *TWSG1* knockout mice have previously been shown to develop a phenotype consistent with agnathia-otocephaly complex, mutations in this gene have not been previously associated with this malformation in humans or other primates. These stillbirths represent the first known instance of agnathia-otocephaly complex in nonhuman primates and extend the findings from knockout mice to a recessive missense mutation in the *TWSG1* gene.

Disclosures: E.J. Vallender: None. **Y. Touissi:** None. **A.A. Saied:** None. **K.J. Vail:** None. **A.K. Myers:** None. **L.A. Doyle-Meyers:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.049/LBA47

Topic: A.07. Developmental Disorders

Support: CURE Epilepsy Taking Flight Award
Taubman Institute Emerging Scholar Award
NIH NINDS K08 NS121464 to J.M.
Louis Bernstein Undergraduate Psychology Research Award to N.E.
NSF GRFP to K.S-C.

Title: Repeated early-life seizures lower seizure threshold and increase SUDEP rate in the Scn1a+/- mouse model of Dravet Syndrome.

Authors: *N. ELDROUBI[1], K. M. SANTIAGO COLON[2], J. BARDEN[1], J. DISLA[3], J. MATTIS[1];
[1]Neurol., [2]Pharmacol., [3]Univ. of Michigan, Ann Arbor, MI

Abstract: Rationale: Dravet Syndrome (DS) is a severe developmental and epileptic encephalopathy characterized by treatment-resistant epilepsy - including seizures triggered by fevers - developmental delay, autistic-like traits, and high rates of Sudden Unexpected Death in Epilepsy (SUDEP). DS is primarily caused by pathogenic variants in the SCN1A gene, which encodes the alpha subunit of the Nav1.1 voltage-gated sodium channel. Preclinical and clinical data suggest that phenotypic variability may arise from the seizure burden of individual subjects. This study examines the effects of early-life hyperthermia-induced seizures on subsequent SUDEP rates in the well-characterized *Scn1a*+/- mouse model of DS.
Methods: All experiments were performed on mice on a 50:50 C57BL/6J:129S6 mixed background. We used hyperthermia to evoke seizures in *Scn1a*+/- mice at postnatal days (P)19, P21, and P23, monitoring seizure threshold and SUDEP rates. Controls included (1) wild-type littermate mice exposed to equivalent hyperthermia, and both (2) *Scn1a*+/- and (3) wild-type mice that were not heated. Given anecdotal reports of heterogeneity in phenotypic severity across different Cre lines, we additionally compared *Scn1a*+/- mice with the F1 progeny from a cross of *Scn1a*+/- mice with double-homozygous Chat-Cre knock-in / tdTomato reporter mice (i.e., triple-transgenic *Scn1a*+/-;Chat-Cre;tdT mice) on the same 50:50 background.
Results: We found a significant decrease in seizure threshold across repeated heating sessions (p=0.001; mixed-effects analysis). Survival curve comparisons (Gehan-Breslow-Wilcoxon test) found that *Scn1a*+/- mice subjected to repeated seizures (n=37) had significantly higher mortality rates than heated WT mice (n=23), non-heated *Scn1a*+/- mice (n=92), and non-heated WT mice (n=155). Triple-transgenic *Scn1a*+/-;Chat-Cre;tdT mice had significantly higher mortality rates than *Scn1a*+/- mice in the non-heated condition (p=0.03; n=27 vs 59), with a more extreme divergence emerging in the heated condition (p=0.004; n=10 vs 27). No significant differences were seen between female and male mice. Seizure thresholds were not predictive of SUDEP rate in any group.
Conclusions: Overall, our results show that early-life seizures worsen phenotype in *Scn1a*+/- mice, as measured by both lowered seizure threshold and higher SUDEP rate. Furthermore, the triple-transgenic mice had higher mortality rates, although both lines were maintained on the same 50:50 C57BL/6J:129S6 background. These significant group differences in short-term SUDEP rates will enable future studies regarding the SUDEP mechanism.

Disclosures: N. Eldroubi: None. **K.M. Santiago Colon:** None. **J. Barden:** None. **J. Disla:** None. **J. Mattis:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.050/LBA48

Topic: A.07. Developmental Disorders

Support: DoD award USAMRAA WS00538832

Title: Effect of 5-HT_{2C} receptor antagonist on locomotor and sociability in Tuberous Sclerosis Complex model mouse

Authors: S. SAGOSHI[1], A. YOSHII[2], S. T. ALFORD[3];
[1]Anat. and Cell Biol., Univ. of Illinois Chicago, Chicago, IL; [2]Anat. & Cell Biol., Univ. of Illinois, Chicago, IL; [3]Anat. and Cell Biol., Univ. of Illinois At Chicago Dept. of Anat. and Cell Biol., Chicago, IL

Abstract: Tuberous sclerosis complex (TSC)-associated neuropsychiatric disorders (TAND) are prominent and include autistic behaviors. TSC gene mutations cause mTOR overactivation directly and via phosphatase and the tensin homolog (PTEN). mTOR suppression by rapamycin (RP) is proposed to correct TSC pathophysiology however its block is neither specific nor fully effective. Preliminary data indicates *Tsc* gene suppression caused cortical hyper-excitability, and Tsc1-/- neurons have recurrent dendritic Ca^{2+} bursts from internal stores. From a microarray screen, the 5-HT_{2C} receptor (5-HT_{2C}R) is the only G protein coupled receptor that explains pan-dendritic Ca^{2+} bursts via IP3Rs and the synaptic protein that directly interacts with PTEN. 5-HT_{2C}R inhibitors in PTEN KO mice showed 5-HT synthesis hotspots at epileptogenic tubers. Therefore, we examined if SB242084, one of the 5-HT_{2C}R inhibitors, improves sociability and locomotor function of the TSC mouse model. We used a cerebellar-specific Tsc1 gene knockout (TSC1-L7KO) mouse and their wild-type (WT) littermates. All mice were treated daily by ip injection with SB242084 (SB: 10mg/kg) or RP (3mg/kg) started at PND5. We conducted 3-chamber test to examine socialability. Vehicle treated WT mice showed a preference to social and novel stimuli mice - these are sociability indicators. Vehicle treated Tsc1-L7KO mice did not exhibit this behavioral phenotype whereas SB or RP treated Tsc1-L7KO mice prefer novel stimuli - similar to WT. Mice were also tested on rotarod to evaluate motor function. The latency to fall in vehicle-treated Tsc1-L7KO mice was shorter than in WT, and SB did not improve this. On the other hand, RP treated Tsc1-L7KO mice did not show any difference from WT. Furthermore, vehicle or SB treated TSC1-L7KO showed slightly lower body weight than WT while both RP treated WT and TSC1-L7KO mice were significantly smaller than other two groups while there was no difference between genotypes. Thus, SB may have mild effects on motor function while it may rescue sociability in TSC mouse models. However, RP decreased bodyweight in both WT and TSC1-L7KO and SB did not affect it. Taken together, SB can be a candidate for pharmacological therapy on neurological symptoms of TAND with milder side effects than RP.

Disclosures: S. Sagoshi: None. **A. Yoshii:** None. **S.T. Alford:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

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Program #/Poster #: LBA001.051/LBA49

Topic: A.07. Developmental Disorders

Support: McCormick Summer Research Grant to DL at University of Puget Sound
Murdock Charitable Trust Bridge Grant 24923 to SR

Title: Putative neural mechanism underlying morphological changes induced by a 5-alpha reductase inhibitor in the pond snail

Authors: *D. LANGEVIN, M. LOPEZ, S. RAMAKRISHNAN;
Neurosci., Univ. of Puget Sound, Tacoma, WA

Abstract: Despite the presence of steroidal androgen genes in gastropod mollusks, their direct effects remain unclear. Dutasteride (DUT), a dual inhibitor of 5α-reductase types I and II, blocks the conversion of testosterone to 5α-dihydrotestosterone, and is used therapeutically to mitigate conditions linked to high testosterone levels in humans. Prior observations in the pond snail Biomphalaria found that developmental DUT exposure altered the shape of the snail shell from helical to a unique banana shape. Studies in our lab in the closely related gastropod Helisoma duryi successfully replicated this phenotype, and further show that DUT exposure during a critical window of 48-72 hours post-deposition consistently induced the banana-shaped shell morphology (92.3%), with significant differences in hatch rates between continuously DUT-treated and control groups (14.3% in DUT, 95.2% in control).
Changes in shell morphology could be explained by altered expression of developmental markers or altered movement due to differential neural inputs in the developing embryo. To determine alterations in developmental markers, we treated snail embryos to varying concentrations of dorsomorphin, an inhibitor of decapentaplegic (dpp) shown to affect shell coiling. Only at the lowest dose, was the banana-shaped coiling observed. We found that immunohistochemical stains for catecholaminergic neurons (dopamine, serotonin) in the developing embryo show differential expression between controls (n = 72) and DUT treated (n = 76) animals, especially in the areas of the foot. We suggest a putative neural mechanism for DUT action on shape changes in the snail embryo - with modified catecholaminergic innervation leading to altered movement, resulting in the morphological change.

Disclosures: D. Langevin: None. **M. Lopez:** None. **S. Ramakrishnan:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.052/LBA50

Topic: A.07. Developmental Disorders

Support: Spanish Research Agency PID2021-122723OA-I00 to MDMS
Spanish Research Agency RYC2022-035648-I

Title: Dynamic regulation of ectodomain shedding: insights into neurodevelopmental conditions

Authors: M. LOBETE, T. SALINAS, S. SOCAS, S. IZQUIERDO-BERMEJO, M. OSET-GASQUE, ***M. D. MARTIN-DE-SAAVEDRA**;
Biochem. and Mol. Biol., Complutense Univ., Madrid, Spain

Abstract: Numerous transmembrane proteins undergo a proteolytic processing referred to as ectodomain shedding (ES). ES is an irreversible process where a protease cleaves a membrane protein close to the membrane region, releasing its extracellular fragment. The group of shed proteins present in a sample is called the sheddome. Interestingly, proteins in the sheddome may exert paracrine and/or autocrine functions, modulating cell-to-cell communication and neuronal activity. ES plays an important role in various pathological processes, ranging from cancer to brain disorders. An emblematic example of ES dysregulation within the brain is the amyloidogenic regulation of APP, leading to the accumulation of Aβ in Alzheimer's disease. Additionally, ES has been implicated in neurodevelopmental conditions (NDCs), prion disease, and epilepsy, among others. Despite growing interest, the molecular and functional composition of the brain sheddome, its regulation, and role in brain conditions remain poorly understood. By combining bioinformatics analysis with mass spectrometry of the brain sheddome, we identified various proteins relevant for neurodevelopment and NDCs. The sheddome is enriched in proteins modulating cell adhesion, axon guidance and synapse organization. It also includes proteins linked to vocalization and social behavior, which are core characteristics affected in autism. We found the sheddome composition is modulated by age, sex and neuroplasticity. At 15 days of age, we observed an enrichment in shed ICAM5 in females and an enrichment of LRP1 in males. In contrast, EPHA4 and EPHB2 were enriched only in 3-month-old males. Fifteen-day-old mice exposed to whisker trimming, which hinders neuroplasticity, showed differential modulation of ES of LDLR and FLRT3, known autism risk factors. In conclusion, ES is emerging as a critical and dynamic process in brain function modulation. The enrichment of the sheddome in proteins associated with NDCs, which regulate essential processes like cell adhesion, neuronal projections, and synapses, underscores the potential impact of ES on these conditions. Further investigation of ES could result in new diagnostic and treatment options for brain conditions, including NDCs.

Disclosures: M. Lobete: None. **T. Salinas:** None. **S. Socas:** None. **S. Izquierdo-Bermejo:** None. **M. Oset-Gasque:** None. **M.D. Martin-de-Saavedra:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.053/LBA51

Topic: A.07. Developmental Disorders

Title: Tracing GABAergic developmental perturbations in psychiatric disorders: a focus on the Klf13 gene

Authors: *M. JARIWALA, E. SANTELLO, X. XIN, N. VASISTHA, K. KHODOSEVICH; Univ. of Copenhagen, Biotech Res. and Innovation Ctr. (BRIC), Copenhagen, Denmark

Abstract: Background: Developmental psychiatric disorders, such as schizophrenia, autism and ADHD, are among the most common human disorders. Characterized by a chronic impact and an early onset, they lead to a significant socio-economic burden and a decrease up to 10-20 years in the patients' life expectancy. **Focal point:** It is now known that 15q13.3 microdeletion in humans is strongly associated with a range of psychiatric manifestations and Klf13 has been shown to play a pivotal role in neuronal precursors and differentiation. Even though the genetic contribution in the genesis of these disorders is clear, it remains difficult to identify the risk genes involved and how they affects development, underlying mechanisms and lead to formation of impaired brain circuits. **Approach:** We have performed experiments to identify how strongly Klf13 mutation impairs brain development and functioning. We chose to understand the maturational dynamics of putative GABAergic neurons in order to see discrepancies in the neuronal composition by performing single nucleus RNA sequencing in ganglionic eminence of embryonic (E) day 13.5 Klf13-/- double knockout mice. **Results:** We successfully detected previously annotated GABAergic clusters. In addition, medial ganglionic eminence (MGE) neuroblasts Lhx8 and MGE immature Mki67 expressing cells showed an increase in knockout samples in the cluster-based compositional shift. On the contrary, caudal ganglionic eminence (CGE) immature Ptprz1-expressing cells showed a negative compositional shift. Performing cluster-free analysis we found aggregated genes that were upregulated (Ash1l and Cacnb2) and downregulated (Med13l and Prpf4b), especially in CGE Ptprz1- expressing cells and MGE Lhx8-expressing cells clusters. These results were consistent with reduced c-Fos expression registered at the adolescent stage in S1BF and PFC of postnatal (P) 40 Klf13+/- mice, as Fos/Jun is tightly regulated by the Klf13 protein domain. **Perspectives:** This information is quite novel as functional role of Klf13 knockout was never studied in the context of neurodevelopmental disorders. Future studies will focus on translational approaches and mainly on identification of other binding targets. Such deep insight to understand the large scale effects of brain circuit perturbations will help to understand clinical role of Klf13 and potential drug targets.

Disclosures: M. Jariwala: None. **E. Santello:** None. **X. Xin:** None. **N. Vasistha:** None. **K. Khodosevich:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.054/LBA52

Topic: A.07. Developmental Disorders

Support: FONDECYT Grant 1211384
FONDECYT Grant 1240604
FONDECYT Grant 11220601
FONDEF Grant ID19I10116
ANID-Basal Grant #FB210024 (IMPACT)

Title: Prenatal stress and neurodevelopment: small extracellular vesicles as novel modulators of mother-to-fetus stress communication

Authors: M. SANCHEZ-RUBIO, S. OYARCE-PEZOA, D. CORVALAN-BUSTOS, V. VIDAL-CAVIEDES, M. MÉNDEZ-RUETTE, A. LUARTE, U. WYNEKEN, ***L. BATIZ**; Ctr. for Biomed. Res. and Innovation (CiiB), Univ. de los Andes, Santiago de Chile, Chile

Abstract: Maternal psychological distress during pregnancy can negatively impact fetal neurodevelopment, resulting in long-lasting consequences for the offspring. These effects show a sex bias. The mechanisms whereby prenatal stress induces functional and/or structural changes in the placental-fetal unit remain poorly understood. Maternal circulating small extracellular vesicles (sEVs), particularly astrocyte-derived sEVs (ADEVs), are good candidates to act as "stress signals" in mother-to-fetus communication. Using a rat chronic mild prenatal stress model based on repetitive (2 hours/day during 10 days) restraint, we first assessed stress-induced changes in circulating maternal sEVs and tested whether they could target placental/fetal tissues. Interestingly, our stress protocol induced anhedonic-like behavior in pregnant dams and led to intrauterine growth restriction (IUGR), particularly in male fetuses and placentas. The concentration and cargo of maternal circulating sEVs changed under stress conditions. Specifically, we found a significant increase in the concentration of blood-borne sEVs under stress conditions. Furthermore, maternal circulating sEVs were characterized by increased astrocyte-derived proteins and reduced neuron-derived protein markers. To study the effect of repetitive restraint stress on the biodistribution of maternal circulating sEVs in the fetoplacental unit, sEVs from pregnant dams exposed to stress or control protocol were labeled with DiR fluorescent die and injected into pregnant females previously exposed to control or stress protocol. Remarkably, maternal circulating sEVs target placental/fetal tissues, and under stress conditions, fetal tissues are more receptive to sEVs. To assess the role of ADEVs in mother-to-fetus communication under stress conditions, we obtained ADEVs from cultured control and corticosterone-treated (stress-like conditions) astrocytes and intravenously injected them in control and stressed pregnant dams at different time points. Curiously, repetitive treatment with ADEVs was sufficient to prevent/rescue stress-induced IUGR and fetal premature neuronal differentiation. Our findings provide evidence that maternal circulating sEVs can act as modulators of mother-to-fetus stress communication. We propose a novel maternal brain-to-fetal brain communication pathway in which maternal ADEVs can modulate the impact of maternal stress on fetal growth and neurogenesis. Further studies are needed to identify placental/fetal

cellular targets of maternal ADEVs and characterize their contribution to sex-specific stress-induced placental and fetal changes.

Disclosures: M. Sanchez-Rubio: None. **S. Oyarce-Pezoa:** None. **D. Corvalan-Bustos:** None. **V. Vidal-Caviedes:** None. **M. Méndez-Ruette:** None. **A. Luarte:** None. **U. Wyneken:** None. **L. Batiz:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.055/Web Only

Topic: A.08. Development of Neural Systems

Support: HORIZON-WIDERA-2021-(GEMSTONE PROJECT GRANT 101078981)

Title: Aberrant development of PV positive interneurons in the somatosensory cortex of rat modelof genetic absence epilepsy

Authors: *F. ONAT[1,2], N. CARCAK YILMAZ[3,2], E. ERDEVE[4], M. S. ANDERSSON[5], D. KIRIK[5];
[1]Med. Pharmacol., Acibadem Univ. Fac. of Med., Istanbul, Turkey; [2]Dept. of Neurosci., Acibadem Mehmet Ali Aydinlar Univ. Inst. of Hlth. Sci., Istanbul, Turkey; [3]Dept. of Pharmacol., Istanbul Univ. Fac. of Pharm., Istanbul, Turkey; [4]Dept. of Pharmacology,, Istanbul Univ. Hlth. Sci. Inst., Istanbul, Turkey; [5]Dept. of Exptl. Med. Sci., Lund Univ., Lund, Sweden

Abstract: The principal neuroanatomical networks mediating absence seizures are thought to involve reciprocal interactions between the thalamus and cortex. In this context, maturation of inhibitory networks and their relationship to the pathophysiology of spike-and-wave discharges (SWDs) remains poorly understood. This study investigates the neurodevelopmental profile of parvalbumin positive (PV+) GABAergic interneurons in rat model of genetic absence epilepsy (GAERS), focusing on their role in providing feed-forward inhibition via thalamocortical projections in the somatosensory cortex (S1). We analysed these interneurons in both superficial/granular (L2/4) and infragranular (L5/6) layers, key regions implicated in the paroxysmal oscillations' characteristic of SWDs during cortical maturation. We examined three critical developmental stages: postnatal day 14 (P14), shortly before tonic $GABA_A$ inhibition increases in the ventrobasal (VB) thalamus, P21 when immature SWDs start to occur and P90, after at least two months of continuous and mature SWDs observed. Comparative analyses were performed with the primary motor cortex (M1), hippocampus and the striatum. Wistar rats served as controls to elucidate the specific alterations in GAERS. We observed a significant reduction in the number of PV+ interneurons at P14 GAERS compared to P14 Wistar rats. This was followed by an overcompensation by P21, resulting in a significantly larger number of PV+

cells located in the L2/4 of the S1 cortex of P21 GAERS when compared to Wistar rats ($p<0,001$). No significant change in PV + cell count was detected between P21 and P90 GAERS. We conclude that the aberrant development of PV+ interneurons in the S1 region of GAERS, characterized by an initial deficit followed by an overcompensation in P21 and is maintained through P90 may contribute to the pathophysiology of SWDs. This abnormal maturation of inhibitory networks likely disrupts the balance of excitation and inhibition, leading to the emergence and persistence of absence seizures. This finding may have implications for understanding the neurodevelopmental dynamics of inhibitory circuitry in epilepsy.

Disclosures: **F. Onat:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); HORIZON-WIDERA-2021-ACCESS-03: GEMSTONE Project (101078981). **N. Carcak Yilmaz:** None. **E. Erdeve:** None. **M.S. Andersson:** None. **D. Kirik:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.056/LBA53

Topic: A.08. Development of Neural Systems

Support: Alzheimer's Association Grant SAGA23-1066776

Title: Sex-specific effects on mouse offspring development trajectories are diminished by maternal Alzheimer’s disease genotype

Authors: M. CARY[1], S. PARPALA[2], E. RAMIREZ[2], S. KUJAWA[2], A. HAWKEY[2], *A. V. PRAKAPENKA[2];
[1]Chicago Col. of Osteo. Med., [2]Col. of Grad. Studies, Midwestern Univ., Downers Grove, IL

Abstract: Alzheimer’s disease (AD) is a neurodegenerative disease accompanied by progressive decline in learning and memory and increased incidence of anxiety and depression. AD neuropathology is linked to high inflammatory states, disrupted metabolism, and mitochondrial dysfunction. Maternal health during and after pregnancy can substantially impact the development of offspring, which has been observed in human and animal models. Of note, prior findings show that pups born to triple transgenic AD (3xTg-AD) dams exhibit reduced hippocampal volume and markers of neurogenesis compared to pups born to wildtype (WT) dams as early as postnatal day (PND) 7. In the present study, we aimed to investigate the impact of pup sex and maternal AD genotype on offspring development trajectories. Two-months-old WT (C57BL/6J) and 3xTg-AD female mice (n = 8 / genotype) were bred with adult WT males so that pregnancy and birth occur prior to the expected onset of AD neuropathology. All females were pregnant and birthed one litter, although pups from two WT litters died after birth.

Offspring development trajectories were evaluated on PND 5-8 using the righting reflex test and on PND 10-13 using the negative geotaxis test. On the righting reflex test, there were no main effects of sex for latency to right by pups born to dams of either genotype. On the negative geotaxis test, there was a main effect of sex for latency to turn upright by pups born to WT dams [$F_{(1,8)} = 7.89$, $p < 0.05$], with shorter latency exhibited by males compared to females, but not by pups born to AD dams. Additionally, in male pups there was a main effect of genotype for latency to turn upright [$F_{(1,8)} = 5.54$, $p < 0.05$], with shorter latency exhibited by male pups born to WT dams compared to AD dams. Altogether, our findings indicate that offspring development trajectories are sex-specific and weakened by the maternal AD genotype. These effects were likely driven by maternal AD genotype modulation of male pup development and not female pup development, with similar offspring development trajectories seen in female pups born to WT dams and all pups born to AD dams. Future research is warranted to understand the mechanisms contributing to the maternal AD genotype effects on male offspring developmental trajectories.

Disclosures: M. Cary: None. **S. Parpala:** None. **E. Ramirez:** None. **S. Kujawa:** None. **A. Hawkey:** None. **A.V. Prakapenka:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.057/LBA54

Topic: A.08. Development of Neural Systems

Support: R01MH118827
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UM1MH130991
P51 OD011106
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SFARI pilot grant
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GM140935

Title: Multimodal analyses reveal genes driving electrophysiological maturation of neurons in the primate prefrontal cortex

Authors: Y. GAO[1], Q. DONG[2], K. HANTHANAN ARACHCHILAGE[5], R. RISGAARD[6], M. SYED[3], J. SHENG[3], S. LIU[3], S. KNAACK[3], J. E. LEVINE[7], D. WANG[8], Q. CHANG[9], *X. ZHAO[4], A. M. SOUSA[10];
[1]Waisman Ctr. and Neurosci., Univ. of Wisconsin-Madison, Madison, WI, WI; [2]Waisman Ctr., [4]Neurosci. and Waisman Ctr., [3]Univ. of Wisconsin-Madison, Madison, WI; [5]Dept. of Biostatistics and Med. Informatics, Waisman Ctr. – Univ. of Wisconsin Madison, Madison, WI; [6]Neurosci., Univ. of Wisconsin, Madison, WI; [7]Wisconsin Natl. Primate Res. Ctr., Madison, WI; [8]Biostatistics and Med. Informatics, Univ. of Wisconsin - Madison, Madison, WI; [9]Genet & Neurol, Univ. Wisconsin-Madison, Madison, WI; [10]Neurosci., UW-Madison, Madison, WI

Abstract: The prefrontal cortex (PFC) is critical for myriad high-cognitive functions and is associated with several neuropsychiatric disorders. Here, using Patch-seq and single-nucleus multiomic analyses, we identified genes and regulatory networks governing the maturation of distinct neuronal populations in the PFC of rhesus macaque. We discovered that specific electrophysiological properties exhibited distinct maturational kinetics and identified key genes underlying these properties. We unveiled that RAPGEF4 is important for the maturation of resting membrane potential and inward sodium current in both macaque and human. We demonstrated that knockdown of *CHD8*, a high-confidence autism risk gene, in human and macaque organotypic slices led to impaired maturation, via downregulation of key genes, including *RAPGEF4*. Restoring the expression of *RAPGEF4* rescued the proper electrophysiological maturation of CHD8-deficient neurons. Our study revealed regulators of neuronal maturation during a critical period of PFC development in primates and implicated such regulators in molecular processes underlying autism.

Disclosures: Y. Gao: None. **Q. Dong:** None. **K. Hanthanan Arachchilage:** None. **R. Risgaard:** None. **M. Syed:** None. **J. Sheng:** None. **S. Liu:** None. **S. Knaack:** None. **J.E. Levine:** None. **D. Wang:** None. **Q. Chang:** None. **X. Zhao:** None. **A.M. Sousa:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.058/LBA55

Topic: A.09. Adolescent Development

Title: Unravelling the mechanism of increased impulsivity in adulthood caused by adolescent cocaine exposure

Authors: *D. TRAN[1], R. BATISTA-BRITO[1], L. L. SJULSON[2];
[1]Dominick P. Purpura Dept. of Neurosci., [2]Dominick P. Purpura Dept. of Neuroscience, Psychiatry, Albert Einstein Col. of Med., Bronx, NY

Abstract: *Cocaine use disorder (CUD)* is a large and growing public health problem for which new treatments are urgently needed. The majority of CUD patients begin misusing stimulants during adolescence, before brain development is complete. This is believed to cause long-lasting neural changes leading to cognitive impairment, impulsivity, and increased propensity for CUD in adulthood. This is supported by work in animal models showing that *adolescent cocaine exposure (ACE)* permanently affects late-maturing parts of the brain, such as the *medial prefrontal cortex (mPFC)*, leading to impulsive behavioral phenotypes in adulthood. However, the nature of the changes in mPFC is not well understood, nor are the mechanisms by which they influence behavior. Theta synchrony between mPFC and mediodorsal thamalus is believed to be a mechanism for top-down inhibitory control over behavior; consistent with this, adult patients with substance use disorders exhibit reduced frontal theta, and interventions that strengthen frontal theta reduce impulsive behaviors. *We hypothesize that ACE prevents the maturation of mPFC theta synchrony at the local circuit level, and these circuit-level changes in mPFC theta impair the ability of mPFC to synchronize with the mediodorsal thamalus at the systems level to suppress impulsivity at the behavioral level.* To test this hypothesis, we trained control and ACE adult mice to perform a head-fixed Go/No-Go task, followed by reversal learning. Although both groups can perform the task successfully, control animals learn the task faster than ACE animals, and their performance improves more rapidly following a reversal of the cue contingencies. ACE-induced deficits in behavioral performance are not due to reduced responding in Go trials, but instead to an impaired ability to withhold responding in No-Go trials. Using Neuropixel 2.0 chronic implants, we recorded simultaneously from mPFC, hippocampus, and mediodorsal thalamus during performance of the Go/No-Go task and reversal learning. Consistent with our hypothesis that ACE prevents the maturation of mPFC theta synchrony, our data suggests that single unit activities within mPFC of ACE animals exhibit an immature extracellular spiking phenotype and lower phase-locking to local theta oscillation. We also found that ACE adults exhibit changes in mPFC theta synchrony with other recorded brain structures. Our next step is determining whether specific changes in frontolimbic theta synchrony are associated with specific behavioral changes. This study will guide future work aiming to develop treatments to ameliorate ACE-induced mPFC dysfunction for the treatment of CUD.

Disclosures: D. Tran: None. **R. Batista-Brito:** None. **L.L. Sjulson:** None.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.059/LBA56

Topic: A.09. Adolescent Development

Support: National Institute of Neurological Disorders and Stroke

Title: Changes in Cellular Composition during Gyrification of the Ferret Visual Cortex

Authors: *S. DOHERTY[1], C. D. KROENKE[2], K. E. GARCIA[3], A. P. BARNES[4], C. HILTS[5]; [1]IUSM, OSHU, zionsville, IN; [2]Adv Imaging Resch Ctr., Oregon Hlth. Sci. Univ., Portland, OR; [3]Indiana Univ. Sch. of Med., Evansville, IN; [4]Knight Cardiovasc. Inst., [5]OHSU, Portland, OR

Abstract: In gyrencephalic species the processes behind cortical folding are not well understood. One explanation is that the expansion of the cortex occurs rapidly, leading to mechanical buckling (folding) of the cortical surface. Neurogenesis is largely completed prior to folding, so this expansion is thought to result from growth of the cortical neuropil. In this study, we sought to quantify cortical expansion, in terms of neuropil and cell size, in the postnatal ferret visual cortex (V1) over the period of active folding at the occipitotemporal sulcus (OTS). We hypothesized that cortical expansion can be primarily attributed to the growth of neuropil over the period of folding, and that growth would be reduced in animals bilaterally enucleated at postnatal day 7 (BEP7). Ferret occipital cortices were extracted, fixed, sectioned at postnatal days 20, 26, 32, or 38 in control (n=11) and BEP7 (n=6) animals, stained with fluoro-Nissl, and imaged with confocal microscopy. ImageJ/FIJI software measured cortical length (V1 surface area), thickness, cell body size, and neuropil volume fraction (NVF) at the superficial, middle, and deepest thirds of the cortex for the lateral gyrus (LG), OTS, and splenial gyrus (SG). Cortical length increased approximately 5%/day for control animals. This rate was diminished by half for the enucleates. Cortical thickness at the OTS increased at a rate similar to length for controls but was higher in enucleates (7.6%/day). NVF increased with age in all regions and layers across the cortex and were most prominent in the superficial 1/3 of the cortex: the NVF increased from 29%, 30%, and 32% at the control LG, OTS, and SG at P20, to 74%, 72%, and 73%, respectively, at P38. Neuropil composition and change in cell area were comparable between gyri and sulci and was consistent between enucleated and control groups. Overall, estimated growth due to change in cell body size and neuropil accounted for approximately 2/3 of cortical growth. We found a substantial increase in cortical volume over time that could be largely attributed to the changes in neuropil composition. Additional change in cortical volume may be impacted by gliogenesis, which should be explored in future work. The OTS did not form in BEP7 animals; however, they still exhibited cortical growth and similar increases in cell area and neuropil composition over time. The primary differences noted between groups were in cortical length and thickness, indicating the cell changes that reduce expansion/folding are subtle. The lack of cortical folding – expected to diminish stresses experienced by the cortex – may be impacting the shape/distribution of the cells as opposed to the cell area or neuropil volume.

Disclosures: S. Doherty: None. **C.D. Kroenke:** A. Employment/Salary (full or part-time):; OHSU. 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.; National Institute of Neurological Disorders and Stroke. **K.E. Garcia:** A. Employment/Salary (full or part-time):; IUSM. 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.; National Institute of Neurological Disorders and Stroke. **A.P. Barnes:** A. Employment/Salary (full or part-time):; OHSU. 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.; National Institute of Neurological Disorders and Stroke. **C. Hilts:** A. Employment/Salary (full or part-time):; OHSU. 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.; National Institute of Neurological Disorders and Stroke.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.060/LBA57

Topic: A.09. Adolescent Development

Support: BGSU CURS 2023

Title: Effects of adolescent cardiovascular and resistance exercise on anxiety, spatial memory and brain development in male and female rats

Authors: *A. GONZALEZ[1], V. R. RIESGO[2], J. WILLING[2];
[2]Psychology, [1]Bowling Green State Univ., Bowling Green, OH

Abstract: While the vast majority of the literature on the positive effects of exercise on the brain have focused on cardiovascular models, less is known about the effects of resistance training. In modern fitness culture, a large population of those who exercise regularly utilize weight training (resistance/hypertrophy model of exercise), making resistance training particularly relevant to study. Previous studies have demonstrated that cardiovascular exercise positively affects performance in learning and memory tasks and increases hippocampal neurogenesis in rat subjects, but less is understood about the effects of resistance exercise on the brain. In addition, previous studies only have utilized male rats, ignoring potential sex effects. Lastly, less is known regarding the effects of exercise during the adolescence period on later adult behavior and neuroanatomy. In the present study, adolescent (P21-P74) male and female Long Evans rats were divided into three conditions: cardiovascular training (CT) rats with access to a running wheel, resistance training (RT) rats that engage in a ladder climbing protocol, and a control (sedentary) group of standardly housed rats. After reaching adulthood, subjects were tested for anxiety-like behavior and spatial memory using the elevated plus maze, open field, and an object placement task. We found CT female rats ran significantly longer than male rats on average. RT females hit puberty significantly later than females in CT and sedentary conditions. Rats in both CT and RT trended towards taking less time to enter the center and spent more time in the center than sedentary in the open field task. In the novel object placement task RT rats spent significantly less time with the old and new objects across both trails, and this effect was stronger in females.

These findings suggest that different forms of exercise during the adolescent period can yield sex-specific effects on pubertal onset, anxiety/exploratory behavior and/or spatial memory.

Disclosures: A. Gonzalez: None. **V.R. Riesgo:** None. **J. Willing:** None.

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Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.061/LBA58

Topic: A.09. Adolescent Development

Support: NIMH Grant MH121518

Title: Socioeconomics: The elephant in the developing brain

Authors: *V. H. NGUYEN[1], S. MAREK[2];
[1]Washington Univ. in St. Louis, St Louis, MO; [2]Mallinckrodt Inst. of Radiology, Washington Univ. Sch. of Med. in St. Louis, St Louis, MO

Abstract: Adolescence is a unique period of lifespan, characterized by increased risk-taking behavior, cognitive ability, and the emergence of many psychiatric disorders. Beyond behavior, brain function, measured by resting-state functional connectivity (RSFC), also exhibits protracted development throughout adolescence. We previously found that socioeconomic opportunity (SES) had the largest association with brain function across 649 variables. SES is the dominant detectable factor in childhood brain organization, subsuming primary neurobiological traits, such as general intelligence. Hence, our main goal is to investigate the RSFC development trajectory in adolescents as a function of SES. We used RSFC data from Discovery (N=1,140) and Replication (N=1,080) ABCD Study datasets as brain development indicators and the Childhood Opportunity Index (COI), a composite of a neighborhood's socioeconomic opportunity (SES). We first median split RSFC data to explore the brain development differences between individuals with high and low SES across two time points. We computed univariate association and variance tests between all brain connectivity features and neighborhood-level SES. Next, we submitted RSFC data to principal component analysis and statistically compared components using ANOVA between high and low SES groups for both time points. A stable and reproducible pattern was shown in RSFC's robust association with SES across both time points ($r = 0.71$). Brain regions most strongly associated with SES were in sensorimotor networks, salience regions, and the recently discovered somato-cognitive action network. There was also evidence for a non-linear effect, where individuals with lower SES levels have stronger correlations between RSFC and SES than individuals from higher SES. Additionally, RSFC differences between low and high SES individuals remained stable across the two time points.This study provided evidence for reproducible and developmentally stable associations

between brain function and neighborhood-level SES. Future analyses may identify mediating factors of associations between SES and brain function to identify putative biobehavioral determinants of adolescent health outcomes.

Disclosures: V.H. Nguyen: None. **S. Marek:** None.

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.062/LBA59

Topic: A.09. Adolescent Development

Support: R37MH101495-10

Title: Hippocampus-dlpfc resting state connectivity mediates the association between early life stress and adolescent psychopathology

Authors: *C. ANTONACCI, J. L. BUTHMANN, I. H. GOTLIB;
Dept. of Psychology, Stanford Univ., Stanford, CA

Abstract: Early environments can exert profound and lasting effects on children's development and well-being. Youth growing up in adverse conditions often experience diverse forms stress including poverty, neglect, air pollution, and maltreatment. This multicollinearity in early exposure has made it challenging to disentangle relations between stressors and outcomes, and to identify psychobiological mechanisms underlying these associations. In the current study, 228 youth (M_{age}=11.33 years, 59%F) completed assessments of early adversity, including stress exposure history, parenting, and neighborhood pollution, and of resting-state neural connectivity (fMRI) at baseline. Two years later, participants completed measures assessing psychopathology and behavioral difficulties. We conducted separate factor analyses on measures of stress exposure in childhood and on measures of psychopathology obtained at follow-up in adolescence. We then examined whether frontolimbic functional connectivity mediated associations between the latent factors of stress exposure and of subsequent psychopathology. Factor analyses yielded three distinct constructs indexing stress exposure: 'Parenting,' 'Deprivation,' and 'Threat/Unpredictability,' and one latent factor indexing 'Psychopathology' at follow-up. Regression analyses indicated that the Parenting (b=.20, p=.003) and Threat/Unpredictability (b=.18, p=.007) factors, but not the Deprivation factor (b=-.003, p=.647), predicted Psychopathology in adolescence. Mediation analyses yielded a significant indirect effect for the association between Threat/Unpredictability and Psychopathology through functional connectivity between the hippocampus and left dorsolateral prefrontal cortex (dlPFC; b=.037, p=.012). Sensitivity analyses indicated that this effect was unique to Threat/Unpredictability, underscoring the potentially domain-specific nature by which early

stressors shape brain development and behavioral outcomes. We found that diverse measures of early stress are reducible to three distinct latent factors, which are differentially related to psychopathology in adolescence. We also found evidence of mechanistic specificity in the association between Threat/Unpredictability and Psychopathology, which was uniquely mediated by connectivity between the hippocampus and dlPFC. Thus, there appears to be broad dimensionality in the relations among stress exposure, psychopathology, and brain development. Further investigation of this dimensionality is warranted, particularly with respect to individual differences and implications for intervention targets.

Disclosures: C. Antonacci: None. **J.L. Buthmann:** None. **I.H. Gotlib:** None.

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.063/LBA60

Topic: A.09. Adolescent Development

Support: R01 AG064247

Title: Hippocampal subfield volumes and relational memory in periadolescent children: Findings from the PRANK study

Authors: *A. F. WILHELM[1], M. K. RAMIREZ[2], A. HELLER-WIGHT[1], J. SEXTON[3], E. ARMBRUSTER[4], C. J. PHIPPS[4], D. E. WARREN[5];
[1]Neurolog. Sci., [2]Neurosci., [3]Dept. of Neurolog. Sci., [5]Neurosciences, [4]Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Relational memory, the ability to bind together arbitrarily related pieces of information, develops throughout childhood and adolescence. This can be observed in the difficulty young children experience in retaining information over time. Such difficulties are often attributed to the immaturity of the hippocampus, a brain structure necessary for normal relational memory. Age-related differences and developmental changes have been observed in the whole hippocampus but also in its component subfields, including cornu ammonis 1 (CA1), CA2/3, dentate gyrus and subiculum. Research indicates that hippocampal subfields increase in volume until about ages 13-15, suggesting an association between these volumetric changes and the development of relational memory. However, the association between relational memory and hippocampal subfield volumes in children is not yet well characterized. For this study, we used data from the Polygenic Risk for Alzheimer's Disease in Nebraska Kids (PRANK) study, a study investigating the impact of polygenic risk for Alzheimer's disease on brain and cognitive development. We examined the association between hippocampal subfield volumes and hippocampal-dependent relational memory in children. A sample of 136 healthy children aged

8-13 years (mAge=10.26 y, 67 F) were drawn from the PRANK study. Participants underwent cognitive testing, along with an MRI scan. The MRI protocol was adapted from the Human Connectome Project. Specifically, we acquired high resolution T2-weighted images of the hippocampus. Segmentation of hippocampal subfields was performed using the Automatic Segmentation of Hippocampal Subfields software. Hippocampal subfield volumes were corrected for intracranial volume using linear regression methods. Relational memory was measured with the Child and Adolescent Memory Profile (ChAMP). Pearson's correlation statistics were used to test the associations between hippocampal subfield volumes and relational memory performance. Our analysis revealed that the volumes of the left CA1 ($r=.32$, $p<.001$) and right CA1 ($r=.33$, $p<0.001$) were significantly correlated with ChAMP object performance, as well as with ChAMP places performance (left CA1: $r=.24$, $p=.0056$; right CA1: $r=.31$, $p<.001$). Supplementary analysis revealed that these associations remain significant after controlling for age using partial correlation. Our study expands on previous research linking relational memory and specific hippocampal subfield contributions. Future work will provide more insight into the development of individual hippocampal subfields and relational memory by using longitudinal data from the PRANK study.

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.064/LBA61

Topic: A.09. Adolescent Development

Support: R01 AG064247

Title: Investigating Brain Activity, Relational Memory Performance, and Their Association in Typically Developing Periadolescent Children Using Task-Based fMRI

Authors: *M. RAMIREZ[1], C. J. PHIPPS[1], A. HELLER-WIGHT[2], J. SEXTON[3], A. WILHELM[1], D. E. WARREN[4];
[2]Neurolog. Sci., [3]Dept. of Neurolog. Sci., [4]Neurosciences, [1]Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Childhood brain development is characterized by significant structural and functional changes associated with cognitive maturation. One notable aspect of this process is the continued development of hippocampal-dependent relational memory (RM). The hippocampus is necessary for normal RM as evidenced by the characteristic pathology and memory deficits in patients with Alzheimer's disease (AD). Meanwhile, susceptibility to AD and other memory impairments in

later life may be influenced by brain development during childhood. This motivates investigation into the developmental trajectory of the brain and its connections to cognitive abilities, including hippocampal-dependent, AD-vulnerable RM. Here, we studied task-related brain activity in typically-developing children using fMRI during a RM task. Data were drawn from the ongoing NIA-funded Polygenic Risk of Alzheimer's disease in Nebraska Kids (PRANK) study. Participants (n = 173, mean = 10.8 yrs, 85F) completed a subsequent memory (SM) task in which they were asked to remember pairs of objects while fMRI-BOLD data were collected. Later, participants completed a memory test for the studied pairs. Controlling for sex, age, and SM performance, we conducted a univariate analysis of fMRI-BOLD activation for successful vs. non-successful SM of studied pairs. Whole-brain statistical maps reflecting the covariates were thresholded at field-standard voxelwise and cluster-extent thresholds ($\alpha = 0.001$ and 0.05, respectively). Controlling for age and sex, successful SM was associated with increased activity in the inferior temporal and superior parietal lobule and decreased activity in the parieto-occipital sulcus. These findings were consistent with the recognized topology of the dorsal attention and parietal memory networks. Additionally, there was increased activity in the bilateral anterior hippocampus. Evaluating effects of SM performance as a covariate, we found similar significant regions during pair learning. Specifically, we observed that improved performance was associated with stronger and more extensive brain activity within the networks observed in the main analysis. Together, our findings reflect activation of brain regions involved in successful encoding of paired items by periadolescents. By elucidating the intricate relationships between functional brain activity and memory, these findings pave the way for a deeper understanding of the development of hippocampal-dependent RM. These insights could help clarify developmental trajectories and inform interventions designed to improve cognitive outcomes during this critical period of neurodevelopment.

Disclosures: M. Ramirez: None. **C.J. Phipps:** None. **A. Heller-Wight:** None. **J. Sexton:** None. **A. Wilhelm:** None. **D.E. Warren:** None.

Late-Breaking Poster

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.065/LBA62

Topic: A.09. Adolescent Development

Support: NIA Grant RO1 AG064247

Title: Associations of sex and age with anterior and posterior hippocampal subfield volumes in periadolescent children

Authors: *E. A. ARMBRUSTER[1], C. J. PHIPPS[2], M. K. RAMIREZ[3], A. HELLER-WIGHT[1], J. SEXTON[4], A. WILHELM[2], D. E. WARREN[5];

[1]Neurolog. Sci., [3]Neurosci., [4]Dept. of Neurolog. Sci., [5]Neurosciences, [2]Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Background. The hippocampus is made up of distinct subfields that vary anatomically along the structure's long axis. Hippocampal subfields also seem to develop heterogeneously across childhood and into adolescence, potentially differing by sex. To investigate how the developmental trajectory of hippocampal subfields may vary interactively with age and sex, the current study examined the effects of sex and age on subfield volumes (CA1, CA2/3, DG, subiculum) across the longitudinal axis (anterior, posterior) in a cross-sectional cohort of periadolescent children. Methods: A sample of 135 healthy periadolescents aged 8-13 years (mean age = 11.6 years, 65 F) enrolled in the NIA-funded Polygenic Risk of Alzheimer's Disease in Nebraska Kids (PRANK, R01 AG064247)) study were included in the analysis. Participants underwent a 3T MRI scan including a T2-weighted ultra-high-resolution slab targeting hippocampus. Hippocampal subfields were segmented from the slab using Automated Segmentation of Hippocampal Subfields software. Anterior and posterior regions of the hippocampus were split using expert rater labeling of the uncle apex. Hippocampal subfield volumes were then corrected for intracranial volume. Associations between age, sex, and hippocampal subfield volumes were analyzed using by multiple regression of subfield volumes on age, sex, and their interaction. Results: Age and sex significantly predicted hippocampal volumes for each of the following results reported, with p-values < .05, in the right anterior CA1, right anterior subiculum, left posterior subiculum, right anterior gyrus. Females on average demonstrated significantly lower volumes in each of these subfields. In the right anterior CA1 a significant interaction emerged here where the relationship between age and volume varied by sex. Conclusion: Age and sex significantly influenced the hippocampal subfield by subregion volumes, in this sample, particularly in the right anterior CA1, subiculum, and dentate gyri, as well as within the left posterior subiculum. Future work will utilize longitudinal data to provide more insight into how sex and age effect the development of anterior and posterior hippocampal subfield volumes.

Disclosures: E.A. Armbruster: None. **C.J. Phipps:** None. **M.K. Ramirez:** None. **A. Heller-Wight:** None. **J. Sexton:** None. **A. Wilhelm:** None. **D.E. Warren:** None.

Late-Breaking Poster

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Program #/Poster #: LBA001.066/LBA63

Topic: A.09. Adolescent Development

Support: Canadian Institutes of Health Research
New Frontiers in Research Fund

Title: Predicting internalizing problems from brain structure features using deep learning

Authors: M. VANDEWOUW[1], J. P. LERCH[2], E. ANAGNOSTOU[1], ***A. KUSHKI**[1];
[1]Holland Bloorview Kids Rehabil. Hosp., Toronto, ON, Canada; [2]Univ. of Oxford, Oxford, United Kingdom

Abstract: Acknowledgements: We would like to acknowledge the members of the pond network who contributed to this work: B. Syed, N. Barnett, A. Arias, E. Kelley, J. Jones, M. Ayub, A. Iaboni, P. D. Arnold, J. Crosbie, R. J. Schachar, and M. J. Taylor.
Background: Internalizing problems in children and youth are associated with profoundly negative outcomes. While we have some understanding of the factors associated with an increased risk of internalizing problems - for example, the presence of a neurodevelopmental (ND) condition - the neurobiological markers are poorly understood. Existing approaches may be sup-optimal for characterizing the multi-dimensional and complex brain-behaviour associations related to mental health, calling for complementary strategies.
Objective: Here, we used deep learning to predict cross-sectional and worsening longitudinal trajectories of internalizing problems from measures of brain structure in neurotypical and neurodivergent children and youth.
Methods: Data were extracted from four large scale datasets of children and adolescents: (1) the Adolescent Brain Cognitive Development study, (2) the Healthy Brain Network, (3) the Human Connectome Project Development study, and (4) the Province of Ontario Neurodevelopmental network. Regional and global thicknesses, surface areas, and volumes were used as measures of brain structure, while internalizing problems were assessed using the Child Behaviour Checklist. Deep learning models were tuned, trained, and tested using a stratified cross-validation scheme to predict (a) clinically significant internalizing problems from brain structure cross-sectionally (N=14,523) and (b) worsening longitudinal trajectories of internalizing problems (N=10,540) from baseline measures of brain structure. Performance was evaluated using the area under the receiving operating characteristic curve (AUC) across the entire sample, as well as stratified by the presence or absence of a ND diagnosis.
Results: The cross-sectional model performed well across the sample, reaching an AUC of 0.80 [95% CI: 0.71, 0.88]. For the longitudinal model, while performance was sub-optimal for predicting worsening trajectories in a sample of the general population (AUC=0.66 [0.65, 0.67]), good performance was reached in a small, external test set of primarily ND conditions (AUC=0.80 [0.78, 0.81]), as well as across all ND conditions (AUC=0.73 [0.70, 0.76]).
Conclusions: Deep learning with features of brain structure is a promising avenue for biomarkers of internalizing problems, particularly for individuals with ND conditions who have a higher likelihood of experiencing difficulties.

Disclosures: M. Vandewouw: None. **J.P. Lerch:** None. **E. anagnostou:** 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.; Roche, Anavex. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AMO Pharma, CRA-Simons Foundation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); APPI, Springer, holly (formerly

Anxiety Meter). F. Consulting Fees (e.g., advisory boards); Roche, Quadrant Therapeutics, Ono, Impel Pharmaceuticals. **A. Kushki:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); holly (formerly Anxiety Meter). F. Consulting Fees (e.g., advisory boards); DNAStack, Shaftesbury.

Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.067/LBA64

Topic: A.10. Development and Evolution

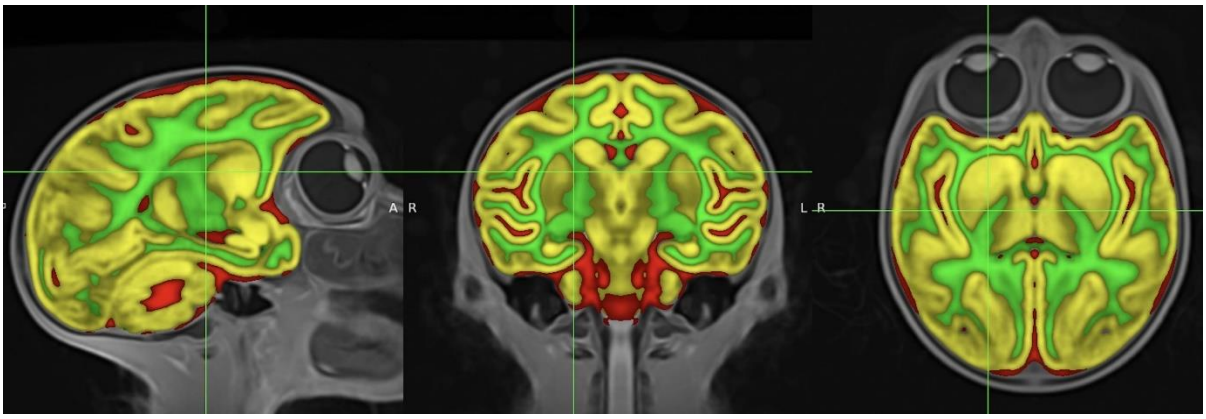
Support: ERC-2016-STG
ANR-12-PDOC-0014-01
ANR-16-CONV-0002
ANR-11-LABX-0036
ANR-11- 656 IDEX-0001-02
Fondation Fyssen

Title: Babacool: a longitudinal MRI template of the baboon brain across development

Authors: *K. L. BRYANT[1], Y. BECKER[3,2], A. LE TROTER[4], D. MEUNIER[4], S. A. LOVE[10], S. BOUZIANE[5], K. LOH[11,6], J. SEIN[7], O. COULON[8,4], A. MEGUERDITCHIAN[9,5,12];
[1]Inst. for Languge, Communication, and the Brain, Aix-Marseille Univ., MARSEILLE, France; [2]Lab. de Psychologie Cognitive, Aix-Marseille Univ., Marseille, France; [3]Max Planck Inst. for Human Cognitive and Brain Sciences, Leipzig, Germany, Leipzig, Germany; [4]Inst. de Neurosciences de la Timone, [5]Ctr. de Recherche en Psychologie et Neurosciences, [6]Lab. de Psychologie Cognitive, Univ. Aix-Marseille, Marseille, France; [7]Inst. de Neurosciences de la Timone, Univ. Aix-Marseille, MARSEILLE, France; [8]Inst. for Language, Cognition, and the Brain, Univ. Aix-Marseille, Marseille, France; [9]Inst. for Language, Cognition, and the Brain, Univ. Aix-Marseille, MARSEILLE, France; [10]UMR Physiologie de la Reproduction et des Comportements, INRAE, Tours, France; [11]Cognitive Neurosci. Unit, Montréal Neurolog. Inst., Montreal, QC, Canada; [12]Station de Primatologie, CNRS-CELPHEDIA UAR846, Rousset, France

Abstract: The baboon (*Papio*) is an invaluable resource within nonhuman primate research, having the advantage of being an Old World monkey with one of the largest brains among non-hominid primates. Combined with their life history characteristics and phylogenetic closeness to humans, makes baboons valuable for understanding human brain evolution and human-specific neuropathologies. We present preliminary results towards building the first population-based developmental multimodal baboon brain template, BabaCOOL: BAby Brain Atlas COnstruction for Optimized Labeled segmentation. This longitudinal template consists of structural and

diffusion data, tissue probability segmentations, and fractional anisotropy maps for a population of 31 baboons (*P. anubis*) at 4 timepoints beginning from 2 weeks after birth (see fig. 1) and continuing into adolescence (5 years).
Animal procedures were approved by the C2EA-71 Ethical Committee of Neurosciences (INT Marseille; APAFIS#13553-201802151547729 v4), conducted at the Station de Primatologie (Rousset-Sur-Arc, France) under agreement C130877 for conducting experiments on vertebrate animals, and performed in accordance with French law, CNRS guidelines and the European Union regulations (Directive 2010/63/EU). From September 2017 to March 2020, *in vivo* acquisition of T1w, T2w, DWI, and resting state fMRI was performed using a 3T MAGNETOM Prisma MRI scanner (Siemens) with 80 mT/m gradients and a 2-channel B1 transmit array (TimTX TrueForm). Preprocessing was done with the Cat12 toolbox (www.neuro.uni-jena.de/cat/) in SPM12 (www.fil.ion.ucl.ac.uk/), implemented in MATLAB (www.mathworks.com/help/matlab/ref/rand.html). Templates were generated using Advanced Normalization Tools (ANTs, stnava.github.io/ANTs/) and nBEST (github.com/TaoZhong11/nBEST).This template resource will provide a normalization target for baboon data across the lifespan, facilitate neuroimaging research in baboons, and comparative research with humans and macaques.



Disclosures: K.L. Bryant: None. **Y. Becker:** None. **A. Le Troter:** None. **D. Meunier:** None. **S.A. Love:** None. **S. Bouziane:** None. **K. Loh:** None. **J. Sein:** None. **O. Coulon:** None. **A. Meguerditchian:** None.
Late-Breaking Poster

LBA001: Theme A Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA001.068/LBA65

Topic: A.10. Development and Evolution

Support: the New York Stem Cell Foundation (NYSCF)
NIH (HD103627-01A1)

Welch Foundation (I-2088)

Title: Generation of rat forebrain tissues in mice

Authors: *J. HUANG;
The Univ. of Texas Southwestern Med. Ctr., DALLAS, TX

Abstract: Interspecies blastocyst complementation (IBC) provides a unique platform to study development and holds the potential to overcome worldwide organ shortages. Despite recent successes, brain tissue has not been achieved through IBC. Here, we developed an optimized IBC strategy based on C-CRISPR, which facilitated rapid screening of candidate genes and identified that *Hesx1* deficiency supported the generation of rat forebrain tissue in mice via IBC. For the first time, we generated functional rat forebrain tissues in mice, integrating the brains of two species that are 13 million years apart in evolution. Xenogeneic rat forebrain tissues in adult mice were structurally and functionally intact and these chimeras are able to survive healthily into adulthood. We observed that the developmental rate of rESC-derived brain tissues aligned with that of the mouse host, indicating the innate adaptability of PSCs concerning differentiation speed and suggesting that the host microenvironment plays a role in regulating the developmental timing of donor cells. Remarkably, the single-cell transcriptomes of rat forebrain tissues generated in mice show more similarity to those in control rats than to mice, suggesting that certain intrinsic features of donor cells are preserved within the interspecies chimeras. Our findings reveal that both cell-autonomous and non-cell-autonomous mechanisms contribute to organ development within an interspecies context. Interspecies forebrain complementation opens the door for studying evolutionarily conserved and divergent mechanisms underlying brain development and cognitive function. The C-CRISPR-based IBC strategy holds great potential to generate forebrain tissues of wild or endangered animals and study their structure and function in the laboratory, expanding brain research from model organisms to other animals.

Disclosures: J. Huang: None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.001/LBA66

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH R44MH119870

Title: Real-time co-detection of dopamine and glutamate in rat striatum

Authors: *J. BERGER[1], L. KIMBLE[4], G. MCCARTY[2], J. MEITZEN[3], L. SOMBERS[5];
[1]North Carolina State Univ., Apex, NC; [3]Biol. Sci., [2]North Carolina State Univ., Raleigh, NC;

[4]The Med. Univ. of South Carolina, Charleston, SC; [5]Pharmacodynamics, Univ. of Florida/Pharmacodynamics, Gainesville, FL

Abstract: The nucleus accumbens (NAc) integrates multiple inputs, including glutamatergic (GLUT) and dopaminergic (DA) afferents, which ultimately affect the functional output of this brain region. The release and removal of GLUT from the synapse occurs within milliseconds, and measuring this activity is critical to understanding how these neurotransmitters work cooperatively to modulate brain function and dysfunction. Fast-scan cyclic voltammetry (FSCV) provides analyte-specific quantitative measurements of electroactive species, but GLUT is inherently non-electroactive and does not readily undergo redox reactions, rendering direct electrochemical detection impossible in the physiological environment. Here, we present the development of a biosensing strategy whereby carbon-fiber microelectrodes are modified with a chitosan matrix containing GLUT oxidase (GlutOx) to allow for the indirect voltammetric detection of GLUT with naturally engineered selectivity. GlutOx catalytically generates hydrogen peroxide (H2O2), a readily detectable electroactive reporter molecule, selectively in the presence of GLUT. Importantly, electroactive DA can be simultaneously detected at the same micron-scale recording site, because DA and H2O2 generate unique cyclic voltammograms. This co-detection method revels the coordination of these distinct neurochemical signals with one another, as a function of time, in live striatal tissue. This work has revealed key differences in the extracellular lifetime of these signaling molecules, suggesting that each can effectively modulate the other. In addition, the neurochemical kinetics are specific to the experimental preparation, with key differences observed between rat striatal slices and intact rat striatum. These findings are important because the co-activation of different neurochemical receptors enables integration of separate intracellular signaling pathways to generate a range of postsynaptic responses, ultimately shaping striatal output.

Disclosures: J. Berger: None. **L. Kimble:** None. **G. McCarty:** None. **J. Meitzen:** None. **L. Sombers:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.002/LBA67

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: FAPESP Grant 2018/15957-2
FAPESP Grant 2023/18269-8
CNPQ Grant 309338/2020-4)

Title: Sustained hypoxia reduces the tonic GABAergic drive but not phasic inhibitory transmission in the NTS neurons of C57Bl/6J mice

Authors: O. AUGUSTO DE CARVALHO MAIA[1], D. ACCORSI-MENDONCA[2], *B. H. MACHADO[3];
[1]Physiol., Sch. of Med. of Ribeirão Preto, Univ. of São Paulo, Ribeirão Preto, Brazil; [2]Physiol., Univ. of Sao Paulo, Ribeirao Preto, Brazil; [3]Physiol., Sch. Med. Ribeirao Preto, USP, Ribeirão Preto, Brazil

Abstract: The nucleus tractus solitarius (NTS) in the brainstem is the gateway for sensory afferent information, including the cardiovascular and respiratory reflexes. The excitatory transmission in the NTS of mice has been described, while the inhibitory neurotransmission/neuromodulation was not yet evaluated. Herein we investigated in mice the impact of sustained hypoxia (SH) in: a) the tonic inhibitory modulation on NTS neurons and b) the phasic signaling [generation of spontaneous inhibitory post-synaptic currents (sIPSCs)]. Brainstem slices containing the intermediate NTS were obtained from the C57Bl/6J male mice (6-7 weeks) after normoxia (FiO_2, 0.21 for 24h) or SH (FiO_2, 0.10 for 24h). Tonic and phasic inhibitory transmissions were evaluated by whole-cell patch-clamp technique. All experimental protocols were approved by the institutional ethics committee (CEUA/FMRP-USP #1109/2022R1). The experiments were performed under voltage-clamp configuration (holding potential, -70mV) and in the presence of DNQX (AMPA/Kainate receptor antagonist) to block excitatory currents. Picrotoxin ($GABA_A$ receptor antagonist) produced greater outward shift in the baseline (I_{hold}) in NTS neurons from normoxia than in SH group [ΔI_{hold}: SH: 4.5 ± 1.1 pA (n=6) vs normoxia: 20.7 ± 1.1 pA (n=8), p= 0.0319], indicating reduction in the inhibitory tonus after SH. Addition of strychnine (glycine receptor antagonist) produced no changes in the I_{hold}. The phasic inhibitory transmission was evaluated by the occurrence of sIPSCs. SH produced no changes in frequency [SH: 5.7 ± 1.2 Hz (n=16) vs. normoxia: 5 ± 0.8 Hz, (n=21), p> 0.05], amplitude (SH: 34.6 ± 4.5 vs. normoxia: 31.1 ± 3.5 pA, p> 0.05)] and half-width (SH: 5.1 ± 0.5, vs. normoxia: 6.1 ± 0.5 ms, p> 0.05) of sIPSCs, which were also not altered after picrotoxin: frequency [SH: 1.5 ± 0.3 Hz (n=11) vs. normoxia: 1.2 ± 0.2 Hz (n=16), p> 0.05], amplitude (SH: 13.8 ± 1.8, vs. normoxia: 15.1 ± 1.8 pA, p> 0.05)] and half-width (SH: 2.6 ± 0.2, vs. normoxia: 3.3 ± 0.2 ms, p> 0.05). Even after picrotoxin+strychnine, we observed some residual sIPSCs similar in both groups: frequency [SH: 0.6 ± 0.1 Hz (n=7) vs. normoxia: 0.4 ± 0.1 Hz (n=10), p> 0.05], amplitude (SH: 10.1 ± 1.2, vs. normoxia: 10.7 ± 1.7 pA, p> 0.05) and half-width (SH: 3.4 ± 0.9, vs. normoxia: 2.7 ± 0.5 ms, p> 0.05)]. These findings are showing that the tonic GABAergic inhibitory drive in the NTS neurons was significantly reduced by SH, while the phasic transmission mediated by GABA and glycine was not affected. The cardiovascular and respiratory implications of these findings in the NTS neurons after SH require further investigation.

Disclosures: O. Augusto de Carvalho Maia: None. **D. Accorsi-Mendonca:** None. **B.H. Machado:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.003/LBA68

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: CIHR

Title: Inhibitory Synaptic Transmission and KCC2 Function in 15q13.3 microdeletion syndrome

Authors: *Z. DARGAEI[1], K. K. SINGH[2], J. S. BAINS[3];
[1]Krembil Res. Inst., Toronto, ON, Canada; [2]DKJEI, [3]Krembil Res. Inst., Univ. Hlth. Network, Toronto, ON, Canada

Abstract: The 15q13.3 microdeletion syndrome is a genetic disorder caused by deletion of several genes on chromosome 15 and is associated with psychiatric disorders and social cognitive deficits [1,2], and these deficits resemble those observed in 15q13.3 mouse models [3]. The underlying mechanisms are unresolved, but alterations in cortical circuits due to reduced inhibitory function have been implicated in social and cognitive impairments in several neurodevelopmental disorders [4]. Inhibitory synaptic transmission in the brain is largely mediated by GABA acting on Cl^--permeable $GABA_A$ receptors. This requires low levels of intracellular Cl^- that are mainly achieved by the K^+-Cl^- cotransporter, KCC2. Decreases in KCC2 expression or KCC2 Cl^- extrusion capacity reduce synaptic inhibition and contribute to the pathophysiology of neurological disorders including to social deficits and repetitive behaviors in other autism mouse models [5,6].We used a combination of electrophysiology, biochemistry and behavioral assays, to investigate the potential contributions of Cl^- regulation and altered inhibitory synaptic transmission to social behavioral deficits in the 15q13.3 microdeletion.We recorded the reversal potential for GABA (E_{GABA}), as an indirect measurement of KCC2 function, in medial prefrontal cortex (mPFC) and found a significant depolarizing shift of E_{GABA} in the 15q13.3 microdeletion brain compared with WT control. We pharmacologically inhibited KCC2 and confirmed that dysfunction contributes to the depolarization of E_{GABA} in mPFC of 15q13.3 mice. In addition, we found that KCC2 protein expression is significantly decreased in mPFC of 15q13.3 mice compared with WT. Our results show that depolarization of E_{GABA} contributes to increased neuronal excitability and spiking activity in 15q13.3 mPFC neurons. We will evaluate the contribution of chloride dysregulation on social behavioral deficits observed in 15q13.3 microdeletion. Understanding KCC2 function and chloride regulation in 15q13.3 and its behavioral consequences could represent novel insights into the pathogenesis of 15q13.3 microdeletion syndrome.

References:
[1]. Miller DT, et al. 2009. J Med Genet. 46:242–248.[2]. Ziats MN. et al, 2016. Genet Med. 18(11):1111-1118. [3]. Nilsson SRO, et al, 2016. Psychopharmacology (Berl). 233(11):2151-2163.[4]. Paine TA, et al, 2017. Behav Brain Res. 15; 317:542-552[5]. Rivera C, et al. Nature.; 397:251–255.[6]. Tyzio R, et al. (2014). Science 343 675–679.

Disclosures: Z. Dargaei: None. **K.K. Singh:** None. **J.S. Bains:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.004/LBA69

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Title: Tau pathology modifies sleep and GABA homeostasis.

Authors: *R. IRMEN[1], C. M. CARROLL[4], N. J. CONSTANTINO[2], A. SNIPES[1], S. L. MACAULEY[3];
[2]Neurosci., [3]Physiol. & Pharmacol., [1]Univ. of Kentucky, Lexington, KY; [4]Neurosci., Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Background: Alzheimer's disease is defined by the pathological development of amyloid-beta (Aβ) and aggregation hyperphosphorylated tau (ptau). While presence of both biomarkers is necessary for diagnosis, tau pathology develops later in disease coinciding with cognitive impairment and neurodegeneration. Over 50% of people diagnosed with AD report sleep disturbances. Currently, it is unclear if this is a cause or consequence of Aβ or tau pathology. Previous work showed that tau pathology corresponds with disrupted sleep. Currently, it is unclear what mechanisms underly sleep-wake changes. Therefore, we investigated how tau pathology alters sleep and neuronal excitability in the P301S PS19 mouse model. Methods: To examine sleep-wake cycles, 3, 6, and 9 month old P301S and WT mice underwent stereotaxic surgery to place cortical EEGs and EMG wires. EEG/EMG recorded cortical activity over 3 days. Recordings were hand scored over a 24-hour period in 10 second epochs as either wake, NREM, or REM according to EEG/EMG characteristics. Fast Fourier Transform (FFT) was utilized to determine power spectral density and categorize EEG into predefined frequency bins. Bulk RNAseq was performed on 9 month old P301S and WT cortical tissue. Expression of GABA and glutamate associated genes were analyzed. Results: Analysis of EEG recordings revealed that tau pathology decreases time spent in NREM and REM specific to the light period as early as 6 months old and is exacerbated at 9 months old. Relative power analysis exhibited decreased beta power (12-30 hz) during wake and NREM due to tau pathology, not age. This led to decreased delta power (1-4hz) during wake, suggesting decreased homeostatic drive for sleep. Since beta power reflects excitatory/inhibitory (E/I) balance and GABAergic tone, we used transcriptomics to explore gene expression related to GABA and glutamate signalling. GABAergic synapse, calcium signalling, and GABA synthesis genes were reduced with pathology, not age. Expression of GABA receptors increased, while genes associated with glutamate synthesis and receptors were dysregulated compared to controls. Conclusion: P301S mice spend decreased time in NREM/REM with tau pathology. EEG spectral analysis indicates decreased beta activity, suggesting diminished GABA transmission. Further, tau pathology alters the expression of GABA and glutamate associated genes. Together, tau

pathology reduces sleep drive and ability to switch between vigilant states despite increased sleep need. These results suggest that tau pathology causes sleep impairments with an underlying potential mechanism of tau pathology induced excitatory/inhibitory imbalance.

Disclosures: R. Irmen: None. **C.M. Carroll:** None. **N.J. Constantino:** None. **A. Snipes:** None. **S.L. Macauley:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.005/LBA70

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Title: Investigating the in vivo function of post-translationally modifiable Histone 3.3 glutamine 5 and 19 using Drosophila

Authors: *H. DELGADO-SEO[1], I. S. MAZE[3], H. DIERICK[2];
[1]Neurosci. Dept., [2]Dept. of Mol. and Human Genet., Baylor Col. of Med., Houston, TX; [3]Dept. of Neurosci., Icahn Sch. of Med. At Mount Sinai, Ossining, NY

Abstract: Breakthroughs in epigenetic discoveries have revealed epigenetic mechanisms that can induce lasting changes in both the structure and function of the nervous system, thereby influencing a spectrum of neurological and psychiatric disorders. Recent work has found that biogenic monoamines like dopamine and serotonin can post-translationally modify Histone 3 (H3) at two specific glutamine (Q) residues (H3Q5 and H3Q19). Initial studies of this process, known as H3 monoaminylation, found that transcriptional and behavioral patterns of cocaine-dependent rats were partially reversible by overexpressing a monoaminyl-deficient H3Q5 variant in the reward circuit. Although H3 monoaminylation has been subsequently linked to mood disorders and other drug addictions, its overall physiological importance and the functional significance of the second monoaminyl site (H3Q19) remain unclear. Therefore, this study aims to probe the functional significance of both H3 monoaminylation sites *in vivo* by using throughput genetic and behavioral techniques in the fruit fly. To investigate the effects of monoaminylation on H3Q5 and H3Q19, *Drosophila* strains with H3 variants mimicking unmodifiable glutamine (Q) residues were designed. This was achieved by amino acid substitutions replacing glutamine (Q) residues with alanine (Q>A) or asparagine (Q>N), in the individual (Q5 or Q19) or combined (Q5+Q19) monoaminylation sites using phiC31-mediated targeted integration. Thus far, we have found that ubiquitous overexpression of individual H3 Q>A and Q>N variants resulted in comparable semi-lethality patterns, suggesting that monoaminyl deficiency rather than specific amino acid substitutions is responsible for this phenotype. Moreover, pan-neuronal overexpression of H3 Q>A variants causes defects in wing expansion behavior, which is regulated by a genetically and neurobiologically traceable

neurohormone signaling cascade. Therefore, we have found a potential pathway for further exploration into the precise function of this novel epigenetic mark *in vivo*.

Disclosures: H. Delgado-Seo: None. **I.S. Maze:** None. **H. Dierick:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.006/LBA71

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Title: Neuropeptide Y potentiates transient vasoconstriction in the mouse retina through activation of the NPY-Y1 receptor in vivo

Authors: *V. PALANIVEL, D. BASAVARAJAPPA, V. GUPTA, S. GRAHAM; Macquarie Univ., Macquarie Park, Australia

Abstract: Neuropeptide Y (NPY), a 36-amino acid peptide, is known for its vasoactive properties, and we have recently demonstrated its potential role as a neuroprotective agent in the retina despite its vasoconstriction properties. NPY exerts its vasoconstrictive effects through the activation of the NPY-Y1 receptors in blood vessels. NPY is endogenously degraded into NPY (3-36) by Dipeptidyl peptidase-4 (DPP4), resulting in a more stable peptide. N-terminally truncated analogs like NPY (3-36) have been found to exhibit lower or no affinity for NPY-Y1 receptors while maintaining similar affinities towards Y2 and Y5 receptors. This study investigated the vasoconstrictive effects of NPY and its truncated form, NPY (3-36), on mouse retinal blood vessels *in vivo*. Wild-type C57-BL6J mice (n=36) were injected intravitreally with NPY (1-36), NPY (3-36), or a scrambled NPY (scNPY) with equal dose. The retinal vasculature was imaged using Phoenix MICRON IV by fluorescein angiography at various time points: 15 minutes, 1 hour, 6 hours, and 24 hours. Vessel diameter was calculated using the FIJI Vessel Analysis plugin. Following treatments, mice were euthanized, and eyes were harvested for further immunofluorescence analysis. Whole-mount retinas were immunostained for NPY receptors (Y1R, Y2R, and Y5R) to observe their localization on blood vessels. Results showed a significant decrease in vessel diameter in the groups treated with NPY at 15 minutes ($p < 0.001$, $n = 6$) and 1 hour ($p < 0.0001$, $n = 6$), but no significant decrease was observed at 6 and 24 hours. In contrast, groups treated with NPY (3-36) and scNPY showed no signs of vasoconstriction at any time point (n=6 per group). Immunostaining revealed co-localization of the NPY-Y1 receptor with isolectin B4, highlighting the endothelial cells of the retinal blood vessels, but not with Y2R or Y5R. These results indicate that NPY induces a strong but transient vasoconstrictive effect in blood vessels through activation of the Y1 receptor, whereas NPY (3-36) does not exert a similar effect due to its inactivity against the Y1 receptor. It is suggested that the transient vasoconstrictive effect of NPY may be due to its endogenous degradation by DPP4

into NPY (3-36). Ongoing studies will be focused on understanding the molecular mechanisms involved in NPY-induced vasoconstriction. This is critical to determine if it could be utilized in the retina as a neuroprotective agent.

Disclosures: V. Palanivel: None. **D. Basavarajappa:** None. **V. Gupta:** None. **S. Graham:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.007/LBA72

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH Grant DA007244
NIH Grant DA048241

Title: Mdma administration alters heroin withdrawal-enhanced fear learning and attenuates dorsal hippocampal il-1β, tnf-α, and gfap

Authors: *C. R. CARDINALE, G. A. BARKELL, S. V. PAREKH, C. M. RUBIN, T. V. SANON, D. T. LYSLE;
Psychology and Neurosci., UNC Chapel Hill, Chapel Hill, NC

Abstract: A significant portion of individuals presenting to a clinic with an opiate use disorder (OUD) are at greater risk for a comorbid diagnosis of post-traumatic stress disorder (PTSD); however, SSRI and cognitive-behavioral therapy have proven largely ineffective at treating these conditions. Recently, phase-III clinical trials utilizing 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy have significantly reduced PTSD symptoms; however, little is known about the mechanism of these effects and if they extend to comorbid models of OUD and PTSD. This study looked at the effects of MDMA on heroin withdrawal-enhanced fear learning (HW-EFL), a preclinical model of comorbid OUD and PTSD, in adult male Sprague-Dawley rats. Animals underwent 10 days of chronic escalating doses of heroin and were subsequently administered MDMA or saline at 0, 24, and 48 hr of heroin withdrawal. One week after the start of heroin withdrawal, animals were exposed to a mild foot shock in a distinct environment and tested subsequently for enhanced fear learning. The results showed that MDMA weakened the heroin withdrawal-induced sensitization to future fear learning. Prior research from our laboratory has shown that increases in proinflammatory cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) within the dentate gyrus (DG) of the dorsal hippocampus (DH) during heroin withdrawal are functionally involved in the development of enhanced fear. Thus, to investigate the mechanism behind the behavioral effect of MDMA, we examined changes in IL-1β, TNF-α, and the astrocyte-specific marker glial fibrillary acidic protein (GFAP)

within the DG of the DH in a separate cohort of animals that received MDMA or saline at 0 and 24 hr of heroin withdrawal. The results showed that MDMA administration attenuated heroin withdrawal-induced increases in IL-1β, TNF-α, and GFAP in the DG of the DH, suggesting that the effect of MDMA during HW-EFL is, in part, due to a neuroimmune mechanism. Together, these experiments are the first to show the behavioral and neuroimmune effects of MDMA in the HW-EFL model of comorbid OUD and PTSD and provide valuable insight for the clinical treatment of this comorbidity.

Disclosures: C.R. Cardinale: None. **G.A. Barkell:** None. **S.V. Parekh:** None. **C.M. Rubin:** None. **T.V. Sanon:** None. **D.T. Lysle:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.008/LBA73

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIDA R01DA046818

Title: Interleukin-1β Expression in the Rat Hippocampus Increases during Prolonged Abstinence from Cocaine Self-Administration

Authors: *A. L. GARCIA LOPEZ, L. M. STRAND, D. FEDERICO, K. HIGDON, X. LI, D. M. DIETZ;
Univ. at Buffalo, Buffalo, NY

Abstract: Interleukin-1β is primarily considered a proinflammatory cytokine that mediates immune responses. Both glial cells and select neuronal populations in the hippocampus have high expression of interleukin-1β and associated receptors, where they are thought to regulate hippocampal synaptic plasticity, such as long-term potentiation (LTP). We previously reported that cellular plasticity in the dorsal hippocampus is essential for cue-induced relapse after prolonged, but not acute, abstinence from cocaine self-administration. In our current studies, we found increased transcription and expression of interleukin-1β, along with increased levels of CCL2 (C-C motif chemokine ligand 2), in hippocampal tissues of male Sprague Dawley rats after prolonged forced abstinence (AD 30) from long-access cocaine self-administration. Double immunolabeling of these proteins and cell type-specific markers revealed that astrocytes in the dorsal hippocampus were responsible for the increase in interleukin-1β expression. Ongoing functional and behavioral studies will enable us to determine the significance of hippocampal interleukin-1β in mediating addiction-like neurobiological and behavioral plasticity.

Disclosures: A.L. Garcia Lopez: None. **L.M. Strand:** None. **D. Federico:** None. **K. Higdon:** None. **X. Li:** None. **D.M. Dietz:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.009/LBA74

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH-R01NS100793
NIH-R36AG083385
Phoenix Children's Mission Support
Midwestern University Kenneth A. Suarez Summer Research Fellowship
Midwestern Graduate Funds

Title: Impact of fbn(c1041g/-) mutation on chronic tgf-beta signaling and its modulation of glutamate neurotransmission in the hippocampus: insights from a marfan syndrome model

Authors: *L. P. CURTIN[1,2], T. CURRY[3], C. HAIR[4], G. KRISHNA[5], T. C. THOMAS[5]; [1]Arizona Col. of Osteo. Med., Midwestern University, Univ. of Arizona Col. of Medicine-Phoenix, Glendale, AZ; [2]Arizona Col. of Osteo. Med., Glendale, AZ; [3]Dept. of Child Hlth., Univ. of Arizona, Mesa, AZ; [4]Child Hlth., Univ. of Arizona, Phoenix, AZ; [5]Dept. of Child Hlth., Univ. of Arizona Col. of Medicine-Phoenix, Phoenix, AZ

Abstract: Transforming Growth Factor-β (TGF-β) is a pluripotent cytokine expressed in virtually every cell type of the human body. When aberrantly activated in the brain, it contributes to various neurological conditions. Marfan Syndrome (MFS), caused by *Fbn1* gene mutations, chronically disrupts TGF-β signaling in the periphery, with its neurological impacts remaining underexplored. We hypothesize that *Fbn1* mutations disrupt brain TGF-β levels, which, in turn, modulate glutamate neurotransmission. Using 6-month-old male and female $Fbn1^{C1041G/-}$ mice and C57BL/6 controls, we quantified levels of TGF-β isoforms in the brain using a multiplex assay (n=31). Resting extracellular glutamate levels and clearance kinetics in the hippocampus were measured using glutamate-selective microelectrode arrays (MEAs) coupled with *in vivo* amperometric recordings in anesthetized mice (urethane, 1.5g/kg, i.p.;n=45). Using a micropipette affixed to the MEA, local application of 100μM isotonic glutamate assessed clearance kinetics. In a male cohort (n=5), volume-matched local applications of TGF-β (25ng/mL) were locally applied to examine changes in extracellular glutamate. Our findings reveal similar hippocampal TGF-β isoform levels between $Fbn^{C1041G/-}$ and control mice, but significantly elevated resting extracellular glutamate levels in $Fbn1^{C1041G/-}$ mice (2.40±0.40μM vs. 0.83±0.17μM; p=0.002; mean±SEM). Local application of TGF-β evoked immediate and reproducible glutamate overflow, peaking at 6.28±1.74μM and remained elevated for 8.53±1.24s before returning to baseline levels compared to physiological saline, indicating a regulatory role. These results demonstrate TGF-β's direct and indirect modulation of hippocampal glutamate

neurotransmission, offering novel insights into MFS neurological manifestations and broader implications for aberrant TGF-β signaling in neuroinflammation, neurodegeneration, and aging.

Disclosures: L.P. Curtin: None. **T. Curry:** None. **C. Hair:** None. **G. Krishna:** None. **T.C. Thomas:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.010/LBA75

Topic: B.03. Ion Channels

Support: Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: Channelpedia: An Updated and Interactive Database for Voltage-Gated Ion Channels

Authors: *K. JOHNSTON, E. SCANTAMBURLO, A. JOURNE, E. LOGETTE, M. HERZOG, M. JOFFRAUD, S. VAN DORP, K. H. ARULKANDARAJAH, H. MARKRAM, R. RANJAN;
Blue Brain Project - EPFL, Geneva, Switzerland

Abstract: Voltage-gated ion channels (VGICs) are membrane proteins that allow ions to pass through cell membranes. They play essential roles in action potential generation and propagation in neurons, muscle contraction, cardiac rhythm regulation. They are crucial for maintaining cellular homeostasis, signal integration, plasticity, and adaptability in the nervous system. Abnormalities in VGICs are linked to various diseases, making them significant targets for medical research and treatment. Over the past four decades, extensive research has elucidated the molecular, structural, and biophysical properties of ion channels. Despite this, no public resource has existed for accessing raw biophysical data of VGICs.
To address this gap, we present Channelpedia (https://channelpedia.epfl.ch), an updated and comprehensive database that consolidates extensive information on ion channels. The latest version of Channelpedia features revised literature pages for all VGICs, raw electrophysiology data, and an AI-based assistant, ChannelAID. Unlike general AI chatbots, ChannelAID is specifically trained on ion channel scientific literature, providing accurate information with references. Additionally, ChannelAID can screen the published literature to list the effect of a drug on VGICs, offering an unprecedented comprehensive overview of the reported pharmacological impacts on these channels. Channelpedia thus serves as a crucial resource for researchers, providing a thorough and interactive platform for studying VGICs.

Disclosures: K. Johnston: None. **E. Scantamburlo:** None. **A. journe:** None. **E. Logette:** None. **M. Herzog:** None. **M. Joffraud:** None. **S. Van Dorp:** None. **K.H. Arulkandarajah:** None. **H. Markram:** None. **R. Ranjan:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.100/LBA163

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: Granés Fundació Scholarship
Carlos III Health Institute RD21/0002/0063
Fundación Francisco Soria Melguizo Ayudas2021FFSM

Title: Mitochondrial microRNA signatures: unraveling biomarkers and mechanisms of mitochondrial dysfunction in primary progressive multiple sclerosis

Authors: *A. MIGUELA BENAVIDES[1], J. HUERTAS PONS[1,2], C. COLL MARTINEZ[1,2], A. GIFREU FRAIXINÓ[1,3], G. ÁLVAREZ-BRAVO[1,3,4], L. RAMIÓ-TORRENTÀ[1,2,4,5], A. QUIROGA[1,2];
[1]Neurodegeneration and Neuroinflam. Res. Group, Girona Biomed. Res. Inst. (IDIBGI), Salt, Spain; [2]Red de Enfermedades Inflamatorias (RICORS, RD21/0002/0063), Carlos III Hlth. Inst., Madrid, Spain; [3]Neuroimmunology and Multiple Sclerosis Unit, Neurol. Dept., Dr. Josep Trueta Univ. Hosp. and Santa Caterina Hosp., Girona, Spain; [4]Dept. of Med. Sci., Univ. of Girona, Girona, Spain; [5]Med. Director, Fundació Hosp. d'Olot i Comarcal de la Garrotxa, Olot, Spain

Abstract: Introduction: Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative disease of the central nervous system (CNS) with a heterogeneous presentation, which complicates diagnosis and treatment. Primary progressive MS (PPMS) is classified into non-active (PPMS-NA) and active (PPMS-A) forms based on MRI activity and lipid-specific oligoclonal IgM bands. PPMS is characterized by neurodegeneration, which has been in turn associated with increased oxidative stress and mitochondrial dysfunction. Current disease-modifying therapies are effective only for PPMS-A, underscoring the need for new therapeutic targets. MicroRNAs (miRNAs) are promising biomarkers, with over 400 of them linked to mitochondrial processes. Objective: To identify differential expression patterns of miRNAs related to mitochondrial function and oxidative stress in the plasma of PPMS patients. Material and methods: Plasma samples were obtained at diagnosis from 83 subjects: 30 PPMS (22 PPMS-NA and 8 PPMS-A) 27 relapsing-remitting MS (RRMS), and 26 patients with other neurological disorders (OND). Plasma levels of 56 miRNAs were determined by quantitative PCR (qPCR), using the OpenArray technology, and their expression was analyzed by non-parametric statistical tests. Results: Circulating miR-197-3p levels were significantly higher in PPMS-A compared to PPMS-NA ($p<0.05$). This miRNA regulates genes involved in mitochondrial apoptosis, such as FOXO3, PAIMP1, and VDAC1, suggesting decreased apoptotic activity in PPMS-A relative to PPMS-NA. Conversely, miR-1-3p levels were significantly lower in PPMS-NA compared to OND ($p<0.01$). This miRNA targets COX1 and ND1, key for mitochondrial function, indicating

potential mitochondrial dysfunction in PPMS-NA. Conclusions: Elevated miR-197-3p levels in PPMS-A are associated with decreased mitochondria-mediated apoptosis, whereas reduced miR-1-3p levels in PPMS-NA suggest mitochondrial dysfunction. These distinct miRNA profiles not only differentiate PPMS subtypes but also provide insights into mitochondrial dysfunction in MS. These findings could guide the development of more precise diagnostic and therapeutic strategies for managing progressive MS.

Disclosures: **A. Miguela Benavides:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Biogen, Sandoz, Horizon Therapeutics, Novartis, Sanofi. **J. Huertas Pons:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Novartis, Sandoz. **C. Coll Martinez:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Merck, Bristol-Myers-Squibb, Sanofi. **A. Gifreu Fraixinó:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); UCB Pharma, Bial Pharmaceutical, Angelini Pharma, Merck, Bristol-Myers-Squibb, Biogen, Janssen. **G. Álvarez-Bravo:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Biogen, Novartis, Merck, Sanofi, Amgen, Roche, Bristol-Myers-Squibb. **L. Ramió-torrentà:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Biogen, Novartis, Bayer, Merck, Sanofi, Genzyme, Roche, Bristol-Myers-Squibb, TEVA, Horizon Therapeutics. **A. Quiroga:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Merck, Novartis, Horizon Therapeutics.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.101/LBA164

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: Research Contract to AG, Myrtelle Inc.
Research Boost award to AG, Wayne State University
SURP program award to AT, Center for Molecular Medicine & Genetics, Wayne State University
UROP program award to AT, Wayne State University

Title: Pre-clinical Model of Pelizaeus-Merzbacher Disease: An In Vivo Study

Authors: *A. TRENDOV[1], U. HAQ[2], E. KOLE[3], R. T. LAYER[4], C. M. SOUTHWOOD[5], A. GOW[5];
[1]Wayne State Univ., Shelby Township, MI; [2]Wayne State Univ., Detroit, MI; [3]Wayne State Univ., Bloomfield Township, MI; [4]Myrtelle, Marlborough, MA; [5]Ctr. Mol. Med. & Genet, Wayne State Univ. Sch. Med., Detroit, MI

Abstract: Pelizaeus-Merzbacher Disease (PMD) is a rare neurodegenerative disorder affecting the brain's white matter, a leukodystrophy primarily affecting myelinogenesis. The disease is principally caused by mutations of the *PROTEOLIPID PROTEIN 1 (PLP1)* gene located on the *X*-chromosome, which encodes the major protein component of CNS myelin. The most common mutations in PMD patients are duplications and triplications of the *PLP1* gene, leading to protein overexpression and causing cellular toxicity and death of oligodendrocytes. A transgenic mouse model of *Plp1* gene duplications (Nave-66) has been studied by several groups including our own. These mice have a lifespan between 150 - 200 days. To mitigate disease symptoms in these transgenic mice, we tested if a single intraventricular injection of an AAV-Olig001 vector - an adeno-associated virus (AAV) with tropism for oligodendrocytes, encoding EGFP and an inhibitory short-hairpin sequence targeting *Plp1* mRNA (shRNA, miR-1333) - into 4-6 days old mice could suppress PLP1 overexpression and reduce cytotoxicity. A scrambled shRNA (miR-1307) was used as a control. This exploratory study aimed to regulate PLP1 levels in mutant mice as a potential treatment strategy for PMD patients. Effectiveness of the AAV treatment was evaluated through various behavioral tests including forearm strength test, rotarod test, and lifespan measures. Further, qPCR was used to examine postmortem *Plp1* expression levels in treated mice. Because PMD is *X*-linked recessive, only male mice between 1 to 6 months of age were included in the study. In all behavioral tests, we did not find evidence of disease mitigation in the Olig001-miR-1333 group compared to the Olig001-miR-1307 controls. Further, Kaplan-Meier analysis indicated that lifespan was not extended. However, we observed an approximate two-fold reduction in levels of *Plp1* mRNA in brain homogenates of active versus scrambled miRNAs (whole tissue between Bregma and Lambda analyzed). The mRNA encoding EGFP was also abundant in this
tissue, indicating that AAV expression persisted for at least 7 months post-injection. Finally, we observed strong and widespread EGFP fluorescence staining in midbrain/brainstem cryostat sections. Our findings underscore the challenges ahead for improving the efficacy of the Olig001 therapy and alleviating PMD symptoms. Nevertheless, we conclude that our approach in *Plp1* overexpressing mice is a technical success, and this preliminary research serves as a critical foundation for future experiments and studies aimed at refining therapeutic strategies for PMD.

Disclosures: A. Trendov: None. **U. Haq:** None. **E. Kole:** None. **R.T. Layer:** A. Employment/Salary (full or part-time):; Myrtelle. **C.M. Southwood:** None. **A. Gow:** 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.; Principal investigator.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.102/LBA165

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: National Multiple Sclerosis Society TA-2008-37043 (Chen)
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (Brian Popko)

Title: Aa147 alleviates clinical symptoms in a mouse model of multiple sclerosis by reducing er stress and oligodendrocyte loss

Authors: *K. P. BRUCE[1], M. AKSU[1], K. KASCHKE[1], I. STECKLER[1], E. GARCIA[1], M. WONG[2], A. COGSWELL[2], J. R. PODOJIL[2], J. W. KELLY[4], R. L. WISEMAN[5], S. D. MILLER[2], B. J. POPKO[3], Y. CHEN[1];
[1]Loyola Univ. of Chicago, Chicago, IL; [2]Dept. of Microbiology-Immunology, [3]Neurol., Northwestern Univ., Chicago, IL; [4]Chem., The Scripps Res. Inst., Chicago, IL; [5]Dept. of Mol. and Exptl. Med., Scripps Res. Inst., La Jolla, CA

Abstract: Current immunomodulatory therapies for multiple sclerosis (MS) have limited benefit. Oligodendrocyte (OL) death and demyelination induced by inflammatory attack and subsequent axonal degeneration are key features of MS. Inflammation-induced endoplasmic reticulum (ER) stress are thought to promote tissue damage in MS. ER stress can trigger the unfolded protein response (UPR), the innate cytoprotective response, which is orchestrated by three transmembrane signal transducers, including activating transcription factor 6 (ATF6). Although the ATF6 arm is not as well characterized, a recent study showed that ATF6 deficiency exacerbated EAE severity and oligodendrocyte loss, indicating its important role in protecting oligodendrocytes from inflammation. AA147, a newly discovered small compound, has been shown to activate the ATF6 pathway through reducing disulfides and enhancing trafficking to Golgi and then nucleus. Unexpectedly, AA147 might activate the antioxidative nuclear factor erythroid 2-related factor 2 (NRF2) pathway in certain neuronal cell lines. NRF2 pathway is known to both maintain intracellular redox homeostasis and mediate anti-inflammatory responses. The purpose of this study is to explore the therapeutic potential of AA147 and its underlying mechanism in a MS mouse model, experimental autoimmune encephalitis (EAE). We demonstrate that AA147 treatment significantly reduced the clinical symptoms in EAE, while deficiency of ATF6 in OLs abrogates the protective effect. Additionally, AA147 provided protection to OL and reduces CNS inflammation and ER stress. Importantly, AA147 significantly increased the expressions of Grp78, an ATF6 target gene, in oligodendrocytes, while enhancing levels of Grp78 as well as Ho-1, an NRF2 target gene, in microglia. Surprisingly, AA147 had no effect on the reactive oxidative species levels in the spinal cords of EAE mice, yet it increased the number of microglia exhibiting anti-inflammatory profile. Overall, our results suggest AA147 as a potential therapeutic opportunity for MS by promoting oligodendrocyte survival and regulating microglia status through distinct mechanisms.

Disclosures: K.P. Bruce: None. **M. Aksu:** None. **K. Kaschke:** None. **I. Steckler:** None. **E. Garcia:** None. **M. Wong:** None. **A. Cogswell:** None. **J.R. Podojil:** None. **J.W. Kelly:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jeffery Kelly and R. Luke Wiseman are shareholders and scientific advisory board members that have licensed UPR activating

compounds including AA147 for therapeutic development. **R.L. Wiseman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jeffery Kelly and R. Luke Wiseman are shareholders and scientific advisory board members that have licensed UPR activating compounds including AA147 for therapeutic development.. F. Consulting Fees (e.g., advisory boards); Jeffery Kelly and R. Luke Wiseman are shareholders and scientific advisory board members that have licensed UPR activating compounds including AA147 for therapeutic development.. **S.D. Miller:** None. **B.J. Popko:** None. **Y. Chen:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.103/LBA166

Topic: B.11. Neuro-Oncology

Title: Mechanism study of circ-ZEB1.33-miR200a-MAGED4 regulating malignant biological behavior of gliomas

Authors: *C. XUE[1,2], W. LIU[3,1], B. LUO[2];
[1]Nantong Univ., Nantong, China; [2]Dept. of Histology and Embryology, Sch. of Basic Med. Sci., Guangxi Med. Univ., Nanning, China; [3]Tongji Univ., Shanghai, China

Abstract: Melanoma-associated antigen MAGED4 is a potential target for cancer immunotherapy. Overexpression of miR-200a in glioma cells can inhibit MAGED4 expression, but the regulatory mechanism of its expression remains unclear. Previous studies have found that circular RNAs (circRNAs) can bind to miRNAs, thereby relieving miRNA-mediated repression of their target genes. This study aims to identify circRNAs in gliomas that can bind to miR-200a, investigate their functions and regulatory mechanisms, and provide new insights for targeting MAGED4 in glioma immunotherapy.In this study, five glioblastoma tissues and five normal brain tissues were collected for circRNA high-throughput sequencing, which identified 879 differentially expressed circRNAs, with 224 upregulated and 655 downregulated. Using ENCORI (https://starbase.sysu.edu.cn/), miR-200a target circRNAs were predicted and intersected with the upregulated circRNAs from the sequencing results, identifying circ-ZEB1.33 as the target for further study.Subsequently, qRT-PCR was used to detect circ-ZEB1.33, MAGED4 mRNA, and miR-200a mRNA in 30 glioma tissues, 5 normal brain tissues, and 5 glioma cell lines. The results showed high expression of circ-ZEB1.33 and MAGED4 mRNA, and low expression of miR-200a mRNA in glioma tissues and cell lines (U251, A172). Wild-type and 3'UTR mutant vectors of circ-ZEB1.33 and MAGED4 were constructed and co-transfected with miR-200a mimics into glioma cells. Luciferase reporter assays confirmed that circ-ZEB1.33 regulates MAGED4 through miR-200a.In U251 and A172 cells, silencing circ-ZEB1.33 decreased the expression of MAGED4 mRNA and protein levels. CCK8 assays were

used to detect proliferation, while wound healing and Transwell assays were used to detect migration and invasion. Compared to the control group, silencing circ-ZEB1.33 significantly inhibited cell proliferation, migration, and invasion. Additionally, co-transfection with miR-200a inhibitors or overexpression of MAGED4 could counteract the inhibitory effects of circ-ZEB1.33 silencing.In conclusion, circ-ZEB1.33 affects MAGED4 expression by targeting miR-200a, thereby regulating malignant biological behaviors such as proliferation, migration, and invasion of glioma cells.

Disclosures: C. Xue: None. **W. Liu:** None. **B. Luo:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.104/LBA167

Topic: B.11. Neuro-Oncology

Support: CONAHCYT Grant CBF2023-2024-1982

Title: Phototoxicity study of zinc phthalocyanine-folic acid-TiO_2 nanoparticles in glioma cells.

Authors: *C. RODRÍGUEZ-PÉREZ[1], E. ORTIZ[2], M.-R. MANRIQUEZ[3], J. GUSTAVO[4]; [1]Natl. Inst. of Neurol. and Neurosurg., MEXICO CITY, Mexico; [2]Natl. Inst. of Neurol. and Neurosurg., Mexico City, Mexico; [3]ISIQIE, IPN, Mexico City, Mexico; [4]UAM-X, Mexico city, Mexico

Abstract: Glioblastoma is the most aggressive brain tumor, and its main treatments are surgery, radiotherapy and chemotherapy, but still, the average life expectancy is 12-18 months. The generation of new therapies is a challenge that requires the development of innovative strategies, and nanotechnology has emerged as a promising tool. Photodynamic therapy involves a photosensitizer application followed by light activation to generate reactive oxygen species (ROS) at the tumor site to kill cancer cells. The aim of this study was to determine the phototoxicity of zinc phthalocyanine- folic acid-TiO_2 nanoparticles (NPs) on glioma cells. The effect *in vitro* of NPs under different conditions, such as concentration, incubation time, and distance of irradiation source was evaluated in glioma cell lines (U87, U251, and U87) using MTT and DCFH-DA assays. Upon irradiation of NPs, cytotoxicity resulted in a significant viability reduction and an enhanced intracellular ROS formation of various glioma cells.

Disclosures: C. Rodríguez-Pérez: A. Employment/Salary (full or part-time):; INNNMVS. **E. Ortiz:** A. Employment/Salary (full or part-time):; INNNMVS. 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.; CONAHCYT. **M. Manriquez:** A. Employment/Salary (full or part-time):; IPN. **J. Gustavo:** A. Employment/Salary (full or part-time):; UAM.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.011/LBA76

Topic: B.03. Ion Channels

Support: NIH R35 NS127216

Title: State-dependent inhibition of Nav1.8 sodium channels by VX-548, VX-150, A-887826, and LTGO-33: relief of inhibition by depolarization

Authors: *S. JO, A. FUJITA, T. OSORNO, R. STEWART, P. VAELLI, B. P. BEAN; Harvard Med. Sch., Boston, MA

Abstract: Nav1.8 sodium channels are expressed in primary pain-sensing neurons with little expression in most other neurons, making them an attractive drug target. We found that several Nav1.8 inhibitors, including A-887826, VX-548 (suzetrigine), and VX-150, have an unusual property whereby inhibition is relieved by depolarization. For example, inhibition by VX-548 is very potent when applied at -100 mV (IC_{50} ~0.3 nM; 27 °C, automated patch clamp) but inhibition can be ~90 % removed by a 200-ms depolarization to +120 mV. Reinhibition when voltage is returned to -100 mV occurs at a rate proportional to drug concentration, consistent with the idea that drug dissociates from channels in the depolarized state with voltage sensors activated and then rebinds when channels return to a high-affinity resting state with voltage sensors deactivated. Relief of inhibition from depolarized channels might be undesirable if it occurred with action potential (AP) waveforms at physiological frequencies. We explored the extent of such “reverse use-dependence” for VX-548, A-887826 and LTGO-33, another compound showing relief by depolarization, doing experiments at 37 °C with AP waveforms applied at 20 Hz. In initial experiments, we found that the potency of VX-548 is significantly temperature-dependent, with weaker binding (to resting state channels) at 37 °C (IC_{50} ~0.3 nM, manual patch clamp) than at 22 °C (~0.1 nM). Using AP waveforms recorded from human DRG neurons at 37 °C, we found that there is minimal reversal of VX-548 inhibition with AP waveforms applied at 20 Hz. Similarly, there was almost no reversal of LTGO-33 inhibition with AP waveforms at 20 Hz. In contrast, there was substantial reversal of inhibition of A-887826. The differences among the compounds can be understood by differences in the voltage-dependence and kinetics with which the compounds dissociate from depolarized channels and rebind to resting state channels. VX-548 required the strongest depolarizations for relief (midpoint near +40 mV), and relief was slow (tau > 300 ms at +20 mV) , so almost no relief occurred during an AP waveform. Relief from A-887826 required weaker depolarizations

(midpoint ~+10 mV) and was much faster, so some relief occurred during each AP waveform and accumulated during 20 Hz trains. Interestingly, LTGO-33 required even weaker depolarizations for relief (midpoint near -10 mV) and relief was even faster than for A-887226, but reinhibition between AP waveforms was much faster than for A-887826, so that relief did not accumulate during AP trains at 20 Hz.

Disclosures: S. Jo: None. **A. Fujita:** None. **T. Osorno:** None. **R. Stewart:** None. **P. Vaelli:** None. **B.P. Bean:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.012/LBA77

Topic: B.03. Ion Channels

Support: NIH R35 NS127216

Title: Subtype selectivity of clinically-used sodium channel inhibitors

Authors: *A. FUJITA, S. JO, T. OSORNO, P. VAELLI, R. STEWART, B. P. BEAN; Dept. of Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Voltage-dependent sodium channels are a proven clinical target for treating epilepsy, arrhythmias, and other disorders. Recent efforts to develop new sodium channel inhibitors for pain and epilepsy have focused on finding compounds that are selective for particular subtypes of sodium channels, for example inhibiting Nav1.7 and Nav1.8 channels expressed in nociceptors without inhibiting cardiac Nav1.5 channels. Yet, virtually all sodium channel inhibitors currently given to patients are relatively non-selective. A priori, non-selective inhibition of sodium channels would seem like a terrible idea, since they are vital for functions such as thinking, moving, and cardiac function. Using automated patch clamp technology (Sophion Qube 384) to enable comprehensive dose-response studies on multiple sodium channel types, we characterized the interaction of a variety of clinically-used sodium channel inhibitors, including amitriptyline, bupivacaine, carbamazepine, cannabidiol, phenytoin, lamotrigine, lacosamide, lidocaine, and riluzole, on multiple sodium channel types, including Nav1.5, Nav1.6, Nav1.7, and Nav1.8. [All of the compounds inhibited all of the channel types but with varying potencies. All of the compounds were strongly state-dependent, with more potent inhibition when channels are partly inactivated.] It is striking that all of the drugs have relatively little selectivity among the different sodium channels, despite being clinically useful and generally safe. Perhaps most strikingly, many of the compounds are highly effective inhibitors of cardiac Nav1.5 channels, yet have minimal effects on cardiac function. The likely explanation is likely two-fold: first, cardiac atrial and ventricular muscle has much more negative resting

potential (near -88 mV) than most neurons (typically -85 to -60 mV), so that a larger fraction of channels are in the resting state with weak drug binding, and second, cardiac muscle cells have a high density of sodium channels, so that inhibition of a substantial fraction of sodium channels can be tolerated with minimal functional consequences. The strong state-dependence of drug action also likely accounts for functional selectivity of drug on neurons to inhibit pathophysiological conditions like pain and epilepsy without major disruption of normal functions.

Disclosures: A. Fujita: None. **S. Jo:** None. **T. Osorno:** None. **P. Vaelli:** None. **R. Stewart:** None. **B.P. Bean:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.013/LBA78

Topic: B.03. Ion Channels

Support: NIH R35 NS127216

Title: Roles of Nav1.7 and Nav1.8 channels in firing of human dorsal root ganglion neurons

Authors: *R. STEWART[1], T. OSORNO[1], S. JO[1], A. FUJITA[1], P. VAELLI[1], K. CARLIN[2], A. FERRAIUOLO[2], C. MAI[2], G. BAUTISTA[2], B. P. BEAN[1];
[1]Neurobio., Harvard Med. Sch., Boston, MA; [2]AnaBios, San Diego, CA

Abstract: Both Nav1.7 and Nav1.8 voltage gated sodium channels are known to be expressed by human primary pain-sensing neurons, and both have been the focus of drug development efforts to find new non-opioid therapies for pain. We explored how each channel type contributes to overall excitability of human dorsal root ganglion (DRG) neurons using pharmacology, doing voltage clamp and current clamp experiments at both 22 °C and 37 °C. We used a preparation of neurons enzymatically dissociated from human DRG neurons and maintained in tissue culture for up to 5 days. The great majority of neurons (>90%) that appeared healthy had currents activated by capsaicin and large components of Nav1.8 current (sensitive to 10 nM or 30 nm VX-548), consistent with being nociceptors. In voltage clamp experiments, it proved possible to separate components of Nav1.7 and Nav1.8 currents by sensitivity to GsAF-1 (30-100 nM) and VX-548 (10-30 nM), respectively. As expected, Nav1.7 currents activated at more negative voltages than Nav1.8 currents, activated and inactivated more rapidly, and inactivated at more negative voltages (midpoint near -55 mV) than Nav1.8 currents (midpoint near -20 mV). In most neurons, current evoked by a voltage step to 0 mV from -80 mV had large components from both Nav1.7 and Nav1.8 channels, and together the two currents typically accounted for >90% of overall sodium current, with a small and variable component from TTX-sensitive channels that

were not blocked by GsAF-1. In action potential clamp experiments using waveforms from neurons that fired repetitively in response to 1-s long current steps, Nav1.7 and Nav1.8 currents were both prominent in the first action potential while Nav1.8 was dominant in later action potentials, although Nav1.7 current was often not completely inactivated in the later action potentials. Consistent with a role of Nav1.8 channels in promoting repetitive firing, in experiments at 22 °C application of 10 nM VX-548 usually (83% of the time) converted repetitive firing to a single action potential. Interestingly, however, at 37 °C, almost a third of the neurons could still fire repetitively in the presence of VX-548, even when the concentration of VX-548 was increased to 30 nM. Overall the results show that although capsaicin-sensitive human DRG neurons have large Nav1.8 currents that help sustain repetitive firing, they also have large Nav1.7 currents and a fairly large fraction of neurons can still fire repetitively even in the presence of concentrations of VX-548 100-fold higher than the IC50 for Nav1.8 inhibition.

Disclosures: R. Stewart: None. **T. Osorno:** None. **S. Jo:** None. **A. Fujita:** None. **P. Vaelli:** None. **K. Carlin:** None. **A. Ferraiuolo:** None. **C. Mai:** None. **G. Bautista:** None. **B.P. Bean:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.014/LBA79

Topic: B.03. Ion Channels

Support: NIH R35 NS127216

Title: Distinct roles of Nav1.7 and Nav1.8 in mouse nociceptor excitability revealed by sodium channel inhibitors

Authors: *T. OSORNO, R. STEWART, S. JO, A. FUJITA, P. VAELLI, B. P. BEAN; Neurobio., Harvard Med. Sch., Boston, MA

Abstract: The voltage-gated sodium channels Nav1.7 and Nav1.8 have emerged as attractive targets for the development of novel pain therapeutics due to their prominent expression in sensory neurons and genetic links to pain phenotypes in humans. Understanding how these ion channels contribute to the excitability of pain-sensing neurons is a key step in the development of novel analgesics. Here, we used the peptide toxin GsAF-I in combination with the Nav1.8 blocker VX-548 (suzetrigine) to dissect Nav1.7 and Nav1.8 currents in mouse peptidergic nociceptors (CGRP+). In voltage clamp experiments. GsAF-I inhibited a fast, tetrodotoxin (TTX)-sensitive sodium current consistent with Nav1.7 channels, whereas VX-548 inhibited a slower, TTX-resistant sodium current matching Nav1.8 channels. There was little or no cross-over in the components of current inhibited by the two agents. We used action potential clamp to

examine the roles of Nav1.7 and Nav1.8 currents in repetitive firing using pre-recorded waveforms of mouse nociceptor repetitive firing. The Nav1.8 (VX-548-sensitive) currents accounted for the majority of the sodium current during repetitive firing, especially after the first action potential. In contrast, the Nav1.7 (GsAF-I) sensitive currents were only prominent in the initial action potential, quickly disappearing in later action potentials due to inactivation of Nav1.7. The patterns of contributions of Nav1.7 and Nav1.8 currents to initial and later action potentials during repetitive firing were similar at 22°C and 37°C. Finally, we tested the roles of Nav1.7 and Nav1.8 channels in action potential firing using current clamp recordings at both 22°C and 37°C . Consistent with the action potential clamp experiments, repetitive firing at 22°C was abolished in the presence of 1 μM VX-548, but not GsAF-I. It is important to note that VX-548 exhibited much lower potency on native mouse Nav1.8 channels (IC50 126 nM) compared to human Nav1.8 channels (IC50 0.27 nM), requiring micromolar concentrations to achieve full block of mouse Nav1.8 channels. At these concentrations we observed off-target effects of VX-548 on Kv currents in the neurons, which were especially prominent at 37°C, limiting our interpretation of current clamp experiments.

Disclosures: T. Osorno: None. **R. Stewart:** None. **S. Jo:** None. **A. Fujita:** None. **P. Vaelli:** None. **B.P. Bean:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.015/LBA80

Topic: B.03. Ion Channels

Title: Standardized kinetic characterization of calcium dependent potassium channels

Authors: *K. H. ARULKANDARAJAH[1], E. LOGETTE[2], M. HERZOG[2], M. JOFFRAUD[2], E. SCANTAMBURLO[2], A. JOURNE[2], H. MARKRAM[2], R. RANJAN[2];
[1]EPFL, Blue Brain Project, Geneva, Switzerland; [2]Blue Brain Project, Brain and Mind Institute, EPFL, Lausanne, Switzerland

Abstract: Voltage-gated ion channels (VGICs) are membrane proteins that allow ions to pass through cell membranes. They play essential roles in action potential generation and propagation in neurons, muscle contraction, cardiac rhythm regulation. Among VGICs, the calcium-activated potassium (KCa) channels, mainly regulated by intracellular calcium concentrations, are crucial for maintaining cellular excitability and function. There are three main subtypes of KCa channels: BK (big-conductance), IK (intermediate-conductance), and SK (small-conductance). Dysfunction in these channels is linked to conditions such as hypertension, asthma, epilepsy, and neurodegenerative disorders.In our ongoing effort to systematically characterize the kinetics of VGICs, we have studied all eight members of the KCa channel family (Slo1, Slo2.1, Slo2.2,

Slo3, SK1, SK2, SK3, and SK4). Using isogenic CHO cell lines over-expressing single KCa channel types in a tetracycline-inducible manner, we employed both manual and automated whole-cell patch-clamping methods to investigate their biophysical properties. This approach enabled us to systematically measure the effects of temperature, voltage, and intracellular calcium concentration on all KCa channels. Our comprehensive dataset, along with the corresponding mathematical models, will be made publicly available at Channelpedia (https://channelpedia.epfl.ch), providing a valuable resource for further research in this field.

Disclosures: K.H. Arulkandarajah: None. **E. Logette:** None. **M. Herzog:** None. **M. Joffraud:** None. **E. Scantamburlo:** None. **A. journe:** None. **H. Markram:** None. **R. Ranjan:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.016/LBA81

Topic: B.03. Ion Channels

Title: Identification of venom fractions as TREK-1 modulators using Qube 384 automated patch clamp system

Authors: A. S. HAWORTH[1], E. L. VEALE[2], A. MATHIE[2], ***C. MATHES**[1], S. A. TRIM[3], E. B. STEVENS[1];
[1]Metrion Biosci. Ltd., Cambridge, United Kingdom; [2]Universities of Greenwich and Kent at Medway, Kent, United Kingdom; [3]Lab., Venomtech Ltd, Sandwich, United Kingdom

Abstract: TREK-1, a member of the two-pore domain K^+ (K_{2P}) channel family, is implicated in a range of neurological disorders due to its role in regulating neuronal membrane potential through a background K^+ conductance (Djillani *et al*., 2019). In particular, TREK-1 represents an attractive drug target for treatment of pain. Here, we develop a high throughput electrophysiological assay capable of detecting both potentiators and inhibitors of hTREK-1 stably expressed in CHO cells. The assay was validated with various reference compounds and used to screen a library of venom fractions (T-VDA™, Venomtech, UK) to identify novel hTREK-1 modulators. Initial assay development was performed on a QPatch 48 platform to optimise conditions suitable for detection of both activators and inhibitors. Baseline channel amplitude (in the absence of a small molecule potentiator) was insufficient for screening of inhibitors. Culturing cells at 30° C and in the presence of sodium butyrate (3 mM, 48 h) provided the most reliable method of increasing baseline current. Current amplitudes at baseline and following activation with BL-1249 (10 μM) were 2.29 ± 0.52 nA and 27.48 ± 7.50 nA (Mean ± SEM, n = 4), respectively, providing a suitable assay window for screening both inhibitors and potentiators. The assay was progressed to Qube 384 for screening of venom fractions. The assay paradigm consisted of two vehicle applications, followed by two test compound applications (at

a single concentration). A variety of reference compounds were tested. Potency values for TREK-1 inhibitors amitriptyline, $BaCl_2$, fluoxetine and quinidine (IC_{50}s of 8.1 μM, 1.5 mM, 10.8 μM and 77.6 μM, respectively) and TREK-1 activators BL-1249 and GI-530159 (EC_{50}s of 5.1 μM and 5.7 μM, respectively) were similar to published data. Finally, a library of venom fractions was screened against hTREK-1. A total of 591 fractions at 10 ng/μl were successfully screened. Significance was defined as a venom fraction that produced a response ± 50 % of the vehicle response. A total of 32 (5.41%) and 4 (0.68%) fractions were identified as potentiators and inhibitors, respectively. Potentiators were enriched with arachnid venoms, with the most efficacious fraction belonging to the scorpion, *Heterometrus silenus*, *w*hereas inhibitors were enriched with snake venoms. A fraction from the elapid, *Oxyuranus scutellatus*, was the most efficacious inhibitor. Here, we have developed a robust hTREK-1 screening assay on the Qube 384 platform. The optimized screening assay was successfully employed in the screening of a venom library, detecting peptides with both inhibitory and potentiating modalities.
Djillani *et al*., 2019, Front Pharmacol 2019; 10: 379

Disclosures: **A.S. Haworth:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd.. **E.L. Veale:** None. **A. Mathie:** None. **C. Mathes:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd. **S.A. Trim:** A. Employment/Salary (full or part-time):; Venomtech Ltd. **E.B. Stevens:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd..

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.017/LBA82

Topic: B.04. Synaptic Transmission

Support: NSERC 05100-2020
FRQNT

Title: Rim1/2 are not required for phasic dopamine release in vivo

Authors: *M. M. MORRIS, K. CAVALLO, C. COSTA, C. SAVIGNY, J. P. BRITT;
Psychology, McGill Univ., Montreal, QC, Canada

Abstract: Dopamine (DA) regulates movement, motivation, and reward valuation. Not only do natural fluctuations in DA correlate with reward prediction errors, but manipulations of DA can drive learning when it otherwise would not occur and prevent learning when it otherwise would occur. However, the question of whether brief fluctuations in DA signaling are truly necessary for learning remains unanswered, because some basal level of DA is needed for healthy network activity, intentional movements, and motivation. Perhaps phasic DA signaling only appears to be

necessary for learning because a basal DA tone is needed to support network function and perform any non-reflexive action. To determine whether phasic release is truly necessary for learning would require clamping DA levels above the threshold necessary for healthy network activity and movement. The presynaptic scaffolding proteins RIM1/2 organize the active zone protein complex which facilitates fast and spatially precise neurotransmitter release (Südhof, 2012). Previous work has established that RIM1/2 are essential for action potential-evoked (tonic and phasic) DA release *in vitro* but that removing these proteins from DA neurons still leaves enough basal DA (~30% of normal) to support healthy signaling and movement. (Liu et al., 2018; Robinson et al., 2019). Using a genetically modified mouse line with a conditional RIM1/2 knockout in DA neurons ($RIMKO^{DA}$) we investigated whether phasic DA release is essential for learning and performance on a Pavlovian task. Water restricted $RIMKO^{DA}$ mice and control littermates completed a headfixed Pavlovian task in which they could lick for water one second after tone presentations, while we recorded nucleus accumbens DA signaling using the fluorescent sensor $GRAB_{DA}3.0$. After 10 training sessions, mice completed three extinction sessions. There were no differences in task performance between $RIMKO^{DA}$ and control mice during training or extinction sessions, and DA responses to water reward and to reward omission were comparable between $RIMKO^{DA}$ mice and controls. Our findings indicate that although RIM protein is essential for evoked DA release in slice, it is not required for evoked DA release in the NAc in the intact brain. Our work suggests that DAergic release machinery is robust to disruption and may rely on redundant processes *in vivo* that are not functional in slice. More generally, our work highlights the disparity between work done *in vivo* and *in vitro* and the need for more comparative studies between the two.

Disclosures: M.M. Morris: None. **K. Cavallo:** None. **C. Costa:** None. **C. Savigny:** None. **J.P. Britt:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.018/LBA83

Topic: B.04. Synaptic Transmission

Support: NSF IOS-1257363
CHEO Research Institute
Colorado State University CRC grant

Title: A novel synaptotagmin mutation results in congenital myasthenic syndrome deficits

Authors: A. R. BOLLEGAR[1], M. J. PLISKIN[1], C. WARING[3], J. A. SEGGIO[3], G. MCMACKEN[4], H. LOCHMULLER[5], ***N. E. REIST**[2];
[1]Neurosciences, [2]Biomed. Sci., Colorado State Univ., Fort Collins, CO; [3]Biol. Sci., Bridgewater

State Univ., Bridgewater, MA; [4]Royal Victoria Hosp. Belfast, Belfast, United Kingdom; [5]Inst. of Genet. Med., Newcastle Univ., Newcastle Upon Tyne, United Kingdom

Abstract: Synaptotagmin (syt) 2 is the Ca2+ sensor for neurotransmitter release at the human neuromuscular junction. Mutations in syt2 are linked to the etiology of congenital myasthenic syndromes (CMS). Hallmarks of syt-based CMS include decreased transmitter release and muscle weakness. Recently, A *de novo* point substitution of an aspartate to glutamate (D301E) in syt was identified by whole exome sequencing of a young human patient with a spontaneous CMS. D301 (referred to henceforth as D1) is the first of 5 negatively-charged residues in the C2B domain of syt coordinating the Ca^{2+} that triggers transmitter release. In model systems, syt-D1N (aspartate to asparagine) does not disrupt release whereas multiple other syt-DtoN mutations in C2B result in severe decreases. Additionally, *in silico* models of syt-D1E do not predict a disruption of the Ca2+-binding pocket nor changes in Ca2+ affinity. Thus, previous work does not indicate an essential role for D1. However, syt-D1E has not been previously studied. To achieve expression similar to human patients, syt-D1E, or a syt-WT control, was expressed from a transgene in flies carrying one copy of the wild type *syt* gene. Here we show that the syt-D1E mutation in these heterozygotes results in a 20% decrease in excitatory junction potential (EJP) amplitude *in vivo* and decreased locomotor activity consistent with muscle weakness. Thus, syt-D1E expressed at the fly neuromuscular junction phenocopies the human patient. In addition, when expressed in the syt-null background, the syt-D1E mutation results in lethality. These results show for the first time that the D1 residue in C2B is essential for synaptotagmin function and that syt-D1E causes CMS-like symptoms. Methods: Transgenic syt-D1E, or syt-WT control, was expressed in fly neurons of males and females. Western analysis shows equal expression from the syt transgene and the single native gene. A student t-test demonstrated statistical significance between EJP amplitudes in mutants vs controls ($n=17$, $p<0.001$). Data and analysis replicated by a second investigator. Locomotor activity was measured using a Drosophila Activity Monitoring assay. Both males and females showed statistically significant decreases in locomotor activity between mutants and controls ($n=47$, $p<0.0002$).

Disclosures: A.R. Bollegar: None. **M.J. Pliskin:** None. **C. Waring:** None. **J.A. Seggio:** None. **G. McMacken:** None. **H. Lochmuller:** None. **N.E. Reist:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.019/LBA84

Topic: B.04. Synaptic Transmission

Support: Senior Fellowship-DBT/Wellcome Trust India Alliance
Institute of Eminenece Program, Indian Institute of Science

SERB, India
Ignite Life Science
PMRF, India

Title: Structured lattice organization of molecules at nanoscale govern information transfer at single synapses.

Authors: P. NETRAKANTI[1], V. DHINGRA[2], S. NADKARNI[3], ***D. NAIR**[2];
[1]Indian Inst. of Sci., Bangalore, India; [2]Indian Inst. of Sci., Bengaluru, India; [3]IISER Pune, Pune, India

Abstract: Synapses, critical for brain communication, rely on precise protein arrangements to ensure efficient information transmission. However, the mechanisms behind synaptic information representation, especially at the finest scale of information processing in the brain, remain elusive. Leveraging advanced technologies such as Single Molecule and Ensemble Super Resolution Microscopy, multivariate statistics, and molecular modeling, we evaluate alterations in thermodynamic signatures, distribution in synaptic functional zones, and nanoscale biochemical maps that emerge within single synapses. In the last decade our lab and others have accumulated compelling evidence confirming that signal processing at synapses is regulated using nanoscale machinery, which can assemble at the postsynaptic membrane and is at least 5-10 times smaller than the synaptic area itself. We present new insights in to the nanoscale distribution of critical synaptic markers, including Bassoon and Voltage-Gated Calcium Channels (VGCCs) at the active zone, as well as the AMPA receptor subunit at the postsynaptic density (Netrakanti et al, unpublished) . From the molecular localization and the heterogeneity in their distribution within synapses, we extract molecular fingerprints contributing to the different outcomes observed in young and mature neurons during homeostatic scaling, a process integral to information processing diversity. These findings provide persuasive evidence that nanodomains result from the condensation of VGCCs and receptors, either independently or in association with scaffolding molecules, following the principles of liquid-liquid phase separation (Rajeev et al, 2022; Dhingra et al, unpublished). In summary, our research emphasizes that the regulation of release events at synapses is a multifaceted process influenced by the coordinated spatial arrangement of molecules at the nanoscale within the active zone and postsynaptic density. In essence, we integrate the concepts of representing uncertainty, probabilistic inference, and the nanoscale spatial organization of these molecules as reference frames to construct a comprehensive model of the synapse as a nanoscale information processing machine (Netrakanti et al (unpublished), Dhingra et al (unpublished).

Disclosures: P. Netrakanti: A. Employment/Salary (full or part-time):; Indian Institute of Science, Bangalore, India. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); ICMR INDIA. **V. Dhingra:** A. Employment/Salary (full or part-time):; Indian Institute of Science, Bangalore, India. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PMRF, India. **S. Nadkarni:** A. Employment/Salary (full or part-time):; IISER, PUNE. **D. Nair:** A. Employment/Salary (full or part-time):; Indian Institute of Science, Bangalore, India. C. Other Research Support (receipt of

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Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.020/LBA85

Topic: B.04. Synaptic Transmission

Support: NIH/NINDS Grant R01 NS123050
USAMRMC/CDMRP (DoD) TSCRP Concept Award TS080043
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University of Iowa OVPR Biological Science Funding Program "Investigating Role of Cyclin G2 Elevation During Cerebellar Development and the Potential Link of its Dysregulation in Medulloblastomas."
NIH/NIGMS Grant R01GM56900-05

Title: The unconventional cyclin and beta-catenin interacting protein, CCNG2, influences spine density and synaptic activity of CA1 hippocampal neurons

Authors: X. XING[1], A. HERGARDEN[3], E. NGUYEN[4], I. TYLER[2], A. JACOBI[2], V. CHANDRASEKAR[2], R. J. WILSON[5], P. J. LEIN[6], J. W. HELL[7], ***M. C. HORNE**[8];
[1]Dept. of Pharmacol., [2]Univ. of California, Davis, Davis, CA; [3]Pharmacol., Univ. of California Davis, Davis, CA; [4]UCLA, Losa Angeles, CA; [6]VM: Mol. Biosci., [7]Dept. of Pharmacol., [5]UC Davis, Davis, CA; [8]Pharmacol., Univerity of California, Davis, Davis, CA

Abstract: Cyclin G2 (CycG2) is an unconventional cyclin homolog well expressed in brain. In non-neuronal cells. CycG2 gene (*CCNG2*) expression is upregulated during cellular stresses, promoting G_2-phase and G_1-phase cell cycle arrest responses to DNA damage and pharmacological blockade of proliferation pathways. We found that transcripts for the CycG2 gene (*Ccng2*) in rodents increased during postnatal cerebellar development, reaching peak levels as granule cell precursors exit the cell cycle and differentiate into neurons. We determined by immunoblot analysis and immunofluorescence microscopy that CycG2 protein expression is abundant in hippocampal and cerebellar neurons and partially partitions to synaptosomes and PSD fractions. As our previous work demonstrated that CycG2 forms a catalytically active complex with the serine/threonine phosphatase PP2A/B' and C subunits in cerebellar tissues, we examined whether neuronal CycG2 interacts with other PP2A associated proteins, including β-catenin. Through immunoprecipitation, pulldown experiments and fluorescence polarization assays we found compelling evidence that CycG2 directly associates with β-catenin, and that β-catenin binds just N-terminal to the PP2A/C and B' subunit binding sites in the carboxy terminus of CycG2. Intriguingly, parallel studies of others in non-neuronal mitotic cell types linked

CycG2 with β-catenin/Wnt signaling functions, repressing β-catenin nuclear functions while augmenting its role in non-neuronal cell adhesion. Imaging of Golgi-stained hippocampi of *Ccng2* KO & WT mice indicates that KO neurons exhibit decreased spine density compared to that in WT animals. Moreover, electrophysiological recordings of CA1 neurons in hippocampal slices from these mice show a decrease in mEPSC frequency and peak amplitude (PA) in the *Ccng2* KO relative to those in WT mice. Ongoing work includes further assessment of how CycG2 loss may affect the localization and interactions of its neuronal binding partners.

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Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.021/LBA86

Topic: B.04. Synaptic Transmission

Support: NIH grant R01 MH119283

Title: Sex differences in the norepinephrine regulation of CRH neurons of the hypothalamic paraventricular nucleusneurons of the hypothalamic paraventricular nucleus

Authors: *R. C. DOS-SANTOS[1,2], C. D. FRIEDMAN[2], B. SWEETEN[2], J. G. TASKER[2,3]; [2]Cell and Mol. Biol., [3]Tulane Brain Inst., [1]Tulane Univ., New Orleans, LA

Abstract: There are profound sex differences in the neuroendocrine response to stress that suggest that the control of PVN CRH neurons differs between the sexes. Norepinephrine (NE) acts on corticotropin releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus (PVN) to initiate the neuroendocrine response to stress, although it is not known whether the NE modulation of CRH neurons is sex-dependent. In male mice, NE activates postsynaptic α1 adrenoreceptors to trigger a neuron-astrocyte retrograde circuit that stimulates presynaptic excitatory circuits. In the present study, we assessed the effects of NE on the PVN CRH neurons of male and female mice using whole-cell patch clamp recordings in ex vivo hypothalamic slices. The resting membrane potential, spontaneous firing frequency, and input resistance did not differ between PVN CRH neurons from male and female mice. NE caused a similar prolonged inward membrane current and depolarization in the majority of CRH neurons from both male and female mice (60% males, 55% females). Interestingly, the excitatory synaptic input to PVN-CRH neurons was different between the sexes. At baseline, the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) was higher in CRH neurons from males than from females, and NE caused an increase in the frequency of sEPSCs in the CRH neurons

from males, but not females. Therefore, the postsynaptic effect of NE on PVN CRH neurons is similar in males and females, but NE activates a presynaptic excitatory circuit in males, but not females, that is likely to shape the sex-dependent response of PVN-CRH neurons to NE-dependent stress activation. Supported by NIH grant R01 MH119283.

Disclosures: R.C. dos-Santos: None. **C.D. Friedman:** None. **B. Sweeten:** None. **J.G. Tasker:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.022/LBA87

Topic: B.04. Synaptic Transmission

Support: KBRI funded by the Ministry of Science and ICT (22-BR-02-02 to J.K.)
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NRF Grant (NRF-2022R1F1A1063437 to M.K.).
NRF Grant (NRF-2023R1A2C2005346 to J.N.).

Title: The mineralocorticoid receptor and extra-synaptic NMDA receptor in the lateral habenula involve in the vulnerability to early life stress in the maternal separation model

Authors: *M. KANG[1], J. NOH[2], J. KIM[3];
[1]Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; [2]Dankook Univ., Youngin, Korea, Republic of; [3]Emotion, Cognition and Behavior Res. group, Korea Brain Res. Institude (KBRI), Daegu, Korea, Republic of

Abstract: The lateral habenula (LHb) plays a pivotal role in regulating emotional responses during stress reactions, and its hyperactivity has been associated with depression. Recently it has been demonstrated that chronic early-life stress results in individual differences in stress vulnerability among rodents. However, how synaptic function in the LHb varies between susceptibility and resilience to early life stress remains elusive. In this study, we used a maternal separation model to assign animals with different stress vulnerabilities into groups and investigated the synaptic responses in the LHb. Our findings indicate that synaptic long-term depression (LTD) was impaired and extra-synaptic LTD was enhanced in the LHb of the susceptible group. To mimic the synaptic alteration in stress situations, when administered corticosterone, a stress hormone, the intervention appeared to impair synaptic LTD in the LHb of the control group, through the activation of mineralocorticoid receptors (MR). Indeed, there was an up-regulation of MR mRNA observed in the susceptible group. Following there was an up-regulation of both NR2A and NR2B subunits in the LHb. These results indicated that MR and extra-synaptic NMDA receptors in LHb are critically engaged in the susceptibilities to stress.

Furthermore, our findings propose potential therapeutic targets for the alleviating stress-related symptoms.

Disclosures: M. Kang: None. **J. noh:** None. **J. Kim:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.023/LBA88

Topic: B.04. Synaptic Transmission

Support: NIH Grant 5R35NS116852

Title: Characterizing $GABA_A$ responses in organotypic hippocampal slice culture using voltage imaging and whole-cell patch clamp

Authors: *T. SHIU[1], K. P. LILLIS[3], K. J. STALEY[2];
[2]Neurol., [1]Massachusetts Gen. Hosp., Boston, MA; [3]Neurol., Harvard Med. School, MGH, Charlestown, MA

Abstract: Release of GABA by interneurons is presumed to exert an inhibitory effect, except in immature brains. However, various studies, including our own, have demonstrated variability in the reversal potential for $GABA_A$ receptors (E_{GABA}) in the healthy hippocampus. Some E_{GABA} values (~12%) surpass the resting membrane potential, indicating a depolarizing $GABA_A$ response. Traditional methods for examining $GABA_A$-mediated responses, such as simultaneous whole cell patch recording to stimulate presynaptic interneurons and measure individual postsynaptic neuron activity due to GABA release, are labor-intensive, low throughput, unable to localize $GABA_A$ responses, and prone to distort E_{GABA}. This exploratory study aims to investigate whether an innovative voltage imaging and whole-cell patch approach can potentially examine the heterogeneity of $GABA_A$ responses by sampling an adequate number of synapses. Individual presynaptic interneurons expressing tdTomato were recorded and/or stimulated via whole-cell patch in organotypic hippocampal slice cultures prepared from P7-8 pups, of both sexes, offspring of DLX-cre mice crossed with tdTomato reporter mice. JEDI-3, a 2-photon-compatible voltage indicator developed by Francois St-Pierre's lab, was expressed under an hSyn promoter in an AAV vector added to the culture media. High-speed two-photon imaging was performed using an 8kHz resonant-galvo scanner over 512x32 pixels at a frame rate of 330Hz. The raw value of the optical response was converted into dynamic fluorescence change ($\Delta F/F_0$), detrended, and filtered using a 1Hz high-pass filter with customized MATLAB code. Membranous JEDI-3 fluorescence signal detected subthreshold membrane voltage activity and action potentials verified via simultaneous whole-cell patch. Subthreshold activity showed an average of -3.8% $\Delta F/F_0$, and action potentials reached up to an average of -8.3% $\Delta F/F_0$. JEDI-3

reliably reported spontaneous spike activities and excitatory and inhibitory postsynaptic activities, indicating its capacity to measure both excitatory and inhibitory $GABA_A$ responses. JEDI-3 signal-to-noise ratio is sufficient to measure large numbers of heterogeneous $GABA_A$-mediated responses in many hippocampal neurons simultaneously, which will make it possible to define the extent of intrasynaptic variability as well as characterize the temporal stability of $GABA_A$ responses.

Disclosures: T. Shiu: None. **K.P. Lillis:** None. **K.J. Staley:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.024/LBA89

Topic: B.04. Synaptic Transmission

Title: Dose dependent differential gene expression following psilocybin administration

Authors: *J. BARNETT;
Mayo Clin., Scottsdale, AZ

Abstract: Dose dependent differential gene expression following psilocybin administration*J. Hudson Barnett, Benjamin Rabichow, Katelin Gibson, Kennedi Todd, Kimberly Olney, John D. Fryer* Psilocybin - a psychotropic compound found in over 200 species of fungi - is currently under phase 3 clinical investigation for Major Depressive Disorder and Treatment Resistant Depression. Psilocybin is a promising drug candidate for a variety of psychiatric disorders for two compelling reasons: 1) like the ubiquitously used Selective Serotonin Reuptake Inhibitors (SSRIs), it targets the serotonin (5-HT) receptor system, and 2) unlike SSRIs, it induces rapid and sustained symptomatic improvement for multiple indications. Psilocybin is a pro-drug that undergoes hepatic dephosphorylation to yield psilocin, the active metabolite with high affinity for 5-HT receptors. Excluding ionotropic $5\text{-}HT_3$, the 5-HT receptor family are transmembrane G protein-coupled receptors (GPCRs) that initiate signaling cascades with downstream effects on neurotransmission, hormone release, and differentially expressed genes (DEGs). Psilocin's action within the 5-HT receptor system remains largely unknown, however, the $5\text{-}HT_{2A}$ receptor is thought to be primarily responsible for its therapeutic effects. To assess the psilocybin evoked transcriptome, we administered psilocybin at a high (1 mg/kg) and low (0.25 mg/kg) doses in male and female C57BL/6J mice and collected hemiforebrain at 4 timepoints over a 28-day period. Total RNA was extracted from N=90 animals and libraries were prepped for sequencing. Compared to vehicle control (0.9% saline), bulk RNAseq analysis of the high and low dose animals showed alterations to DEGs involved in synaptic regulation at 24-hours post psilocybin administration. Interestingly, differential gene expression of high, but not low dose psilocybin was attenuated at the 7-day timepoint. The results of these studies indicate

that high and low doses of psilocybin may have distinct biological effects and encourage further investigation into differential dosing paradigms.

Disclosures: J. Barnett: None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.025/LBA90

Topic: B.05. Synaptic Plasticity

Support: Long-Term Funding by the PAS and U.S. NAS Grant
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NCN Miniatura 7 2023/07/X/NZ1/01669
Ministry of Education and Science of Ukraine Grant PH/28–2023

Title: Hippocalcin interaction with adaptor protein complex 2 underlies localization and duration of hippocampal LTD induction

Authors: B. OLIFIROV[1], O. FEDCHENKO[1], *N. VOITENKO[2,3], V. CHERKAS[4,1], **P. BELAN[1,2];**
[1]Dept. of Mol. Biophysics, Bogomoletz Inst. of Physiol. of NAS of Ukraine, Kyiv, Ukraine; [2]Chair of Biomedicine and Neurosci., Kyiv Academic Univ., Kyiv, Ukraine; [3]Dobrobut Acad. Med. Sch., Kyiv, Ukraine; [4]Lab. of Mol. Assays and Imaging, Inst. of Bioorganic Chem. PAS, Poznan, Poland

Abstract: NMDA receptor (NMDAR)-dependent long-term depression (LTD) at hippocampal glutamatergic synapses is manifested by AMPA receptor endocytosis induced by Ca^{2+} entry through NMDARs. It has been shown that the neuronal calcium sensor protein, hippocalcin (HPCA), functions as a Ca^{2+} sensor in the induction of LTD. Previous biochemical studies indicate a potential interaction of HPCA with the beta subunit of the adaptor protein complex 2 (AP2B1), which may represent an early signaling stage in the initiation of clathrin-mediated endocytosis (CME).This interaction may explain the coupling of NMDAR activation to the regulated endocytosis of AMPARs. However, despite the potential significance of this interaction in LTD regulation, it has not yet been demonstrated or investigated in living hippocampal neurons. Here, we used a live-cell imaging and FRET-based approach applied to rat cultured hippocampal neurons to study the translocation and interaction of fluorescently tagged HPCA and AP2B1 during the induction of chemical LTD. The local iontophoretic application of NMDA, used to induce LTD, resulted in HPCA translocation to the plasma membrane in both dendritic spines and shafts of hippocampal neurons. While translocation with moderate amplitude (0.1-0.3 of $\Delta F/F_0$) was observed in the shafts, translocation to the spine regions

demonstrated a faster rise and 2-3 times higher amplitudes. Simultaneously, a gradual increase in FRET efficiency between HPCA and AP2B1 was observed in spines only, indicating protein interaction in the vicinity of postsynaptic densities. Moreover, the initial rise in FRET efficiency was followed by a plateau phase and did not demonstrate significant decay after the termination of NMDA iontophoresis, implying a long-lasting interaction between the proteins under study. Thus, the prolonged Ca^{2+}-dependent interaction of HPCA with AP2B1 suggests that HPCA may be involved in the late stages of CME rather than being a shuttle for adaptor protein complex 2 delivery to the plasma membrane (Palmer et al., 2005). HPCA translocation and interaction appear to determine the localization of AMPAR endocytosis in the endocytic zones of synapses. The gradual accumulation of HPCA in the endocytic zones and its prolonged interaction with AP2B1 after NMDAR activation may account for the long duration necessary to induce LTD. We conclude that the Ca^{2+}-dependent HPCA/AP2B1 interaction on the plasma membrane may underlie important characteristics of hippocampal LTD.

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Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.026/LBA91

Topic: B.05. Synaptic Plasticity

Support: NCNP Research Grant

Title: Nmda mediated metaplasticity is elevated in the mouse model of fragile x syndrome

Authors: *T. NOMURA[1], C. MORTON[2], A. CONTRACTOR[3];
[1]Northwestern Univ. - Chicago, Chicago, IL; [2]Northwestern Univ., chicago, IL; [3]Neurosci., Northwestern Univ., Chicago, IL

Abstract: Fragile X syndrome (FXS), the most common inherited form of intellectual disability and autism, is caused by the loss of expression of the RNA binding protein Fragile X messenger ribonucleoprotein 1 protein (FMRP) which results in many synaptic disruptions. Several forms of synaptic plasticity have been demonstrated to be altered in the *Fmr1* KO mouse, the mouse model of FXS. Metaplasticity is a higher order form of plasticity that effects the threshold for the induction of synaptic plasticity through a preceding “priming” activity. Little is known about metaplasticity in *Fmr1* KO mice and the objective of this study was to determine whether and how metaplasticity is affected in *Fmr1* KO mice. We tested this in the CA1 subregion of the hippocampus in 3-5 week old juvenile male *Fmr1* WT and KO mice. We observed that high frequency induced NMDA receptor dependent LTP of Schaffer collateral (SC) – CA1 synapses

in *Fmr1* KO mice was normal consistent with previous work. Using a priming stimulus by administration of a low concentration of NMDA (1 μM) for 10 mins inhibited subsequent LTP induction in both *Fmr1* WT and KO mice, but this metaplastic LTP inhibition was greater in KO mice. The amplitude of the NMDA receptor mediated EPSC ($EPSC_{NMDAR}$) in CA1 neurons was not affected in *Fmr1* KO mice, suggesting that downstream signaling or other molecules cause the elevated metaplasticity in *Fmr1* KO mice. To explore the mechanistic basis of NMDA mediated metaplasticity, we performed 2-photon laser scanning microscopy (2PLSM) Ca^{2+} imaging as a proxy for dendritic excitability of CA1 pyramidal neurons. NMDA priming decreased the dendritic Ca^{2+} signal in both *Fmr1* WT and KO mice, but the reduction was stronger in KO mice, suggesting that priming has a larger effect on dendritic excitability in *Fmr1* KO mice. We tested whether this difference in modulation of dendritic excitability was because of the activity of Ca^{2+} dependent K^+ (SK) channels that are known to regulate dendritic excitability and directly interact with FMRP. Application of a low concentration of NMDA increased SK channel mediated currents in *Fmr1* KO mice whereas inhibition of SK channels by the selective blocker apamin (300 nM) rectified the exaggerated priming effect observed in *Fmr1* KO mice. These results demonstrate that altered coupling of priming stimulus and K^+ channel activity shifts the plasticity threshold for hippocampal CA1 synapses which may contribute to various clinical manifestations in FXS including cognitive defects associated with loss of FMRP.

Disclosures: T. Nomura: None. **C. Morton:** None. **A. Contractor:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.027/LBA92

Topic: B.05. Synaptic Plasticity

Support: R01 plasticity
R01 A1 plasticity
DSPANF99/K00

Title: Arc mediates a novel form of intercellular long-term synaptic plasticity

Authors: *K. SULLIVAN[1], A. L. RAVENS[1], J. D. SHEPHERD[2];
[2]Neurobio., [1]Univ. of Utah, Salt Lake City, UT

Abstract: Arc mediates a novel form of intercellular synaptic plasticity via IRSp53
We recently discovered that *Arc,* a neuronal gene required for synaptic plasticity and memory evolved from an ancient retrotransposon. Arc protein has retained the viral-like properties of the ancestral retrotransposon and is capable of self-assembling into virus-like capsids that encapsulate genetic material. Arc capsids can be transferred cell-to-cell in extracellular vesicles

(EVs) and deliver nucleic acids, similar to retroviruses. These findings suggest that evolution exploited viral machinery to facilitate memory formation. However, the function of Arc mediated intercellular communication and the role of virus-like capsids in memory formation is unclear. Here we show that Arc capsid assembly and release occurs during long-term potentiation (LTP) through direct interaction with the I-BAR protein IRSp53. Using time-lapse imaging we observed colocalization and anterograde trafficking of Arc and IRSp53 puncta in dendrites that are released from neurons during LTP. In addition, biochemically purified IRSp53 protein facilitates Arc capsid assembly *in vitro*. These results suggest that IRSp53 assembles Arc capsids that are released during LTP to mediate intercellular signaling. To determine whether released Arc can regulate synaptic function in recipient neurons, we sparsely transfected Arc or GFP in primary cultured Arc KO neurons. Untransfected dendrites neighboring Arc transfected neurons had low levels of Arc transfer while GFP transfer was not observed. In dendrites where Arc transfer occurred, there was a reduction in surface AMPA receptors (GluA1). In addition, neurons incubated with Arc containing EVs have lower surface GluA1 levels. Whereas EVs from Arc KO neurons had no effect.Together, our results show that Arc mediates an intercellular form of synaptic plasticity. Neurons that undergo high intensity neuronal activity induce LTP and expression of Arc that associates with IRSp53. IRSp53 acts as a molecular switch that facilitates Arc capsid assembly and release. Arc that is transferred in EVs induces synaptic depression in neighboring dendrites. We propose that neurons incorporated into the memory "engram" that undergo LTP release Arc to increase the "signal-to-noise" of memory circuits by weakening synapses on neurons not active during memory encoding.

Disclosures: K. Sullivan: None. **A.L. Ravens:** None. **J.D. Shepherd:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.028/LBA93

Topic: B.05. Synaptic Plasticity

Support: Grant
Grant

Title: Cholecystokinin modulate corticothalamic neuroplasticity and alleviate tinnitus in adult mice

Authors: *N. ABBAS[1], M. ASIM[2];
[1]Ctr. for Regenerative Med. & Health, Hong Kong Inst. of Sci. & Innovation, Chinese Acad, Hong kong, Hong Kong; [2]Neurosci., City Univ. of Hong Kong, Gujranwala, Pakistan

Abstract: Tinnitus is the phantom perception of sound in the absence of external acoustic cues. Hearing loss-induced tinnitus is primarily caused by irreparable damage to the peripheral auditory organ and dysregulation of the corticothalamic pathway. It is not clear how dysregulation in the corticothalamic pathway is driving tinnitus. We hypothesize that the rewiring of the neural connections between the auditory cortex and auditory thalamus neurons by pharmacological and sound therapy may alleviate tinnitus. Here, we report that noise-induced tinnitus is accompanied by significant induction of neuroinflammation evidenced by the upregulation of pro-inflammatory cytokines such as IL-1β, TNFa, and IL-18 in the auditory system. Interestingly, we found that cholecystokinin (CCK) and targeted sound therapy restore the corticothalamic synaptic neuroplasticity, reversibly alleviating neuroinflammatory changes and tinnitus-related behavior. Further, electrophysiological recordings confirmed significant restoration of the patterns of neuronal activity within the auditory cortex and thalamus neurons. These results suggest that targeting the corticothalamic pathway may be a promising approach to treating tinnitus and further warrants a potential mechanism by which CCK-agonist and targeted sound therapy exert their therapeutic effects.

Disclosures: N. Abbas: None. **M. Asim:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.029/LBA94

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 1R15DA049260-01A1

Title: Lsd reverses morphine-induced elimination of plasticity in vta gaba cells and attenuates morphine-induced conditioned place preference

Authors: *M. VON GUNTEN[1], T. RUSSELL[1], J. G. EDWARDS[2];
[2]PDBio, [1]Brigham Young Univ., Provo, UT

Abstract: Psychedelics have gained recent attention due to their remarkable ability to treat a vast array of disorders, including substance use disorders and depression. Some researchers suggest that psychedelic drugs such as LSD induce plasticity and epigenetic alterations that in essence reset brain circuits thus providing a potential treatment of these disorders, but research in this area is still in its infancy. Here we explore the physiological, behavioral, and epigenetic impacts of LSD on morphine treated young male and female mice. Our findings show that a single treatment of LSD (0.3 mg/kg) causes extinction of morphine-induced conditioned place preference after 48 hours ($n = 9$, $p < 0.05$). Further exploration using whole-cell patch clamping shows that excitatory LTD of VTA GABA cells is eliminated in morphine-treated mice ($n = 9$, p

> 0.05). Remarkably, this LTD is restored 24 hours after a single LSD treatment ($n = 7$, $p < 0.001$), but remains eliminated in mice treated with a vehicle control instead of LSD. To further explore LSD impact on morphine exposure at a behavioral level, we treated another cohort of mice with a combination of morphine (10 mg/kg) and low dose (sub-hallucinogenic) of LSD (0.03 mg/kg). Interestingly, four low doses of LSD had a similar effect to the single high dose on reducing morphine preference, with the extinction of morphine preference occurring after 48 hours. ($n = 9$, $p < 0.05$). However, although the behavioral effects were similar between the groups that received a single high dose of LSD or 4 microdoses of LSD, the physiology was different. Mice co-treated with morphine and microdoses of LSD did not manifest restored LTD in VTA GABA cells ($n = 6$, $p > 0.05$). It is unclear why the similarities in behavior do not correlate to similar effects seen with the physiology, but it likely has to do with the acute effect of the microdose of LSD, or circuits being impacted. To further explore LSD impact on morphine-treated mice, we are currently investigating DNA methylation alterations in the VTA of morphine-treated mice that did or did not receive a single dose of LSD after being treated with morphine. Our findings illustrate a possible mechanism through which LSD could treat several psychological disorders, including reversing maladaptive plasticity that was contributing to drug-dependence. Further research of the corticolimbic system is needed to understand the full extent of LSD impact on plasticity related to dependence and other psychological disorders.

Disclosures: M. Von Gunten: None. **T. Russell:** None. **J.G. Edwards:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.030/LBA95

Topic: B.05. Synaptic Plasticity

Support: Supported by the Chilean Scientific Millennium Initiative, grant P09-015F.

Title: Obese Mice Display Defective Synaptic Plasticity and Impaired Spatial Memory

Authors: *A. ARIAS-CAVIERES[1], J. MORE[2], P. LLANOS[3], C. HIDALGO[5], G. BARRIENTOS[4];
[1]Univ. of Chicago, Chicago, IL; [2]2Center for Advanced Clin. Investigation (CICA), Hosp. Clínico, [3]Inst. for Res. in Dent. Sci. (ICOD), Fac. of Dent., [4]Physiol. and Biophysics Program, ICBM, Fac. of Med., Univ. de Chile, Santiago, Chile; [5]Dept. of Neurosciences and Biomed. Res. Inst. (BNI), Facultad de Medicina, U. Chile, Santiago, Chile

Abstract: The World Health Organization estimates that more than 420 million people live with type-2 diabetes, a common disease of the obese population, whereas annually around 3 million deaths globally are obesity-related. Recent studies in rodent models suggest that obesity causes

neurological damage. However, the underlying mechanisms remain unclear. Therefore, we investigated the effects of obesity on hippocampal synaptic plasticity and spatial memory in mice. Adult C57BL/6 mice were fed a high-fat diet for 20 weeks to induce obesity, resulting in significant weight gain and insulin resistance. The obese mice exhibited marked reductions in both hippocampal long-term potentiation and long-term depression, impaired performance in an object-location memory task, and increased anxiety-associated behavior in an open field test. In addition, obese mice displayed significant increases in the hippocampal protein content of the ryanodine receptor (RyR) isoforms RyR2 and RyR3. We propose that the elevated levels of these endoplasmic reticulum calcium release channels disturb normal calcium homeostasis and signaling in obese mice, leading to defective synaptic plasticity and impaired memory formation.Supported by the Chilean Scientific Millennium Initiative, grant P09-015F.

Disclosures: A. Arias-Cavieres: None. **J. More:** None. **P. Llanos:** None. **C. Hidalgo:** None. **G. Barrientos:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.031/LBA96

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 1R01MH120300-01A1

Title: The spacing effect is an emergent property of molecular signaling in non-neural cells

Authors: N. V. KUKUSHKIN[1,2], ***R. E. CARNEY**[1], T. TABASSUM[3], T. J. CAREW[1];
[1]Ctr. for Neural Sci., [2]Liberal Studies, [3]Ctr. For Neural Sci., New York Univ., New York, NY

Abstract: A canonical feature of learning and memory is the observation that repeated exposure to shorter training sessions separated by periods of rest enhances behavioral output when compared to a single massed training exposure. This phenomenon is named the spacing effect. Given that memory formation is classically regarded as a byproduct of neurons and neural circuitry, one might expect that the spacing effect is an emergent property exclusive to neural systems. However, the molecular mechanisms which underlie synaptic plasticity and, as a consequence, memory storage are highly evolutionarily conserved and active in many cell types. Therefore, features of memory such as the spacing effect may be intrinsic to molecular signaling cascades. We now demonstrate the spacing effect in two non-neural, immortalized cell lines stably expressing a short-lived luciferase reporter controlled by a CREB-dependent promoter. CREB-dependent immediate-early gene (IEG) transcription is a hallmark of potentiation/memory formation in neurons and was therefore chosen as a proxy of memory in our system. We emulated training using repeated pulses of forskolin and/or TPA and measured

CREB-dependent luciferase expression at various points after training. Four spaced pulses of either agonist elicited stronger and more sustained luciferase expression than a single “massed” pulse, demonstrating a form of temporal pattern discrimination thus far only observed in neural systems. Spaced pulses also resulted in stronger and more sustained activation of ERK and CREB, and inhibition of ERK or CREB blocked the spacing effect. Our findings show that canonical features of memory do not necessarily depend on neural circuitry, but can be embedded in the dynamics of signaling cascades conserved across different cell types.

Disclosures: N.V. Kukushkin: None. **R.E. Carney:** None. **T. Tabassum:** None. **T.J. Carew:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.032/LBA97

Topic: B.05. Synaptic Plasticity

Support: Spanish Agencia Estatal de Investigación Grant PID2022-136597NB-I00

Title: Two novel forms of presynaptic spike timing-dependent depression at entorhinal cortex-hippocampal synapses

Authors: I. MARTÍNEZ GALLEGO, H. COATL CUAYA, ***A. RODRIGUEZ-MORENO**; Univ. Pablo de Olavide, Sevilla, Spain

Abstract: The entorhinal cortex (EC) connects to the hippocampus sending different information from cortical areas that is first processed at the dentate gyrus (DG) including spatial, limbic, and sensory and information. Excitatory afferents from lateral (LPP) and medial (MPP) perforant pathways of the EC connecting to granule cells (GC) of the DG play a role in memory encoding and information processing. LPP- and MPP-GC synapses have distinct electrophysiological properties, and these differences potentially affecting the functional processing of information. However, the plasticity of these synapses is not well known yet, as are not known the forms of long-term depression (LTD) existing at those connections. We investigated whether spike timing-dependent long-term depression (t-LTD) exists at these two different EC-DG synaptic connections in mice, and whether they have different action mechanisms. We have found two different forms of t-LTD, at LPP- and MPP-GC synapses, and characterised their cellular and intracellular mechanistic requirement. The most relevant results showed that both forms of t-LTD are expressed presynaptically and that whereas t-LTD at MPP-GC requires ionotropic NMDAR containing GluN2A subunits, t-LTD at LPP-GC synapses does not require NMDAR. In addtion, the two forms of t-LTD require different group I mGluR, postsynaptic calcium, synthesis and release of endocannabinoids by the postsynaptic cell, as well as astrocyte activity

releasing glutamate. Therefore, we discovered two novel forms of presynaptic t-LTD that requires astrocytes at EC-GC synapses with different action mechanisms, which could contribute to the functional processing of the different information.

Disclosures: I. Martínez Gallego: None. **H. Coatl Cuaya:** None. **A. Rodriguez-Moreno:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.033/LBA98

Topic: B.05. Synaptic Plasticity

Support: NIH grant R01MH121848
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NIH grant R00NS114166
NIH grant R01NS133434
NIH grant R01DA059378
NIH training grant T32NS041228

Title: Cortical pyramidal circuits and 5-HT_{2A} receptors underlying psilocybin's therapeutic effects

Authors: *L. SHAO, C. LIAO, A. C. KWAN;
Biomed. Engin., Cornell Univ., Ithaca, NY

Abstract: Psilocybin is a serotonergic psychedelic with rapid and long-lasting therapeutic potential for various mental disorders. At cellular resolution, current evidence shows that psychedelics promote structural plasticity, exemplified by the treatment evoked growth and remodeling of dendritic spines in frontal cortex. However, the key question of how the cellular modifications map onto cell-type specific circuits and serotonin receptors to produce the behavioral actions and synaptic plasticity of psychedelics remains unknown. Here we used in vivo two-photon imaging, chemogenetic manipulation, and cell-type specific electrophysiology to investigate the impact of psilocybin on the two main subtypes of pyramidal cells in the mouse medial frontal cortex. We found that a single dose of psilocybin (1 mg/kg, i.p.) shows therapeutic effects in stress-related phenotypes. Silencing pyramidal tract /extratelencephalic (PT) neurons eliminates psilocybin's ability to ameliorate stress-related phenotypes, whereas inactivation of intratelencephalic (IT) neurons has no detectable effect. For structural plasticity, psilocybin induced differential alterations in the morphology of dendritic spines in PT and IT neurons. Furthermore, only in PT neurons, psilocybin boosted synaptic calcium transients and elevates

firing rates acutely in both of dendritic branches and spines after administration. Targeted knockout of 5-HT_{2A} receptors abolishes psilocybin's effects on stress-related behavior and structural plasticity. Taken together, our results identify a cortical pyramidal circuit and the 5-HT_{2A} receptor as critical for psilocybin's long-term structural and behavioral consequences, which would further scientifically understanding of psilocybin's effects on neuroplasticity and its potential therapeutic effects.

Disclosures: L. Shao: None. **C. Liao:** None. **A.C. Kwan:** 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.; Intra-Cellular Therapies Inc. F. Consulting Fees (e.g., advisory boards); Biohaven Pharmaceuticals, Empyrean Neuroscience, Freedom Biosciences, Psylo.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.034/LBA99

Topic: B.05. Synaptic Plasticity

Support: NRFK Grant RS-2024-00353822
NRFK Grant 2022R1A2C1091994

Title: Role of GT1b in activity-dependent spinal synapse remodeling following peripheral nerve injury

Authors: *J. LEE;
Seoul Natl. Univ., Seoul, Republic of Korea, Korea, Republic of

Abstract: An imbalance in excitatory and inhibitory synaptic transmission at the spinal cord level is implicated as a key mechanism underlying central sensitization in pain. However, the mechanism by which peripheral nerve injury leads to this synaptic imbalance remains elusive. This study used a pH-reporter system to investigate synaptic reorganization in the spinal dorsal horn following peripheral nerve injury. Nerve injury selectively reorganizes excitatory synapses, dependent on glial phagocytosis of the excitatory pre-synaptic compartment. Notably, this synaptic reorganization is influenced by the presence of the ganglioside GT1b on the synaptic membrane. Inhibiting GT1b synthesis using PDMP or deleting ST3gal2, a GT1b-synthesizing enzyme, enhanced glial phagocytosis of excitatory pre-synapses and reduced excitatory synapses post-injury. *In vitro* analyses revealed a positive correlation between GT1b accumulation and the frequency of pre-synaptic calcium activity, along with GT1b-mediated suppression of glial phagocytosis through SYK dephosphorylation. Our findings highlight that GT1b accumulation at

excitatory pre-synapses protects against glial phagocytosis, underscoring the function of GT1b as a novel “don’t eat me” signal that influences activity-dependent spinal synapse remodeling.

Disclosures: J. Lee: None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.035/LBA100

Topic: B.05. Synaptic Plasticity

Support: NIMH - R01MH095980
NSF NeuroNex 2014862

Title: Roles of dendritic spines and the spine apparatus in the development and maturation of LTP: Why we produced the synaptopodin KO rat.

Authors: *K. HARRIS[1], M. KUWAJIMA[2], O. I. OSTROVSKAYA[3], L. M. KIRK[2];
[1]Univ. Of Texas At Austin, Austin, TX; [2]Neurosci., Univ. of Texas at Austin, Austin, TX; [3]The Ctr. for Learning & Memory, The Univ. of Texas At Austin, Austin, TX

Abstract: The initial saturation of LTP in hippocampus of adult rats occurs following 8 trains of theta burst stimulation. Beginning 90 minutes later, recovery from saturation expands the capacity for new LTP. By 2 hr after LTP, large spines containing a spine apparatus have the greatest synapse enlargement and smaller spines cluster in their vicinity. Small spine outgrowth is stalled with distance along the dendrite from the spines that contain a spine apparatus. We have determined that an immature pattern of LTP in rat hippocampus begins distinctly at postnatal (P)12 with a slow onset and lower magnitude. Using 3D electron microscopy (EM) we show that spines first appear at P12. By P21, we show LTP has a mature pattern with rapid onset, coinciding with the first appearance of the spine apparatus. The frequency of spines with a spine apparatus doubles by P60. To test whether the spine apparatus is necessary for the maturation of LTP and spine clustering we developed two rat models eliminating Synaptopodin, a protein required for spine apparatus formation. Although a congenital *synaptopodin* knockout (KO) model exists in the mouse, the development and maturation of LTP in the mouse hippocampus is unpredictable over 2-5 weeks, making this model insufficient. We demonstrate through 3DEM that the spine apparatus is absent in our congenital KO rat. The animals develop normally through P35 (female) and P45 (male), and LTP is substantially diminished at P60 in the KO rats. However, the animals show signs of diminished weight gain and shorter bones in adults. To avoid these off-target effects, we have also developed a neuron-specific inducible synaptopodin KO rat illustrated in Fig. 1. Together these rat synaptopodin model systems open the door to new

investigation about the role of the spine apparatus in coordinating spine clustering and enhancing the capacity for LTP.

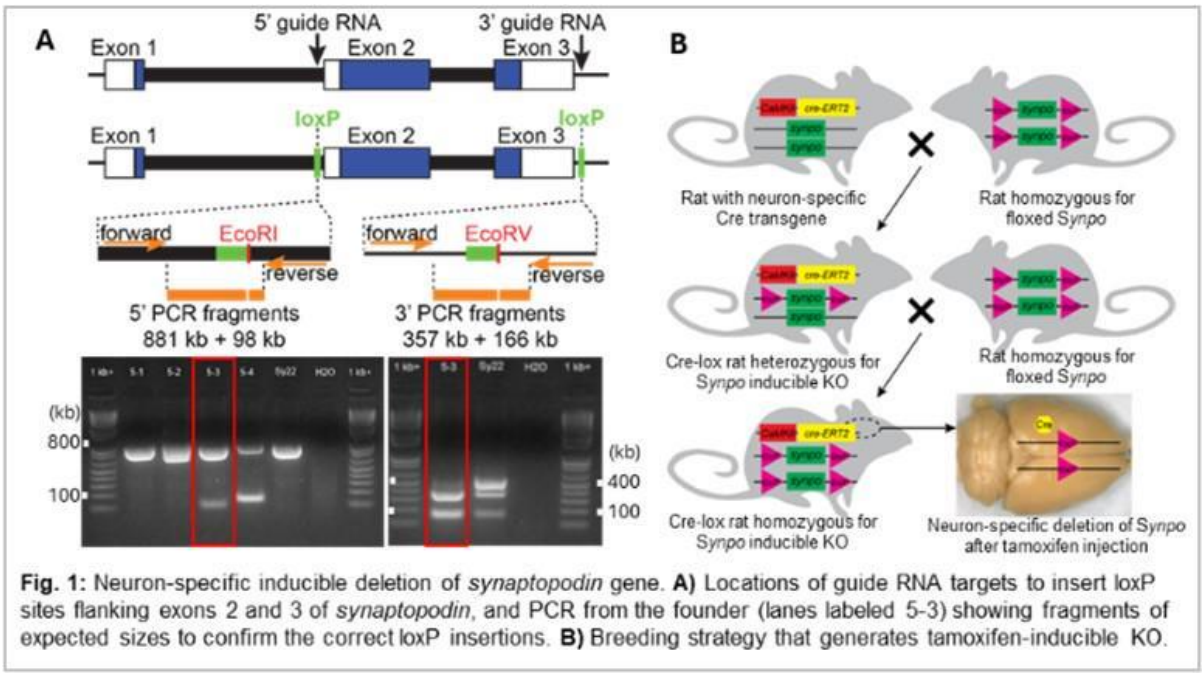


Fig. 1: Neuron-specific inducible deletion of *synaptopodin* gene. **A)** Locations of guide RNA targets to insert loxP sites flanking exons 2 and 3 of *synaptopodin*, and PCR from the founder (lanes labeled 5-3) showing fragments of expected sizes to confirm the correct loxP insertions. **B)** Breeding strategy that generates tamoxifen-inducible KO.

Disclosures: K. Harris: None. **M. Kuwajima:** None. **O.I. Ostrovskaya:** None. **L.M. Kirk:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.036/LBA101

Topic: B.05. Synaptic Plasticity

Support: RGPIN-2022-04134
CIHR (MOP-142209)
CIHR (PJT-178353)

Title: Molecular logic of pathway-specific synaptic plasticity, network function and behavior

Authors: *B. KARIMI[1,2], D. J. TERSTEGE[3], M. ABRAR BASHA[2], S. JABEEN[3], D. SARGIN[4], T. J. SIDDIQUI[2];
[1]Johns Hopkins Med., Baltimore, MD; [2]Univ. of Manitoba, Winnipeg, MB, Canada; [4]Dept. of Psychology, [3]Univ. of Calgary, Calgary, AB, Canada

Abstract: Impaired CA3-CA1 circuitry and abnormal synaptic plasticity of the CA3-CA1 synapses cause cognitive deficits in several neuropsychiatric disorders. Here, we identified leucine-rich-repeat transmembrane neuronal protein 1 (LRRTM1), a postsynaptic cell-adhesion molecule, as an essential synaptic transmission and plasticity regulator in the mouse dorsal CA1. LRRTM1 is strongly associated with schizophrenia and handedness and is highly expressed in the hippocampus CA regions and the dentate gyrus. Conditional deletion of *Lrrtm1* in the CA1 in adult mice reduced synaptic transmission and caused a deficit in long-term potentiation in the stratum radiatum but not stratum lacunosum-moleculare. The deficits were reversed by the reintroduction of LRRTM1 or perfusion with GluR2^{3Y}, a peptide that blocks endocytosis of GluA2 containing AMPARs. Network activity was impaired in the CA3-CA1 pathway of mice lacking *Lrrtm1*, as revealed by fiber photometry analysis. Mice lacking *Lrtm1* in the dorsal CA1 exhibited reduced dynamic range of calcium signals during freezing bouts in the contextual fear conditioning test. Additionally, the maximum peak amplitude was significantly reduced in mice lacking *Lrrtm1* in the dorsal CA1. Our results indicate that chronic reduction of synaptic strength in the dorsal CA1 by targeted deletion of *Lrrtm1* functionally disengages the CA3 from the CA1 and may account for contextual memory and other cognitive deficits observed in several neuropsychiatric disorders.

Disclosures: B. Karimi: None. **D.J. Terstege:** None. **M. Abrar basha:** None. **S. Jabeen:** None. **D. Sargin:** None. **T.J. Siddiqui:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.037/LBA102

Topic: B.05. Synaptic Plasticity

Title: Synaptic Terminals and Axon Outgrowth in White Adipose Tissue: Potential Targets for Treating Peripheral Neuropathy with Obesity

Authors: *J. WILLOWS[1], M. BLASZKIEWICZ[3], K. L. TOWNSEND[2];
[1]The Ohio State Univ., Columbus, OH; [2]The Ohio State Univ., Worthington, OH; [3]The Ohio State Univ. Col. of Med., Columbus, OH

Abstract: Age, obesity, and diabetes are significant risk factors for peripheral neuropathy (PN), a condition impacting the skin, muscle, and adipose tissue. PN involves the loss of nerve connections to these tissues and organs, disrupting communication with the brain, impairing tissue function, and causing discomfort. As the U.S. population ages and the rates of obesity and diabetes rise, understanding PN is increasingly crucial. Adipose tissue, especially subcutaneous white adipose tissue (scWAT), is extensively innervated by both sensory and sympathetic nerves. These nerves engage in bidirectional communication with the brain, crucial for regulating

adipose tissue functions. scWAT is notably adaptable, capable of remodeling itself in response to metabolic demands by altering its cellular structure, vascularity, neural innervation, and nerve activity. Disruptions in this neural circuitry can contribute to metabolic dysfunction. Previously, it was thought that axons in adipose tissue communicated with adipocytes by releasing neurotransmitters diffusely throughout the tissue. However, our recent research has identified a novel structure known as the neuro-adipose nexus (NAN). NANs are characterized by distinct nerve terminals with varicose axons that express markers for synaptic vesicles and proteins, uniquely wrapping around individual adipocytes. This discovery represents a significant advancement in our understanding of adipose tissue innervation. We found that the number of NANs increases with obesity and aging, although their precise functions remain unclear. Given their expression of sensory nerve markers and their increase during inflammation, we hypothesize that NANs may play a role in nociception or interoception. To explore the mechanisms underlying neuroplasticity affecting adipose innervation and NAN numbers, we investigated Sema7A, an axonal guidance molecule, using a genetic knock-out model. We observed that Sema7A-deficient mice exhibited reduced adipose tissue innervation and significant whole-body metabolic impairments. These findings underscore the crucial role of Sema7A in maintaining proper adipose tissue function and neural connectivity, offering new insights into the complex nervous system of adipose tissue and its role in metabolic regulation.

Disclosures: J. Willows: None. **M. Blaszkiewicz:** None. **K.L. Townsend:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.038/LBA103

Topic: B.05. Synaptic Plasticity

Support: NSERC Discovery Grant
FRQS - Fonds de recherche du Quebec - Santé

Title: The impact of attention allocation on exercise-induced M1 interneuron plasticity

Authors: *A. O'FARRELL[1], L. YOUSSEF[1], N. HARROUM[2], J. L. NEVA[3];
[1]Univ. de Montréal, Montreal, QC, Canada; [3]École de kinésiologie et des sciences de l'activité physique, [2]Univ. de Montréal, Montréal, QC, Canada

Abstract: A single session of acute aerobic exercise can enhance neuroplasticity, as assessed by primary motor cortex (M1) excitability modulation using transcranial magnetic stimulation (TMS). Specifically, acute exercise can enhance the response to plasticity-inducing repetitive TMS protocols, such as paired-associative stimulation (PAS). PAS uses repetitive peripheral nerve stimulation in combination with TMS to induce an increase in M1 excitability. This PAS-

induced effect is more pronounced when task-relevant attention is directed to the hand receiving the stimulation (PAS_{att+}) and decreased when attention is directed to the opposite hand (PAS_{att-}), suggesting involvement of prefrontal circuits in this PAS-induced effect. Gathering research suggests that increased M1 excitability following acute exercise is impacted by prefrontal circuits that underlie attention allocation, yet no study has directly tested this question. Additionally, acute exercise has been shown to enhance unique M1 interneuron excitability, by altering the TMS current to the anterior-posterior (AP) direction compared to the traditional posterior-anterior (PA) direction. Yet, no study has investigated the impact of exercise or the role of attention allocation during PAS on unique M1 interneuron plasticity. This study investigates the role of attention-related prefrontal circuits in exercise-induced M1 interneuron plasticity by applying PAS following acute exercise, while controlling attention allocation during PAS. TMS measures were performed in both the PA and AP current directions, to assess unique interneuron plasticity. Participants took part in 4 conditions: 1) acute exercise + PAS_{att+}, 2) acute exercise + PAS_{att-}, 3) rest + PAS_{att+}, 4) rest + PAS_{att-}. We hypothesised that acute exercise would accentuate exercise-induced neuroplasticity to the greatest extent following PAS_{att+}, particularly for measurement with AP TMS current. Further, we expected that PAS_{att-} would reduce the priming effect of exercise. Preliminary results suggest that acute exercise accentuates exercise-enhanced neuroplasticity following PAS_{att+}, whereas following PAS_{att-} the opposite was found. Interestingly, PA interneuron plasticity increases more with PAS_{att+} following acute exercise, and AP interneuron plasticity is enhanced following PAS_{att-}, regardless of prior acute exercise or rest. These results suggest that attention-related prefrontal circuits may play an important role in exercise-enhanced M1 neuroplasticity as well as M1 interneuron plasticity.

Disclosures: A. O'Farrell: None. **L. Youssef:** None. **N. Harroum:** None. **J.L. Neva:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.039/LBA104

Topic: B.05. Synaptic Plasticity

Support: NIH EY031597
NIH GM103533
NIH MH067880
NIH AG075862
NIH AG 067331
NIH AG 069206

Title: Activity-dependent synthesis of Emerin gates neuronal plasticity through regulating proteostasis

Authors: *Y. XIE[1], R. WANG[2], D. B. MCCLATCHY[3], Y. MA[2], M. SANCHEZ-ALAVEZ[4], M. PETRASCHECK[4], J. R. YATES, III[6], H. T. CLINE[5];
[1]Neurosci., Scripps Res. Inst., San Diego, CA; [2]The Scripps Res. Inst., San Diego, CA; [3]Chem. Physiol., The Scripps Res. Inst., La Jolla, CA; [4]Neurosci., The Scripps Res. Inst., San Diego, CA; [5]Neurosci., The Scripps Res. Inst., La Jolla, CA; [6]The Scripps Res. Inst. - Grad. Program, La Jolla, CA

Abstract: Neurons dynamically regulate their proteome in response to sensory input, a key process underlying experience-dependent plasticity. We characterized the visual experience-dependent nascent proteome within a brief, defined time window after stimulation using an optimized metabolic labeling approach. Visual experience induced cell type-specific and age-dependent alterations in the nascent proteome, including proteostasis-related processes. We identified Emerin as the top activity-induced candidate plasticity protein and demonstrated that its rapid activity-induced synthesis is transcription-independent. In contrast to its nuclear localization and function in myocytes, activity-induced neuronal Emerin is abundant in the endoplasmic reticulum and broadly inhibits protein synthesis, including translation regulators and synaptic proteins. Downregulating Emerin shifted the dendritic spine population from predominantly mushroom morphology to filopodia and decreased network connectivity. In mice, decreased Emerin reduced visual response magnitude and impaired visual information processing. Our findings support an experience-dependent feed-forward role for Emerin in temporally gating neuronal plasticity by negatively regulating translation.

Disclosures: Y. Xie: None. **R. Wang:** None. **D.B. McClatchy:** None. **Y. Ma:** None. **M. Sanchez-Alavez:** None. **M. Petrascheck:** None. **J.R. Yates:** None. **H.T. Cline:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.040/LBA105

Topic: B.05. Synaptic Plasticity

Title: Enteric motor complexes are modulated by psychedelics

Authors: *A. ALEJANDRO-GARCÍA[1], A. M. GOMEZ[2];
[1]Neurosci., UC Berkeley, Berkeley, CA; [2]UC Berkeley, Richmond, CA

Abstract: Enteric neurons drive diverse, tissue-specific motor patterns in the gastrointestinal (GI) tract for digestion. Visual motion data of rhythmic activity can capture dynamics of gut motility with high spatiotemporal resolution and potentially parameterize disease states in animal models of gastrointestinal dysfunction. However, implementation of motion data has been previously limited to clinical settings. Here, we adapt an optical flow analysis from open-source

computer vision software to estimate 2D motion over an ex vivo preparation of the mouse jejunum. Using conventional darkfield or epifluorescence microscopy at high temporal resolution (20 ms) we developed an analysis workflow that quantifies magnitudes of distinct components of gut motility. Dense optical flow vectors calculated over several minutes identify fine motion patterns at the scale of tens of micrometers. Using Fourier analysis we characterize temporal frequency components altered pharmacologically, with caffeine or serotonergic agonists. Together, we confirm optical flow as a reliable method to parameterize simple and complex motility patterns in the gut and demonstrate its application in the mouse jejunum.

Disclosures: A. Alejandro-García: None. **A.M. Gomez:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.041/LBA106

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Title: Low-threshold and calcium-dependent potassium currents regulate the intrinsic firing properties of forebrain-projecting HVC_{RA} neurons in zebra finches

Authors: *A. DAOU[1,2], D. MARGOLIASH[2];
[1]American Univ. of Beirut, Beirut, Lebanon; [2]Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: In zebra finch, the song system nucleus HVC produces stereotyped instructions leading to precise, learned vocalizations. The intrinsic properties (IPs) of different classes of HVC neurons help predict the firing properties of those neurons both *in vivo* and *in vitro* and recent results relate IPs of the HVC_X (basal ganglia projecting) neurons to individual-specific learned features of song. We extended these studies by performing brain slice whole cell current-clamp recordings on premotor HVC_{RA} neurons, that play a critical role in adult song production. We show that HVC_{RA} neurons exhibit diversity in their spiking activity when stimulated with current pulses in slices, ranging from transient to stuttering patterns. Simple features of the raw data clearly subdivide the neurons into two frequently encountered classes (Class 1 and Class 2). An infrequently encountered Class 3 has properties intermediate between Class 1 and 2 and may represent a terminal phase of newly born neurons. Morphological analysis of filled cells independently confirms the Class 1/2 categorical distinctions. We developed conductance-based models for the different neurons in each subtype and calibrated the models using data from the slice recordings, yielding mechanistic descriptions of how the interplay of ion currents gives rise to the response properties of each neuronal class. These predictions were then tested and verified in the slice with pharmacological manipulations. The models and the pharmacology highlighted low-threshold potassium currents (D-type Kv1 channel and M-type Kv7 channel) as well as the

Ca^{2+}-dependent K^+ current in driving the characteristic neural patterns observed in HVC_{RA}. The relative strengths of different currents give rise to the physiological features observed across the three classes of HVC_{RA} neurons. The data suggest that the intrinsic properties for Class 2 HVC_{RA} exhibit a within-bird homogeneity and across-birds heterogeneity, suggesting a role of learning in shaping the firing properties of these neurons. This plus the relative abundance of these neurons (roughly 15% in our recordings) suggests that these might be Uva (thalamic) receiving HVC_{RA}. These results begin to establish a mechanistic basis for examining much debated circuit and network properties of HVC_{RA} neurons.

Disclosures: A. Daou: None. **D. Margoliash:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.042/LBA107

Topic: B.06. Intrinsic Membrane Properties and Signal integration

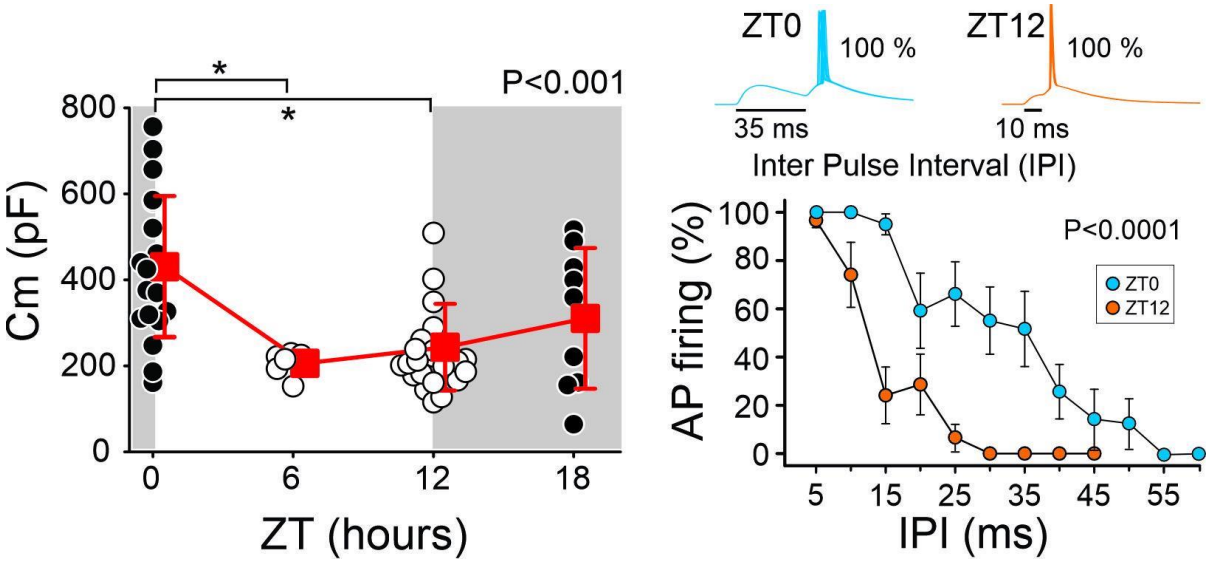
Support: NIH 5R01-EY12124 (A.K.)
NSF 2320895 (j.G.)

Title: Neuronal membrane capacitance changes between day and night

Authors: D. SEVERIN[1], C. MORENO[2], T. TRAN[1], C. WESSELBORG[3], S. SHIRLEY[5], A. CONTRERAS[6], A. KIRKWOOD[4], ***J. GOLOWASCH**[7];
[1]Zanvyl Krieger Mind/Brain Inst., [3]Dept. of Biol., [4]Mind Brain Inst., [2]Johns Hopkins Univ., Baltimore, MD; [5]NIMH, Bethesda, MD; [6]Biol., JHU, Baltimore, MD; [7]Biol. Sci., New Jersey Inst. of Technol., Newark, NJ

Abstract: The properties of the lipid fraction of a membrane determine a cell's membrane capacitance, *Cm*. Neuronal morphological changes also modify *Cm* but mainly during the early stages of development when neurons are growing. In adult neurons, *Cm* is widely considered to be stable. Here we report large and significant *Cm* changes in adult excitatory neurons. We measured *Cm* at 4 times during a 24 hr cycle in visual cortex pyramidal cells (PCs) and hippocampal granule cells (GCs) of adult mice. Surprisingly, we observed highly significant *Cm* changes of 60 to 100%, with a maximum at ZT0 (end of dark phase, PCs: 430.7 ± 164.4 pF (Fig); GCs: 119.8 ± 46.0 pF) and a minimum between ZT6-12 (middle to end of light phase, PCs: 243.5 ± 100.8 pF; GCs: 81.0 ± 34.9 pF). Inhibitory cortical PV^+ cells showed no such variations (ZT0: 239.3 ± 173.9 pF; ZT12: 183.6 ± 146.2 pF). PV^+ cells are encapsulated in peri-neuronal nets (PNNs). We treated them with chondroitinase ABC (ChABC) to dissolve the PNNs and assess if they contribute to regulate (or occlude) *Cm* changes in these cells. We observed no effects of ChABC on the *Cm* of PV^+ cells (ZT0: 189.5 ± 139.8 pF; ZT12: 199.5 ±

146.6 pF). In neurons, *Cm* is a determining factor of synaptic integration, action potential propagation speed and firing frequency due to its direct effect on the membrane time constant. We examined the effect of light-dark *Cm* changes on the synaptic integration properties of PCs using a mouse strain that expresses channelrhodopsin 2, optically activating apical and basal dendrites with varying inter-pulse intervals (IPI). Consistent with the daily capacitance fluctuations, the time window for synaptic integration showed a highly significant increase at ZT0 compared to ZT12 and by an amount very similar to the difference in time constant that results from the *Cm* changes observed (Fig). We confirmed with a simplified conductance-based model that *Cm* changes are sufficient to explain the changes in the integration time window observed. Thus, we conclude that neuronal membrane capacitance is not highly stable as often assumed but is a new potential locus of neuronal plasticity.



Disclosures: D. Severin: None. **C. Moreno:** None. **T. Tran:** None. **C. Wesselborg:** None. **S. Shirley:** None. **A. Contreras:** None. **A. Kirkwood:** None. **J. Golowasch:** None.
Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.043/LBA108

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH K99HL168434
NIH R01HL162575

Title: Spatiotemporal Ca^{2+} dynamics between cellular compartments affect the intrinsic excitability of vasopressin neurons

Authors: *M. K. KIRCHNER, J. E. STERN;
Ctr. for Neuroinflam. and Cardiometabolic Dis., Georgia State Univ., Atlanta, GA

Abstract: Calcium (Ca^{2+}) is a critical secondary messenger in all neurons that coordinates important mechanisms of cell physiology. In vasopressin (VP) neurons of supraoptic nucleus (SON), it's required for somatodendritic release of VP and activates various intrinsic excitability mechanisms, such as the slow afterhyperpolarization (sAHP). These mechanisms coordinate neuronal output and thus influence stimulus-secretion coupling. Recently, our lab demonstrated that VP sAHPs require endoplasmic reticulum (ER) Ca^{2+} for activation and that mitochondrial Ca^{2+} buffering shapes its spatiotemporal trajectory. We also have recent data demonstrating electrotonic segregation between cellular compartments. Given the Ca^{2+} dependence of somatodendritic release and sAHPs, delineation of somatodendritic release from axonal release, and the decoupling of somatic and dendritic electrotonic properties, we hypothesized that calcium dynamics also may be compartmentally segregated as well. Utilizing patch clamp electrophysiology, live calcium imaging, and targeted Ca^{2+} uncaging, we probed the spatiotemporal trajectory of rapidly evoked Ca^{2+} responses in VP neuron somas and dendrites with corresponding membrane potential. Ca^{2+} uncaging at the soma evokes a membrane sAHP and robust increase in cytosolic Ca^{2+} that propagates into the dendrites. Conversely, Ca^{2+} uncaged in dendrites propagates bidirectionally from the UV flash but does not penetrate the soma; no membrane hyperpolarization was observed under these conditions. Disabling mitochondrial Ca^{2+} buffering with Ru360 in the pipette amplifies Ca^{2+} signals and sAHPs in somas and dendrites; Ca^{2+} uncaging in dendrites mostly fails to penetrate soma, suggesting other mechanisms restrict dendrite Ca^{2+} diffusion into soma. Together, these results suggest that under normal conditions, Ca^{2+} movement between compartments in VP neurons is unidirectional (soma to dendrite), and that sAHP channels require somatic Ca^{2+} increases. Moreover, Ca^{2+} uptake by mitochondria is a critical mechanism that tightly controls the magnitude and propagation of dendritic Ca^{2+} signals between dendritic and somatic compartments, thus playing an important role in regulating intrinsic mechanisms and ultimately, their neuronal output.

Disclosures: M.K. Kirchner: None. **J.E. Stern:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.044/LBA109

Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH Grant NS118114

Title: Ectopic action potentials in excitatory cells in the anesthetized mouse

Authors: *F. POUILLE[1], B. B. THEYEL[2,1];
[1]Brown Univ., Providence, RI; [2]Warren Alpert Med. Sch. - Brown Univ., Providence, RI

Abstract: In most neurons, action potentials (APs) arise at the axon initial segment (AIS) near the cell body, then propagate to the terminals. Here, we will refer to these as "AIS-APs." Following intense neuronal activity, APs can also emerge in axons' distal branches and terminals. These "Ectopic" APs (EAPs) then travel antidromically towards the cell body and propagate in the axonal arbor, where they trigger vesicular release. While prominent in crustacean literature, mammalian EAPs had primarily been detected in pathological tissue until the 2010s, when they were observed in "normal" mouse hippocampus in vitro. We recently observed that most excitatory pyramidal neurons and parvalbumin-expressing (PV+) interneurons in layers 2/3 and 4 in mouse somatosensory and orbitofrontal cortices can generate EAPs in vitro (Zhang et al., 2023; Theyel et al., 2024). With deficiencies in pyramidal and PV+ neurons function linked to epilepsy and major neuropsychiatric disorders, it is crucial to understand how EAPs contribute to both normal and pathological activity in these cells. Here, we demonstrate that EAPs occur in cortical pyramidal neurons in vivo. We obtained whole-cell current-clamp recordings of layer 2/3 neurons in the somatosensory cortex of ketamine-anesthetized double-transgenic mice expressing channel-rhodopsin 2 in PV+ cells. Cells exhibiting laser-evoked inhibitory post-synaptic potentials and regular-spiking firing properties were classified as pyramidal neurons. EAPs were induced by triggering up to ~8000 AIS-APs through repetitive trains (1 sec long, every 10 sec) of current pulses (4ms long, amplitude titrated to at least 80% chance of firing an AIS-AP) at a set frequency (30, 60 or 100Hz). EAPs were identified by their lower apparent threshold and by their longer repolarization time (~17mV / ~one order of magnitude average difference, respectively) compared to AIS-APs. We found that 74% of pyramidal neurons exhibited EAPs (versus ~2/3rd in vitro), indicating that EAPs are also prominent in vivo. EAPs occurred more often during down-states, suggesting possible coordination between the mechanisms generating EAPs and up/down-states. Finally, AIS-APs firing strongly decreased during EAP firing, implying that intense activity transiently shifts the spike output generation zone from peri-somatic to distal axonal compartments. These results indicate that EAPs are common in a key excitatory neuron of the mouse living brain, that their occurrence could reflect brain state, and that they can temporarily replace AIS-APs as the main site of AP generation.

Disclosures: F. Pouille: None. **B.B. Theyel:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.045/Web Only

Topic: B.07. Network Interactions

Support: Wellcome Trust/DBT India Alliance IA/S/18/2/504003
Tata Trusts
Pratiksha Postdoctoral Fellowship

Title: Slow and fast gamma oscillations show phase-amplitude coupling with different high-frequency bands in macaque primary visual cortex

Authors: *P. PRABHU, S. RAY;
Ctr. for Neurosci., Indian Inst. of Sci., Bengaluru, India

Abstract: Gamma oscillations (30-70 Hz) can be induced in the visual cortex by presentation of appropriate stimuli such as gratings. In particular, large stimuli produce two distinct gamma oscillations in primate primary visual cortex (V1) - slow (20-40 Hz) and fast (40-70 Hz), which could potentially be due to two different interneuronal networks (somatostatin and parvalbumin expressing interneurons for slow and fast gamma bands, respectively). Earlier studies in primate V1 have shown spikes tend to preferentially lock to fast gamma, so role of slow gamma in cortical processing remains unclear. Previously, several studies have shown that phase of an oscillation can modulate the amplitude in a higher frequency band, and this phase-amplitude coupling (PAC) could potentially play an important role in cortical processing. We therefore tested whether slow and fast gamma also show PAC with higher frequencies. We used simultaneously recorded spiking activity, local field potential (LFP) and electrocorticogram (ECoG) from two adult female monkeys who viewed fullscreen and full contrast static gratings at different orientations and spatial frequencies. PAC analysis in LFP data is prone to artifacts since occurrence of action potentials are associated with a spike-related-transient in the LFP, which has power at many frequencies. Hence, if spikes are locked to a particular rhythm, there is artefactual PAC between the rhythm and a broad range of frequencies. We therefore first developed a novel method to reduce the spike-related-transient using matching pursuit and then computed PAC. Strong PAC was observed between theta (6-10 Hz) and a broad frequency range between 30-100 Hz, which was strongly attenuated once the spike-related transient was accounted for. Fast gamma showed strong PAC at high frequencies above 150-500 Hz, potentially reflecting spike-locking. Surprisingly, slow gamma showed strong PAC in a distinct frequency range between 80-150 Hz. This slow gamma PAC was even more prominent in simultaneously recorded ECoG, which did not show fast gamma and high-frequency PAC. We verified our PAC results by computing spike-field coherence, which showed higher spike-locking to fast gamma than to slow gamma. We found that slow and fast gamma PAC varied with orientation and spatial frequency consistently, reflecting changes in power in slow and fast gamma bands, again reflecting distinct origins and mechanisms underlying the two PAC signatures. While fast gamma could be more involved in local processing that involves changes in spike timing modulation, slow gamma could represent a modulatory signal which acts by amplitude modulation between 80-150 Hz at a more global scale.

Disclosures: P. Prabhu: None. **S. Ray:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.046/LBA110

Topic: B.07. Network Interactions

Title: Phase and amplitude-based beta-band oscillation localization in Parkinson's disease using sensing-enabled deep brain stimulation

Authors: *F. MAPAR[1,2], M. BEAUZILE[3], F. CHINEA[4], T. HERRINGTON[1,2];
[1]Neurol., Massachusetts Gen. Hosp. - Harvard Med. Sch., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Icahn Sch. of Med., Mount Sinai, New York, NY; [4]Massachusetts Gen. Hosp., Boston, MA

Abstract: Pathologically enhanced beta-band (13-30 Hz) oscillations in sensorimotor networks correlate with the severity of Parkinson's disease (PD) motor symptoms. Identifying such networks as well as using them to guide targeting of clinical deep brain stimulation (DBS) electrodes within the subthalamic nucleus (STN) and globus pallidus internus (GPi) require precise spatial localization of this network oscillopathy. While current sensing-enabled DBS systems support chronic recording of local field potential (LFP), the configuration is limited to referential recordings across stimulation contact pairs on the same DBS electrode, limiting the ability to localize LFP features accurately by only the signal's amplitude, with potentially misleading results. We propose a systemic approach to localize the beta oscillation origin using a combination of LFP amplitude and relative phase obtained from referential recordings re-referenced to adjacent contact pairs and demonstrate the potential inaccuracy of the sole amplitude-based approach. We analyzed LFP data from 93 PD patients treated with bilateral DBS (50 STN and 43 GPi). Amplitude and instantaneous phase of beta oscillation were calculated from the power spectral density (PSD) and Hilbert transformation, respectively. A contact is defined as beta "source" if a) all montages involving the contact exhibit distinct beta oscillation on PSD, and b) the beta-band exhibits a phase reversal at the shared contact. A statistical cross-correlation analysis between the identified beta source contacts using our approach versus the amplitude-based method demonstrate that in 96% of STN and 97% of GPi electrodes, the recording pair across the beta source contact did not exhibit the largest beta-band amplitude (both $p < 0.001$, permutation test). Furthermore, to assess spatial distribution of beta source contacts by an anatomical aggregate analysis, DBS electrode contacts were localized to an MNI atlas of anatomic DBS targets using a nonlinear transformation of the post-operative imaging in Lead-DBS platform. Beta source contacts were predominantly localized to posterior GPi and dorsolateral STN, corresponding to the sensorimotor subregion, in line with prior recordings intraoperatively and using externalized DBS electrodes. Our findings highlight the limitations of amplitude-based localization with the current state of DBS programming technology, offer an approach to more accurately target stimulation to regions of maximal pathophysiology with the potential to explore an improved clinical outcome, and provide spatial map of beta oscillation within STN and GPi to enhance our understanding of PD neurophysiology.

Disclosures: F. Mapar: None. **M. Beauzile:** None. **F. Chinea:** None. **T. Herrington:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.047/LBA111

Topic: B.07. Network Interactions

Support: DFG 436260547
NSF 2015276

Title: From mice to humans - Neuronal high bandwidth encoding across different species.

Authors: *S. POMMER[1,2], R. M. MERINO[3], J. C. MARTINEZ-TRUJILLO[4], J. F. STAIGER[5,1], F. WOLF[6,7,2], A. NEEF[2,6,7];
[1]Dept. of Neuroanatomy, Univ. Med. Ctr. Göttingen, Göttingen, Germany; [2]Campus Inst. for Dynamics of biological Networks, Univ. Göttingen, Goettingen, Germany; [3]MPI Dynamics and Self-Organization, Goettingen, Germany; [4]Dept. of Physiol. and Pharmacol. and Psychiatry, Schulich Sch. of Med. and Dentistry, Western Inst. for Neuroscience, Western Univ., London, ON, Canada; [5]Dept. of Neuroanatomy, Georg-August-University, Göttingen, Germany; [6]MPI Dynamics & Self-Organization, Goettingen, Germany; [7]Bernstein Ctr. for Computat. Neurosci., Goettingen, Germany

Abstract: Recent studies suggested a link between high bandwidth of input encoding and unique morphological features in human neurons and based on this possibly even a connection between neuron size and general intelligence. Here, we investigate how the capability to process high frequency input varies among different species and across different neuron types within a species. We used the dynamic gain function (DGF) to capture the frequency preference of neurons and their ability to tune-in to rhythmic inputs, and studied different cortical neuron classes in acute brain slices from multiple species: rodents, lemurs, marmosets, macaques and humans. Because a neuron's DGF is sensitive to the spectral composition of the input, and therefore to the brain state, we used in vivo-like stochastic inputs of different correlation times. We found that DFG features can differ substantially between cell types and input correlations, while the differences between species were gradual: 1.) The encoded input frequency bandwidth was alike, with cut-off frequencies around 400 Hz, suggesting ultrafast encoding to be general feature, independent of density. 2) Slow input correlations resulted in improved high-frequency encoding almost universally, showing comparable frequency preference adaptability. In addition, we observed an exception of a few neurons in our marmoset dataset, which showed a near constant DGF. In conclusion, morphological diverse neurons from a range of mammals achieve similarly high bandwidth of input encoding. Therefore, the ability to precisely time population responses to common input exists not only in higher primates. Input correlation-related, i.e.

brain-state dependent switching of frequency preference is also present across species. Correlates of higher brain functions and general intelligence are likely realized through higher order network effects.

Disclosures: S. Pommer: None. **R.M. Merino:** None. **J.C. Martinez-Trujillo:** None. **J.F. Staiger:** None. **F. Wolf:** None. **A. Neef:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Program #/Poster #: LBA002.048/LBA112

Topic: B.07. Network Interactions

Title: Ultraflexible Neuroelectrodes Optimized for Longitudinal Low Amplitude Stimulation of Neural Circuits

Authors: *R. LYCKE[1], C. XIE[2], R. KIM[1], L. LUAN[2];
[1]Rice Neuroengineering Initiative, Houston, TX; [2]Rice Univ., Houston, TX

Abstract: Intracortical microstimulation (ICMS) enables a wide range of applications from neuroprosthetics to targeted circuit manipulations. However, conventional neural electrodes are limited in chronic performance, neuromodulation spatial precision, and recording stability due mainly to adverse immune responses to the indwelling implants. In response to these shortcomings, we developed stimulating nanoelectronic thread (StimNET) probes to address these limitations by employing microns thin cross-sections, flexible polymers, and functionalized contact sites to avoid evoking a chronic immune response while establishing a seamless interface for precise, stable, low-amplitude neuromodulation. In this work, we assessed the longitudinal stability to record and modulate the neural activity of the implants was tested in awake, behaving mouse models, finding high signal to noise recordings over time, consistent focal stimulation capabilities, and the ability to provide behaviorally detectable stimulation amplitudes as low as 0.25 nc per phase for over a year post implantation. These observations, paired with quantified histology finding no significant immune response and active, healthy neural circuits in the immediate proximity of implanted devices, highlight how flexible implants can provide a functional interface to the brain without the confounds limiting the efficacy of prior implant designs. By coupling the stable stimulating and recording capabilities of StimNETs with an implanted cranial window and longitudinal behavioral tasks, this study assessed the neural response to low-amplitude neural stimulation over weeks of training. Longitudinal calcium imaging and electrophysiological recording of neural activity show an increase in neural activation to fixed stimulation over time, indicating neuroplastic changes to stimulation in the absence of a changing tissue electrode interface, an observation previously confounded by implants that induced chronic changes in the tissue electrode interface. These results highlight

how ultraflexible devices, which minimize tissue disruption, maximize stability, and leverage low amplitude stimulation to achieve precise neuromodulation, can provide a new path forward in neuroscience to interface with the brain and serve as a novel tool to investigate changes in the brain and neural circuits over time.

Disclosures: R. Lycke: None. **C. Xie:** None. **R. Kim:** None. **L. Luan:** None.

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Title: Disinhibitory circuits enhance information integration in converging feedforward networks of cortical columns

Authors: *S.-Y. LEE[1,3], J.-H. HAN[2], H. JANG[3];
[1]Artificial Intelligence, [2]Brain and Cognitive Egnineering, Korea Univ., Seoul, Korea, Republic of; [3]Ctr. for Neuromorphic Engin., Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: Disinhibition, a neural mechanism that inhibits inhibitory connections, is emerging as a critical circuit motif in the modular architecture of the brain. Within the cortical column, comprising a six-layered organized structure, the cortical disinhibitory circuit has been demonstrated to be crucial for sensory integration, decision making, and cortical learning. However, the role of disinhibition mediated by inter-columnar or inter-areal connections remains elusive. To investigate this phenomenon, we constructed three feedforward network models mimicking the canonical feedforward pathway of the primary visual cortex (V1) and primary auditory cortex (A1): one without inter-columnar connections, one with only excitatory inter-columnar connections, and another with an inter-columnar disinhibitory circuit. Each network comprised two separate four-layer Hodgkin-Huxley-type feedforward networks integrated into a single output layer. The inter-columnar feedforward disinhibitory circuit consisted of an inhibitory neuron that inhibited another inhibitory neuron, which in turn provided inhibition to an excitatory neuron within the column. To elucidate the role of inter-columnar feedforward disinhibitory circuit, we quantified the amount of information about two different inputs contained in the output layer by calculating mutual information. The network with inter-columnar excitatory connectivity exhibited the mutual information value of 1.22, higher than the

network without it, which had a mutual information of 1.20, indicating that the inter-columnar excitatory connectivity enhances the propagation of information across different columns integrated in the output layer. Notably, compared to the other two types of network models, the network model with the inter-columnar feedforward disinhibitory circuit demonstrated the highest mutual information of 1.28, suggesting that inter-columnar disinhibitory circuit most effectively promotes reliable integration of inputs. Our findings indicate that disinhibitory circuits play a crucial role in information integration between multiple functional modules of the brain, potentially providing new insights into the mechanisms underlying complex cognitive processes and sensory integration.

Disclosures: S. Lee: None. **J. Han:** None. **H. Jang:** None.

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Title: Biophysical sources of LFP/CSD oscillatory activity in a multiscale mechanistic model of auditory thalamocortical circuits

Authors: N. NOVIKOV[1], S. MCELROY[1], C. MACKEY[2], A. BARCZAK[2], N. O CONNELL[2], C. E. SCHROEDER[2], *S. NEYMOTIN[3], S. DURA-BERNAL[1];
[1]Physiol. & Pharmacol., State Univ. of New York (SUNY) Downstate Hlth. Sci. Univ., Brooklyn, NY; [2]Translational Neurosci. Div., [3]Ctr. for Biomed. Imaging and Neuromodulation, Nathan Kline Inst. for Psychiatric Res., Orangeburg, NY

Abstract: Neural oscillations are an important hallmark of brain activity, often abnormal in neuropsychiatric disorders. Understanding their mechanisms is crucial for developing therapeutic interventions. One of the challenges is to identify oscillatory generators within the laminar structure of the cortex. In experimental recordings, the spectral peaks of local field potential (LFP) and current source density (CSD) may be located in different layers (e.g., alpha peaks deeply for LFP but superficially for CSD in primates), but the biophysical underpinnings of this

discrepancy are not fully understood. Multiscale biophysical mechanistic models of brain circuits could help disentangle the laminar dynamics and resolve the sources of oscillatory generators. In this study, we utilized our previously developed biophysically detailed model of an auditory (A1) thalamocortical circuit and investigated its oscillatory properties. First, we explored the intrinsic oscillatory behavior of the original model. We examined the depth profiles of low- and high-frequency LFP and CSD activity of the model. Both for LFP and CSD, we observed a prominent low-frequency peak in the middle cortical layers and a slightly more superficial high-frequency peak. CSD additionally revealed a superficial peak for both high- and low-frequency activities, and a high-frequency peak in the deep layers.
Subsequently, we investigated the model's activity under the influence of experimentally-constrained external oscillatory inputs. Our findings indicate that the model's intrinsic alpha activity became coupled with the oscillations entrained by the external input. For a low-frequency input, the phase of the entrained oscillations controlled the alpha amplitude, while for a high-frequency input, the entrained amplitude was controlled by the alpha phase. When the stimulation frequency was close to the natural alpha frequency, it was imposed on the model, so the self-generated oscillations locked to the input signal, and their frequencies became matched. Our results contribute to a deeper understanding of the mechanisms that underlie neural oscillations observed in A1 LFP/CSD recordings - both intrinsic and driven by inputs from other brain regions. This work lays the basis for further investigation of oscillatory activity in the detailed A1 model, which may open the way for new approaches in the treatment of neuropsychiatric disorders.

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Late-Breaking Poster

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Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

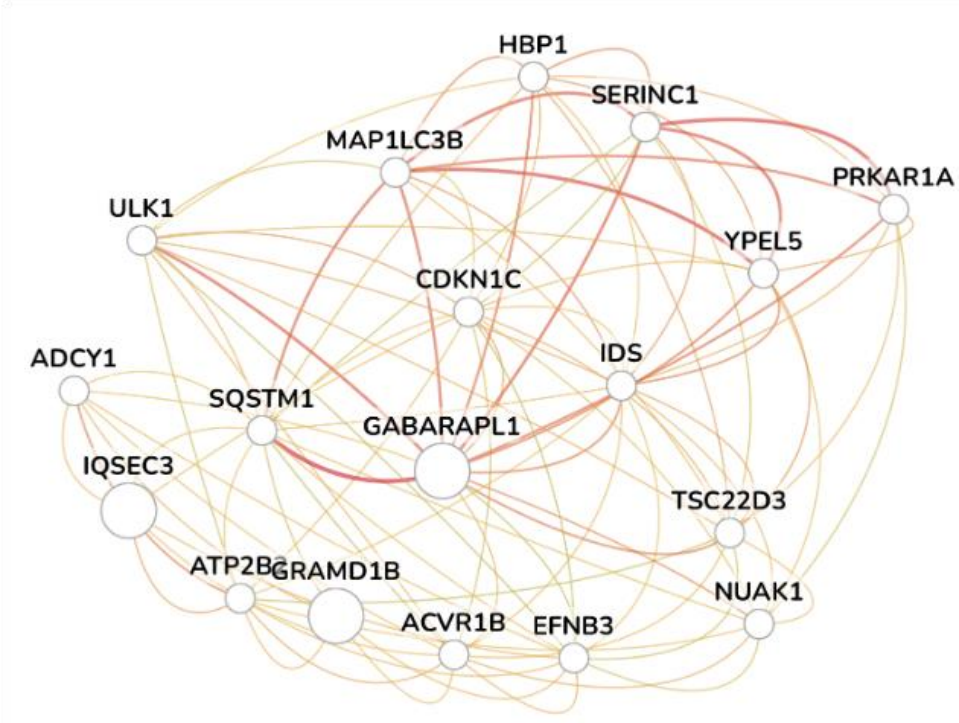
Program #/Poster #: LBA002.051/LBA115

Topic: B.08. Epilepsy

Title: Genes associated with glioma-related epilepsy: a data-driven prediction for tissue-specific gene interactions.

Authors: *L. E. ÁLVAREZ-PALAZUELOS[1], J. E. GRANADOS[2], A. RUIZ RAMIREZ[4], **A. M. ASHLEY**[5], D. L. MASON, III[3], K. AHMAD[6];
[1]Neurosci. and Res., Univ. De Guadalajara, Guadalajara, Mexico; [2]Neurosci., Univ. Autónoma de Guadalajara, Lacey, WA; [3]Neurosci., Univ. Autónoma de Guadalajara, CASA GRANDE, AZ; [4]Neurosci. and Res., Univ. Autónoma de Guadalajara, Guadalajara, Mexico; [5]Neurosci., Univ. Autonoma de Guadalajara, Wichita, KS; [6]Intl. Program of Med., Univ. Autónoma de Gudalajara, Zapopan, Mexico

Abstract: Introduction. Brain tumors are the second most frequent histopathological diagnosis in surgical specimens of epilepsy patients. Over 500 genes associated with epilepsy have been identified. Epileptogenesis is complex, with glutamate playing a critical role in tumor-associated seizures. Wang et al. (2022) analyzed microRNA, mRNA, and lncRNA expression in glioma-related epilepsy (GRE) patients compared to those with glioma without epilepsy (GNE). They found GABARAPL1, GRAMD1B, and IQSEC3 genes had over twofold higher expression in GRE than GNE. Our aim was to decipher the interplay of these genes in a functional interaction network. Methods. Using the Tissue-Specific Gene Network (GIANT) tool, process-specific functional relationship networks of GABARAPL1, GRAMD1B, and IQSEC3 were constructed. In this network, each node represents a gene, each edge a functional relationship, probabilistically weighted based on experimental evidence. Results. A network of the three key genes in GRE patients was constructed, finding 15 genes with functional relationships. Biological process associations were identified, with data available only for GABARAPL1, showing high confidence for selective autophagy, regulation of proteasomal protein catabolic process, and regulation of proteolysis in cellular protein catabolic process. Experimentally and computationally predicted associations of the three genes with various diseases found combined interactions with autism spectrum disorder, peripheral nervous system disease, epilepsy, and retinal disease. Conclusions. In Tuberous sclerosis complex and focal cortical dysplasia models, higher mTOR activity affects the severity of epilepsy and neuropathology, suggesting a connection to symptom severity. Impaired autophagy, due to mTOR overactivation, contributes to epilepsy. Recent evidence focuses on mTOR's effect on autophagy but may overlook other relevant molecules. We propose new intervention targets to modify epilepsy severity, especially GRE.



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Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.052/LBA116

Topic: B.08. Epilepsy

Title: Beyond the Improbable: Coexistence of Refractory Structural Epilepsy, Anti-GAD65+ Autoimmune Encephalitis with Negative Anti-NMDA, and Functional Pituitary Macroadenoma: A Case Report

Authors: *A. GUECHI[1], C. R. OSORNIO[2], M. RUBIO OSORNIO[3];
[1]Mol. Biol. and Genomics, Inst. of Mol. Biol. in Med. and Gene Therapy, Guadalajara, Mexico; [2]Neurophisiology, INNN MVS, México, D.F., Mexico; [3]Neurochemistry, Inst. Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City, Mexico

Abstract: TITLE: Beyond the Improbable: Coexistence of Refractory Structural Epilepsy, Anti-GAD65+ Autoimmune Encephalitis with Negative Anti-NMDA, and Functional Pituitary Macroadenoma: A Case ReportINTRODUCTION: Epilepsy is a chronic neurological disorder characterized by its tendency to generate bursts of excessive or synchronized electrical activity in neuronal tissue, and it impacts over 65 million people globally. The prevalence rate is estimated to be between 4-8 per 1,000 individuals and an incidence of 67.8 cases per 100,000 people, of which 30-33% will be refractory to treatment. The International League Against Epilepsy (ILAE) categorizes epilepsy based on its underlying causes, which include structural abnormalities, genetic factors, infections, metabolic disorders, autoimmune conditions, and cases with unknown causes. Among the various etiologies are rare inflammatory disorders, such as intracranial neoplasms, functioning pituitary macroadenomas (3.9-7.4 cases per 100,000 individuals), and autoimmune encephalitis associated with anti-GAD65 antibodies (<200 reported cases).OBJECTIVE: To describe a rare instance of treatment-resistant epilepsy linked to anti-GAD65 autoimmune encephalitis, with negative anti-NMDA, and the coincidental discovery of a functional pituitary macroadenoma.CASE: 33-year-old male with structural epilepsy refractory to treatment and a history of TBI debuted with a 30-second epileptic cluster with post-ictal psychosis. The semiology of left cephalic version and tonic-clonic bilateralization; EEG with generalized dysfunction of frontocentral predominance and left temporal epileptic activity; MRI with pituitary macroadenoma; and PET with hypometabolism in temporal neocortex, insula, opercular area, and left frontal superior inferior gyrus. Due to psychotic alterations added to the baseline semiology, a lumbar puncture was performed with an approach for autoimmune encephalitis, resulting in negative anti-NMDA and positive anti-GAD65, suggesting immunomodulatory management. CONCLUSIONS: Anti-GAD65, due to

the poor prognosis and heterogeneity of the semiology, should be evaluated in patients with epilepsy who are refractory to treatment of unknown origin. Following a two-year course of immunosuppressive and antiepileptic therapy, the patient has successfully managed to control his epileptic seizures. KEYWORDS: epilepsy, epileptic seizures, refractory epilepsy, cryptogenic epilepsy, structural epilepsy, encephalitis, autoimmune encephalitis, GAD65, macroadenoma.

Disclosures: A. Guechi: None. **C.R. Osornio:** A. Employment/Salary (full or part-time):; Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez. **M. Rubio Osornio:** A. Employment/Salary (full or part-time):; Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez.

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.053/LBA117

Topic: B.08. Epilepsy

Support: NS138649

Title: Model of temporal lobe epilepsy revisited: improved pilocarpine protocol that minimizes animal loss and maximizes the likelihood of spontaneous seizures

Authors: *A. MACIEJCZUK, R. P. GAYKEMA, M. FAILOR, E. PEREZ-REYES; Pharmacol., Univ. of Virginia, Charlottesville, VA

Abstract: Temporal lobe epilepsy (TLE) is the most common focal epilepsy, however there's still a lack of effective treatment for almost a third of the patients. In order to reach our long-term goal, which is to develop a gene therapy to treat TLE, first we need to have a reliable, suitable animal model. One of the compounds that have been used in last few decades to induce TLE in rodents is the cholinergic agonist pilocarpine. Although the pilocarpine model of epilepsy is one of the oldest and well-studied ones, there are still issues that need to be addressed. The high mortality rate associated with the pilocarpine-induced epilepsy model in mice is a significant concern in experimental research. Mice exhibit varying sensitivity to pilocarpine, leading to differences in seizure susceptibility and mortality rates. Factors such as age, strain, and genetic background can influence how mice respond to pilocarpine-induced seizures. Therefore, it is essential to establish a method for closely monitoring the mouse during pilocarpine administration.

Here we present an improved pilocarpine treatment protocol based on pharmacokinetics that applies both to wild type and transgenic mice. Before the systemic administration of pilocarpine, we implant each mouse with stimulating/recording electrodes in the hippocampus and an EEG headset. This allows us to monitor discrete electrographic seizures and implement electrical

kindling if the initial dose fails to induce *status epilepticus* (SE).
We conducted studies using this improved pilocarpine protocol in two groups: TRAP2/Ai9 transgenic mice and C57BL/6J mice. We successfully induced SE in 6 out of 10 TRAP2/Ai9 mice and all 12 C57BL/6J mice, all of which subsequently developed spontaneous seizures. Only 2 out of 22 mice did not survive the procedure. Importantly, the resulting spontaneous seizures occurred regularly (2 per day, every day) and continued for over 4 weeks.
Our updated protocol aims to minimize animal loss while maximizing the likelihood of spontaneous seizure development in mice. This protocol enables us to screen gene therapies on seizures that are both electrographic and tonic-clonic motor behaviors, thereby mimicking human TLE. In pursuit of our long-term goal to develop gene therapy for TLE, our new pilocarpine treatment protocol provides a robust platform for studying seizure mechanisms and evaluating potential therapeutic interventions.

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Topic: B.08. Epilepsy

Support: DBT/IYBA/AD-2019
MG-2LA

Title: The Role of the Fibronectin1-Src Kinase Pathway in Modulating Excitatory Synaptic Transmission in Temporal Lobe Epilepsy

Authors: *N. YADAV[1], P. PRIYA[1], S. ANAND[3], N. DIXIT[1], R. MITTAL[1], J. BANERJEE[4], A. B. DIXIT[2];
[2]ACBR, [1]Dr BR Ambedkar Ctr. for Biomed. Research, Univ. of Delhi, Delhi, India; [3]Dept. of Acute Brain Damage & Cardiovasc. Res., Mario Negri Inst. of Pharmacol. Res., Milano, Italy; [4]Biophysics, All India Inst. of Med. Sci. (AIIMS), New Delhi, India, New Delhi Delhi, India

Abstract: The Role of the Fibronectin1-Src Kinase Pathway in Modulating Excitatory Synaptic Transmission in Temporal Lobe Epilepsy
INTRODUCTION
FN1 is an extra-cellular matrix protein that modulates Src kinase via transmembrane integrins. Src family kinases are crucial points of convergence for various signaling pathways. NMDARs, which are regulated by Src kinase, are important in epileptogenesis and play a role in excitatory synaptic transmission in the brain. This study is designed to test the hypothesis that FN1-altered

Src kinase functions may contribute to hyperexcitability in MTLE.

MATERIALS AND METHODS

Hippocampal and ATL tissue samples from MTLE patients who had undergone surgical resection were acquired for this investigation. Real-time PCR & Western blotting was used to examine the mRNA and protein expression in the hippocampal and ATL areas of both acute and chronic TLE rats and humans. Kinase assay was used to determine functional Src activity. IHC and histopathological examinations were carried out. Functional validation using EPSCs was done using Patch-clamp. **RESULTS**

A significant increase in FN1 mRNA was observed in ATL (10.25±1.59 fold, p=0.001) and hippocampus (6.73±2.59 fold, p=0.024) in MTLE patients. FN1 protein levels were significantly higher in ATL (p=<0.01) and hippocampal region (p=<0.01) of MTLE as compared to the control. IHC also revealed upregulation of FN1 protein in MTLE patients. Src was found to be upregulated in the histopathological, immunohistochemical, and protein level findings of the hippocampus. Kinase activity was higher in the TLE model. A significant increase in Src was observed in the chronic model of TLE with no significant changes in the acute TLE model. PP2 blocker resulted in alterations in EPSC from MTS patients.

CONCLUSION

Our results are indicative of the role of FN1-mediated Src kinase signaling in hyperexcitability via modulating the regulation of NMDA receptors in MTLE. These findings will greatly improve our understanding of the molecular mechanisms and synaptic plasticity involved in the pathogenesis of MTLE, and Src may represent new potential therapeutic drug targets.

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Topic: B.08. Epilepsy

Support: NIH Grant R01NS131865
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Title: Effect of Extracellular Citrate on Neuronal Excitability in SLC13A5 Epilepsy

Authors: *A. LIN[1], L.-J. CHEW[2], K. A. DE LEON[3], H. HIGASHIMORI[4], A. ZENG[5], D. CHEONG[6], E. KUROV[6], I. YOO[6], I. S. JIN[6], J. S. LIU[7];
[1]Brown Univ. Neurosci. Grad. Program, Providence, RI; [2]Dept Mol BIol, Cell Biol and

Biochem, [3]Neurosci., [4]Sch. of Med., [5]Dept. of Mol. Biology, Cell Biology, and Biochem., [7]Neurol., [6]Brown Univ., Providence, RI

Abstract: SLC13A5 Epilepsy is a rare genetic disorder caused by mutations in SLC13A5, a sodium-citrate transporter. Individuals born with mutations in SLC13A5 are affected by severe multi-focal seizures within 24 hours of birth and subsequently develop cognitive and motor impairments. SLC13A5 regulates the import of citrate across the plasma membrane and, in humans, is highly expressed in the brain and liver, but the exact relationship between SLC13A5 expression levels, citrate levels and the observed epileptiform activity in patients is unclear. To investigate the role of endogenous SLC13A5 in varying tissue types and how it affects neuronal activity, we generated tissue-specific conditional SLC13A5 knockout mice: i) full-body SLC13A5 knockout; ii) liver-specific SLC13A5 knockout; and iii) brain-specific SLC13A5 knockout. We subsequently recorded video-electroencephalography (EEG) data from these mice and analyzed for epileptiform activity. Tissue-specific knockout of SLC13A5 in our mouse models were confirmed via quantitative PCR experiments. Preliminary EEG analysis revealed increased numbers of interictal discharges in both full-body and liver-specific SLC13A5 knockout animals, regardless of sex, suggesting that liver-specific expression of SLC13A5 may play a greater role in epileptogenesis than expression in other tissues. To investigate the effect of citrate on neuronal activity, we performed local field potential and whole-cell patch-clamp experiments to assess the relationship between extracellular citrate levels and neuronal excitability. Our results demonstrate increased numbers of interictal discharges upon addition of citrate during local field potential recordings but no significant change in the intrinsic firing properties of regular spiking cells in wild-type animals upon increasing extracellular citrate concentrations. These findings suggest that changes in neuronal excitability in response to changing extracellular citrate concentrations are mediated largely by inhibitory interneurons. Future directions include further analysis of EEG data, specifically assessing seizure frequency and duration in addition to power spectral analyses, as well as further whole-cell patch-clamp experiments examining the effect of extracellular citrate levels on the intrinsic firing properties of inhibitory interneurons.

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Topic: B.08. Epilepsy

Support: University of Alabama Start-Up Funds
R01 NS115776A1

Title: Recurrent spontaneous seizures caused by glial-Dube3a overexpression can be suppressed through modulation of 5-HT signaling

Authors: *S. LANDAVERDE[1], R. D. SCHUBACK[2], S. TAN[2], L. REITER[3], A. IYENGAR[2]; [2]Dept. of Biol. Sci., [1]The Univ. of Alabama, Tuscaloosa, AL; [3]Sch. of Med., Tulane Univ., New Orleans, LA

Abstract: The E3 ubiquitin ligase UBE3A catalyzes the transfer of ubiquitin to substrate proteins marking them for proteolysis. Over-expression of UBE3A is thought to contribute to Duplication 15q syndrome since UBE3A is located within the 15q11.2-q13.1 duplication. Dup15q patients often display autism, muscle hypotonia, and epilepsy. In vertebrate models, overexpressing *UBE3A* in neurons recapitulates several aspects of Dup15q syndrome, but not epilepsy phenotypes. Previous work in Drosophila indicates that overexpression of *Dube3a* (homolog of *UBE3A*) in glia leads to a "bang-sensitive" hyperexcitable phenotype. Here, we used the Gal4-UAS system to compare overexpression of *Dub3a* in glial and neuronal cells (using the *repo*-Gal4 and *nsyb*-Gal4 drivers respectively) to determine if either manipulation led to spontaneous seizure phenotypes. In an intact tethered fly preparation, we recorded action potentials from the indirect flight muscles (dorsal longitudinal muscles, DLMs). We found recurrent, spontaneous spike discharge in *repo > Dube3a* flies ($\bar{x}$ = 2.19 Hz; 0.387 burst freq. min^{-1}) but not *repo > w^{1118}* control flies ($\bar{x}$ = 0.11 Hz; 0 burst freq. min^{-1}) These bursts originated centrally and were correlated between the left and right sides. Furthermore, blocking central excitatory neurotransmission (via the nAChR antagonist Mecamylamine) stopped bursting activity. In contrast, we did not observe spontaneous spike discharges in *nsyb > Dube3a* flies. These studies confirm previous work suggesting that glial rather than neuronal overexpression of *Dube3a* is the main contributor to spontaneous seizure activity. The lack of effective treatment options for Dup15q-associated epilepsy presents a hurdle in seizure management. Previous work has identified, Vortioxetine (a 5-HT1A agonist) and Ketanserin (5-HT2A receptor antagonist) as potential treatment options for Dup15q-associated epilepsy. We reared *repo > Dub3a* and *repo > w^{1118}* flies with these pharmacological agents (40nM and 400nM) to evaluate their efficacy in treating the seizure phenotype. We found both pharmacological agents were successful in eliminating spontaneous spike discharges in *repo > Dube3a* flies. Our findings highlight the potential for glial pathophysiology in underpinning seizures associated Dup15q syndrome.

Disclosures: S. Landaverde: None. **R.D. Schuback:** None. **S. Tan:** None. **L. Reiter:** None. **A. Iyengar:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.057/LBA121

Topic: B.08. Epilepsy

Support: University of Michigan BioInterfaces Institute, NIH NS094399

Title: Pattern matching of clinical intracranial EEG with NeuroPace recordings to identify biomarkers of seizure onset

Authors: *G. BARKELEW[1], K. E. FINN[1], W. C. STACEY[1,2,3];
[1]Biomed. Engin., [2]Neurol., Univ. of Michigan, Ann Arbor, MI; [3]VA Ann Arbor Hlth. Syst., Ann Arbor, MI

Abstract: Closed-loop responsive neurostimulators, such as the NeuroPace RNS System, continuously monitor brain activity and deliver electrical stimulation in response to seizures detected in patients with drug-resistant epilepsy. Battery life constraints limit the sampling rate and bit precision of these devices, reducing the quality of EEG recordings. In this work, we introduce a novel technique to convert high-resolution intracranial EEG obtained from inpatient monitoring into the same format and parameters produced by the RNS System. Data for this study was previously collected from patients who underwent both intracranial EEG monitoring and surgical implantation of the RNS System at the University of Michigan Hospital. Electrodes from the iEEG and NeuroPace were coregistered onto the same 3-D coordinate grid via FreeSurfer post-op structural MRI analysis. Vector math was applied to determine the closest field approximation between the RNS electrodes and intracranial electrodes. Through spectral analysis, we derived a transfer function that accounts for the effects of analog and digital filters on neural signals to approximate the idealized filter response of the RNS System. Visual and spectral analysis of the time-series waveforms and frequency spectra of EEG from each source confirmed seizure onset characteristics were correctly transformed by the filtering function, allowing analysis of how iEEG signals would appear within NeuroPace. These findings suggest that it may be possible to extract biomarkers from high-resolution intracranial EEG and detect them in other implantable devices. This provides an opportunity to develop patient-specific seizure detection parameters and investigate the long-term effects of neurostimulation therapy.

Disclosures: G. Barkelew: None. **K.E. Finn:** None. **W.C. Stacey:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.058/LBA122

Topic: B.08. Epilepsy

Title: Evaluation of the anti-inflammatory effect of Levetiracetam during chronic epilepsy

Authors: *L. A. PICHARDO-MACIAS[1], B. V. PHILLIPS-FARFAN[2], M. GARCIA-CRUZ[3], S. R. ZAMUDIO[6], P. V. CORREA LOPEZ[7], N. CÁRDENAS-RODRÍGUEZ[4], J. MENDOZA TORREBLANCA[5];

[1]Inst. Politecnico Nacional, México, Mexico; [2]Nutrición Exptl., Inst. Nacional Pediatría, Mexico City, Mexico; [3]Inst. Nacional de Pediatría, CDMX, Mexico; [4]Neurosci. Lab., Inst. Nacional de Pediatría, Mexico City, Mexico; [5]Inst. Nacional de Pediatría, Mexico, Mexico; [6]INSTITUTO POLITÉCNICO NACIONAL, CIUDAD DE MEXICO, Mexico; [7]FISIOLOGÍA, Escuela Nacional de Ciencias Biológicas del IPN, México, Mexico

Abstract: Epilepsy is a chronic neurological disease characterized by a predisposition to generate seizures. Evidence is emerging that inflammation might be a consequence, as well as a cause of epilepsy. Experimental studies have shown that seizure activity *per se* can induce brain inflammation and that recurrent seizures perpetuate chronic inflammation. Levetiracetam (LEV) is a second-generation anti-epileptic drug that is highly effective for seizure control. There are controversial results regarding its anti-inflammatory effects, which have been evaluated in the acute phase and during epileptogenesis. For this reason, the present work aims to evaluate the anti-inflammatory effect of LEV in the chronic stage of the disease. For this purpose, male Wistar rats were divided into the following groups: Control, Control + LEV, epileptic and epileptic + LEV. Epilepsy was induced by systemic administration of lithium plus pilocarpine and was determined by monitoring behavior using video recordings. LEV treatment (300 mg/kg/d) lasted one week and was accomplished with osmotic mini-pumps. The brain was obtained and the hippocampus was micro-dissected 2 or 5 months after SE. TNF-α, IL-6 and IL-1β concentrations were quantified. LEV treatment decreased the frequency of seizures on both evaluation periods and decreased the concentration of IL-6 and TNF-α at 2 and 5 months, respectively. Epilepsy increased the concentration of IL-6 at 2 months and TNF-α at 5 months after SE. IL-6 did not show changes. In conclusion, the results showed that epilepsy increased specific inflammatory mediators. This suggests that LEV has anti-ictogenic effects by decreasing neuroinflammation.

Disclosures: L.A. Pichardo-Macias: None. **B.V. Phillips-Farfan:** None. **M. Garcia-cruz:** None. **S.R. Zamudio:** None. **P.V. Correa lopez:** None. **N. Cárdenas-Rodríguez:** None. **J. Mendoza torreblanca:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.059/LBA123

Topic: B.08. Epilepsy

Title: Deciphering the Anticonvulsant Code: Temporal Dynamics and Asynchronous Patterns in Basolateral Amygdala Electrical Stimulation for Seizure Control in the PTZ Model.

Authors: *A. RODRIGUES[1], L. O. GUARNIERI[2], V. R. COTA, Sr.[3], M. F. MORAES[4]; [1]Dept. of Physiol. and Pharmacol., Univ. Federal de Minas Gerais, Belo Horizonte, Brazil;

[2]Dept. de Ciências Fisiologicas, Univ. Federal De Minas Gerais - Núcleo De N, Belo Horizonte, Brazil; [3]Rehab Technologies Lab., Inst. Italiano di Tecnologia, Genova, Italy; [4]Nucleo de Neurociencias (NNC) - Univ. Federal de Minas Gerais, Belo Horizonte, Brazil

Abstract: Introduction: The development of neuromodulation protocols using electrical stimulation is a promising therapeutic option for drug-resistant epilepsy. Our research shows that distinct temporal patterns of electrical stimulation, varying from periodic to temporally complex NPS, can promote or inhibit epileptic seizures. This study explores how stimulation patterns composed of binary-coded words, made up of 14 ms bins dividing a theta oscillation, may affect long-range connectivity of epileptiform activity based on "word regularity."Objectives: Determine the effectiveness of non-periodic versus periodic ES patterns in reducing seizure frequency and severity in a PTZ-induced seizure model.Methods: Male Wistar rats (8-10 weeks; 250-300g) from the ICB Bioterium Vivarium at UFMG were used, housed under controlled conditions following ethical guidelines. The protocol was approved by the Animal Ethics Committee (19/2024). Rats were divided into four groups, subjected to different ES patterns via implanted bipolar electrodes in the basolateral amygdala: GE1 (fixed word 4-stimuli/second - FIXw non-periodic organized), GE2 (PS fixed 250 ms inter-pulse intervals), GE3 (non-periodic with restricted randomization, NPSRR), and GE4 (multiple words - MULTw non-periodic disorganized, NPSD), all at 4Hz. One week post-surgery, baseline seizure thresholds were determined. On the experiment day, rats received a PTZ ramp infusion (tail vein 10 mg/ml PTZ 1 ml/min) alongside ES protocols. Behavioral responses were recorded to assess latency to forelimb clonus and tonic-clonic seizures. Post-experiment, rats were euthanized and analyzed using Fluoro-Jade B staining and C-Fos expression for neuronal damage and activation.Results: Significant differences in seizure onset latency were observed across different ES patterns. NPSD(GE4) significantly increased latency to seizure onset compared to PS(GE2), indicating enhanced seizure suppression. Neuronal activity analysis in the basolateral amygdala showed reduced activation in non-periodic groups, particularly GE4. Converting the PTZ threshold into drug volume injected, we have: NPSD: 2 ml (Mean: 1.75 ml),FIXw: 1 ml (Mean: 1.1 ml), PS: 0.5 ml (Mean: 0.55 ml), and NPSRR: 1.8 ml (Mean: 1.9 ml). The ANOVA p-value was 0.1049, and the total normalized standard deviation was 0.05. The c-Fos and FluoroJ data are still being analyzed.Conclusion: This research presents non-periodic electrical stimulation (NPS) as a novel, effective treatment for drug-resistant epilepsy, offering significant therapeutic benefits and potential to improve patient quality of life by reducing uncontrolled seizures.

Disclosures: A. Rodrigues: None. **L.O. Guarnieri:** None. **V.R. Cota:** None. **M.F. Moraes:** 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.; CNPq 408170/2023-9.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.060/LBA124

Topic: B.08. Epilepsy

Support: STI2030-Major Projects 2021ZD0202103

Title: Termination of convulsion seizures by destabilizing and perturbing seizure memory engrams

Authors: *Z. HUANG;
Peking Univ., Beijing, China

Abstract: Epileptogenesis, arising from alterations in synaptic strength, shares mechanistic and phenotypic parallels with memory formation. However, direct evidence supporting the existence of seizure memory remains scarce. Leveraging a conditioned seizure memory (CSM) paradigm, we found that CSM enabled the environmental cue to trigger seizure repetitively, and activating cue-responding engram cells could generate CSM artificially. Moreover, cue exposure initiated an analogous process of memory reconsolidation driven by mTOR-BDNF signaling. Pharmacological targeting of the mTOR pathway within a limited time window reduced seizures in animals and interictal epileptiform discharges (IEDs) in patients with refractory seizures. Our findings reveal a causal link between seizure memory engrams and seizures, which leads us to a deeper understanding of epileptogenesis and points to a promising direction for epilepsy treatment.

Disclosures: Z. Huang: None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.061/LBA125

Topic: B.08. Epilepsy

Title: Model-based cost-effectiveness estimates of hormonal treatment strategies in children with Infantile epileptic spasms syndrome

Authors: *N. DEVI;
Chandigarh Col. of Pharmacy, Landran, Mohali, India

Abstract: Background: Due to the conflict evidences in cost-effectiveness of hormonal therapy for children with Infantile epileptic spasms syndrome (IESS), including West syndrome (WS), there is a need to explore real-world treatment patterns. **Objective:** This study was focused on assessing treatment effectiveness, safety, Health-Related Quality of Life (HRQoL), and conducting a cost-effectiveness analysis (CEA) for hormonal therapies in managing children

with IESS. **Methods:** A prospective observational study with a two-week follow-up assessment was conducted at a tertiary-care centre in North India. Children with WS (aged 3-18 months) either advised adrenocorticotrophic hormone (ACTH) or oral prednisolone were included and compared for cessation of spasms, occurrence of treatment-emergent adverse events (TEAEs), Health related quality of life (assessed through Hi-QUALIN) scores and CEA. The statistical significance was assessed using chi-square test for categorical data or t-test for continuous data. A decision-tree model to predict the benefit and costs of ACTH and oral prednisolone in children with WS. One-way sensitivity analyses were performed to understand the impact of a single variable on the cost-effectiveness (CE) model and visualized in the Tornado diagram. **Results:** Of 93 children diagnosed with WS [73 (79%) boys; mean age (SD)= 10.1 (3.7) months; median (IQR) spasms burden: 27.8 (14.0, 61.9)], 55 (59%) were initiated on ACTH, while the rest on oral prednisolone (38 (41%)). After two weeks of treatment, 29/55 (53%) on ACTH and 13/34 (34%) patients on oral prednisolone achieved spasm cessation. Additionally, a higher number of TEAEs (non-significant) were reported in ACTH treated group (23/55 (42%)) as compared with the oral prednisolone group (19/38 (50%)). The children aged 3 to 12 months were showed statistically significant improvement in HRQoL after two weeks of treatment (p-value: <0.01). Using a decision tree model CEA resulted with higher ICER (1,22,185 INR; ~1468.90 USD) for ACTH than oral prednisolone which suggests payer's need to spend 1,22,185 INR one unit increase to be spasm free with the treatment of ACTH. **Conclusion:** The study findings suggested ACTH is possibly more cost-effective than oral prednisolone for the management of WS. Additionally, the hormonal therapy is more likely capable of improving the HRQoL in children with WS.

Disclosures: N. Devi: None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.062/LBA126

Topic: B.08. Epilepsy

Support: INP EO22 program, protocol 85/2010.

Title: Effect of ketogenic diet on KCC2 expression in the hippocampal strata of rats with seizures induced by amygdaloid kindling

Authors: *L. GRANADOS-ROJAS[1,2], L. F. HERNANDEZ, Jr.[3], E. L. BAHENA[2], T. E. JUÁREZ ZEPEDA[2], V. CUSTODIO[3], A. C. VAZQUEZ VEGA[2], J. G. MARTÍNEZ-GALINDO[4], K. JERONIMO CRUZ[2], A. VANOYE CARLO[2], P. DURAN[5], C. OSORNIO[3]; [1]Neurociencias II, Natl. Inst. of Pediatrics (Mexico), México city, Mexico; [2]Neurosciences II Lab., Natl. Inst. of Pediatrics, Mexico city, Mexico; [3]Neurophysiol., [4]Dementia Lab., Natl. Inst.

of Neurol. and Neurosurg., Mexico city, Mexico; [5]Exptl. Animal Biol. Lab., UNAM, Mexico city, Mexico

Abstract: The ketogenic diet (KD), a high-fat, low-carbohydrates, adequate-protein diet, is a non-pharmacological treatment used in refractory epilepsy. Its mechanism of action is not yet fully understood. The cation-chloride cotransporter, KCC2, transports chloride out of neurons, thus contributing to the intraneuronal concentration of this ion, which in turn determines the inhibitory or excitatory effect of the neurotransmitter GABA that regulates brain excitability in epilepsy. Modifications in the expression of KCC2 by KD could explain the beneficial effect of this diet on epilepsy. This work aimed to determine the impact of the KD on the expression of the KCC2 cotransporter in the hippocampal strata: oriens, pyramidal, lucidum and the rest strata (radiatum-lacunosum-moleculare) of rats with seizures induced by amygdaloid electrical kindling, an epilepsy model. Male Sprague-Dawley rats were separated into groups fed with normal diet (ND) or KD, with or without kindling, sham and intact (n = 8 in each group). At the beginning and end of the experimental treatments, glucose and β-hydroxybutarate concentration were quantified in peripheral blood. KCC2 cotransporter was detected by immunohistochemistry in the hippocampal strata sections, afterwards, the KCC2 expression was evaluated by optical density. The results were analyzed by applying a 3-way mixed factorial ANOVA (glucose and β-hydroxybutarate) and a two-way factorial ANOVA (optical density) ($p < 0.05$). At the end of the experiment, KD-fed groups showed a reduction of glucose and an increase in β-hydroxybutarate concentration. The latency to reach kindling stage 2 was higher in the KD-fed group. Pyramidal and lucidum strata, presented an increase in KCC2 in the KD when compared to the DN-fed groups. The kindling groups presented lower levels of KCC2 than those without kindling, sham or intact. Thus, KD maintained the expression levels of KCC2 in the pyramidal and lucidum hippocampal strata. The modulation of the expression of the KCC2 cotransporter is probably the mechanism of action of KD as an adjuvant in the control of epilepsy.

Disclosures: L. Granados-Rojas: None. **L.F. Hernandez:** None. **E.L. Bahena:** None. **T.E. Juárez Zepeda:** None. **V. Custodio:** None. **A.C. Vazquez Vega:** None. **J.G. Martínez-Galindo:** None. **K. Jeronimo Cruz:** None. **A. vanoye carlo:** None. **P. Duran:** None. **C. Osornio:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.063/LBA127

Topic: B.08. Epilepsy

Support: INP E022 program protocol 85/2010

Title: Effect of ketogenic diet on drug metabolizing enzymes CYP2E1 and CYP3A2 in rat brain

Authors: *T. JUÁREZ ZEPEDA[1], A. VENCES-MEJIA[2], D. MOLINA-ORTIZ[2], C. TORRES-ZÁRATE[2], P. DURAN[4], L. GRANADOS-ROJAS[3];
[1]Neurosci. II Lab., [2]Genet. Toxicology Lab., Natl. Inst. of Pediatrics, Mexico City, Mexico; [3]Neurosciences II Lab., Natl. Inst. of Pediatrics, Mexico city, Mexico; [4]Exptl. Animal Biol. Lab., UNAM, Mexico City, Mexico

Abstract: The ketogenic diet (KD) is a high-fat, low-carbohydrate, and adequate-protein diet used asa non-pharmacological treatment for refractory epilepsy. Cytochrome P450 (CYPs)enzymes are responsible for the metabolism of many exogenous and endogenouscompounds. CYPs are abundant in the liver and are also expressed in many extra-hepatictissues including the brain. Variations in drug metabolism between subjects have long beenconsidered the source of diverse drug responses, clinical relevance of such variabilitytranslates into both therapeutic failure and the appearance of associated adverse effects.This study was designed to analyze the effects of a KD on CYP2E1 and CYP3A2 expressionin the brain and liver of young Wistar rats. Animals were randomly assigned to one of thefollowing groups: rats fed *ad libitum* with KD or standard rodent laboratory diet (n = 12 ineach group). The treatment regimen was extended for three months, and the brain (cortexand cerebellum) and liver tissues were collected for further analysis. The mRNA and proteinexpression of CYP2E1 and CYP3A2 in brain, cerebellum, and liver tissue samples wereanalyzed by qRT-PCR and Western blot assays, respectively. The data were statisticallyanalyzed by the SPSS version 16.0 statistical package. Data expressed as the mean ± SE.Differences between the groups were assessed using one-way analysis of variance(ANOVA). Differences were considered statistically significant at $P < 0.05$. Our resultsshowed that KD significantly induced significantly CYP2E1 mRNA and protein in the cerebralcortex and cerebellum without modifying them in the liver, while CYP3A2 mRNA and proteinexpression were increased in both the brain and liver. The induction of CYP2E1 in the brainby KD could have an important local therapeutic effect since this CYP participates inconverting glucose into acetone, which has an anticonvulsant effect. Therefore, DC-inducedCYP2E mRNA and protein, as well as the increase of CYP3A2 protein in rat brain, could beconsidered a decisive factor in the variation of drug response and toxicity affecting themetabolism of endogenous and xenobiotic compounds, including hormones, and numeroustherapeutic drugs. Furthermore, induction of CYP2E1 in the CNS could increaseneurotoxicity risks through bioactivation, lipid peroxidation, and DNA damage.

Disclosures: T. Juárez Zepeda: None. **A. Vences-Mejia:** None. **D. Molina-Ortiz:** None. **C. Torres-Zárate:** None. **P. Duran:** None. **L. Granados-Rojas:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.064/LBA128

Topic: B.08. Epilepsy

Support: NIH R01-NS094399

Title: Classifiers trained on physician EEG labeling improve specificity of automated HFO detectors in refractory human epilepsy

Authors: *S. TAN[1], S. V. GLISKE[3], W. C. STACEY[2];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Neurol., Univ. of Michigan, Saline, MI; [3]Neurosurg., Univ. of Nebraska Med. Center, Dept. of Neurosurg., Omaha, NE

Abstract: High frequency oscillations (HFOs) in EEG are a promising biomarker for localizing the epileptogenic zone (EZ) and predicting seizure outcomes. While automated HFO detectors have helped to alleviate the labor-intensive labeling of HFOs, they are mostly trained on data from individual EEG channels. These detectors create false positive detections due to EEG artifacts, many of which are not apparent when viewed on individual EEG channels. When putative detected HFOs are marked and displayed within clinical EEG software with data from all channels at once, such artifacts are readily visible to clinicians, who lose confidence in the accuracy of an HFO detector if it becomes apparent that the detector is finding false positives. Similarly, analysis of HFOs with false positives will be less reliable. Thus, there is a need to improve the specificity of HFO detections. We hypothesize that training classifiers to identify false positive HFOs using expert-marked data will enable better identification of true HFOs and fewer false positives. An automated HFO detector was used to detect HFOs from the EEG data of 20 patients. The HFO events were labeled within the Persyst viewer. Six trained clinicians each reviewed 200 HFO events from each patient and labeled them as being clearly artifacts, clearly physiological brain signals, or uncertain. Three reviewers labeled each event independently. We trained a logistic regression model and a neural network with various subsets of expert-derived features, consisting of features computed across multiple or individual EEG channels, to identify false positive HFOs. 23.83% of the HFO events were unanimously labeled as artifacts. Multiple model variants with leave-one-out cross-validation demonstrated at least a mean of 0.75 across sensitivity, specificity, and area under the receiver operating characteristic curve. These models include those trained on features derived from either scalp, intracranial, or both scalp and intracranial channels, and computed from EEG across single, multiple, or both single and multiple channels. The best models were identified and used to investigate features that contribute to effective representations of the artifacts. The resulting algorithms can be used to screen for artifactual HFOs after automated HFO detections to potentially enable better localization of EZs and seizure outcomes after surgical removal of EZs.

Disclosures: S. Tan: None. **S.V. Gliske:** None. **W.C. Stacey:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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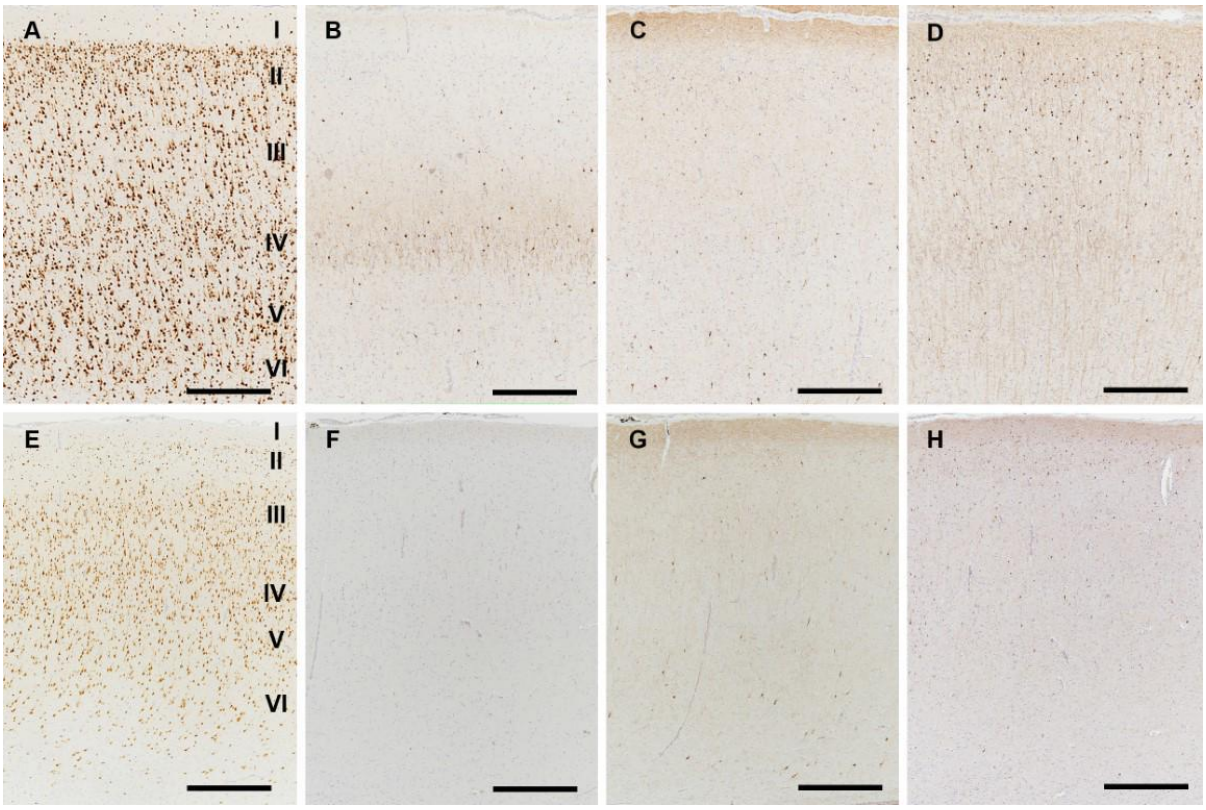
Topic: B.08. Epilepsy

Support: AMED (JP21wm0425019)
an intramural fund from NCNP (3-8, MT)
Kakenhi (21K06417, 18K06506)

Title: Parvalbumin-positive neuron density is lower in patients with temporal lobe sclerosis

Authors: *M. MIZUTANI[1], T. SANO[2], M. TAKAO[2], M. IWASAKI[3];
[1]Dept. of Neuropsychiatry, The Univ. of Tokyo, Tokyo, Japan; [2]Lab. Med., [3]Dept. of Neurosurg., Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan

Abstract: Background: Temporal lobe sclerosis (TLS) is characterized by laminar neuronal loss and gliosis in the neocortex, occurring alongside hippocampal sclerosis. Its clinical and neuropathological features remain incompletely understood. This study aimed to reveal the clinical and electrophysiological features of patients with TLS. Methods: The study included 15 patients with TLS (8 moderate, 7 severe) and 15 patients without TLS who underwent anterior temporal lobectomy for drug-resistant mesial temporal lobe epilepsy. Clinical information—including seizure frequency, seizure types, past medical history, psychiatric symptoms, and seizure outcomes—and the density of inhibitory neurons such as parvalbumin-, somatostatin-, and calretinin-positive neurons in the temporal cortex were compared between patients with and without TLS. Results: Cases with TLS tended to have a history of initial precipitating episode in childhood (p=0.002), especially a history of encephalopathy or encephalitis (p=0.017) including viral encephalitis. Immunohistologically, the density of all neurons and parvalbumin-positive neurons was significantly lower in the temporal cortex of patients with TLS (7.80 vs. 2.81/mm2, p=0.001). No significant differences were observed in somatostatin- or calretinin-positive neuron densities between groups. The reduction in parvalbumin-positive neurons was evident in both superficial and deep cortical layers, suggesting a widespread impact on inhibitory circuits. No significant associations were found between TLS and other clinical features such as seizure frequency, postoperative seizure outcomes, or psychiatric symptoms. Conclusions: This study demonstrated that the development of TLS is related to a history of encephalopathy in infancy. A decrease in parvalbumin-positive neuron density may be associated with TLS pathogenesis. Future pathologic research is warranted to clarify the mechanisms underlying TLS development and its impact on epileptogenesis.



Disclosures: M. Mizutani: None. **T. sano:** None. **M. Takao:** None. **M. Iwasaki:** None.
Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Program #/Poster #: LBA002.066/LBA130

Topic: B.08. Epilepsy

Support: German Research Foundation (grant number: DO 2542/1-1)
Research Commission, Medical Faculty - University of Freiburg (grant DON 1207/19)

Title: Focal cortical dysplasia-dependend altered myelination in the human frontal lobe

Authors: *C. DONKELS[1], S. HUBER[2], T. DEMERATH[2], M. HEERS[2], A. SCHULZE-BONHAGE[2], M. PRINZ[4], U. HAUSSLER[5], A. VLACHOS[6], J. NAKAGAWA[3], C. A. HAAS[4]; [1]Univ. Med. Ctr. Freiburg, Freiburg im Breisgau, Germany; [3]Translational Epilepsy Research, Dept. of Neurosurg., [2]Univ. Med. Ctr. of Freiburg, Freiburg, Germany; [4]Univ. of Freiburg, Freiburg, Germany; [5]Exptl. Epilepsy Research, Dept. of Neurosurgery, Univ. of Freiburg, Freiburg, Germany; [6]Neuroanatomy, Med. Faculty, Univ. of Freiburg, Freiburg, Germany

Abstract: Focal cortical dysplasias (FCDs) are local malformations of the human neocortex and a leading cause of intractable epilepsy. FCDs are classified into different subtypes including FCD IIa and IIb, characterized by a blurred gray-white matter boundary or a transmantle sign indicating abnormal white matter myelination. Recently, we have shown that myelination is also compromised in the gray matter of FCD IIa of the temporal lobe. Since myelination is key for brain function and is imbalanced in epilepsy, we investigated myelination in the gray matter of FCD IIa, FCD IIb and non-dysplastic epileptic controls from the frontal lobe. We applied *in situ* hybridization, immunohistochemistry and electron microscopy to quantify oligodendrocytes, to visualize the myelination pattern and to determine ultrastructurally the axon diameter and the myelin sheath thickness. In addition, we analyzed the transcriptional regulation of myelin-associated transcripts by real-time RT-qPCR and chromatin immunoprecipitation (ChIP). We found that in particular frontal lobe FCD IIb showed myelination disturbances such as significantly increased numbers of myelinating oligodendrocytes (OLs) and an irregular and disorganized myelination pattern covering an enlarged area in comparison to FCD IIa and controls. Interestingly, both FCD types presented with larger axon diameters when compared to controls. A significant correlation of axon diameter and myelin sheath thickness was found for FCD IIb and controls, whereas in FCD IIa large caliber axons were less myelinated. On the level of gene expression, FCD IIb presented with a significant up-regulation of myelin-associated mRNA synthesis in comparison to FCD IIa and by enhanced binding-capacities of the transcription factor MYRF to promoters of myelin-associated genes reflecting the need for more myelin due to increased axon diameters. These data show that FCD IIa and IIb are characterized by divergent signs of altered myelination which may contribute to the epileptic phenotype.

Disclosures: C. Donkels: None. **S. Huber:** None. **T. Demerath:** None. **M. Heers:** None. **A. Schulze-Bonhage:** None. **M. Prinz:** None. **U. Haussler:** None. **A. Vlachos:** None. **J. Nakagawa:** None. **C.A. Haas:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.067/LBA131

Topic: B.08. Epilepsy

Support: Hamot Foundation to Gonzalez-Martinez

Title: Thalamocortical Interactions in Focal Epilepsy: Implications for Personalized Thalamic Electrical Stimulation Therapies

Authors: *A. DAMIANI[1], J. HO[2], S. V. SARMA[5], E. PIRONDINI[3], J. A. GONZÁLEZ-MARTÍNEZ[4];

[2]Rehab and Neural Engin. Labs, [3]Rehabil. and Neural Engin. Labs., [4]Neurolog. Surgery, [1]Univ. of Pittsburgh, Pittsburgh, PA; [5]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Delivery of electrical stimulation to specific thalamic regions offers a therapeutic approach for patients with refractory focal and generalized epilepsy who are not candidates for resective surgery. However, outcomes vary significantly, in particular for focal epilepsy, influenced by various factors, notably the precise anatomical and functional alignment between cortical regions generating epileptic discharges and the targeted thalamic stimulation sites.Here we hypothesized that targeting thalamic nuclei with precise anatomical and functional connections to epileptic cortical areas (an approach that we refer to as hodological matching) could enhance neuromodulatory effects on focal epileptic discharges. To investigate this, we examined three thalamic subnuclei (pulvinar nucleus, anterior nucleus, and ventral intermediate nucleus/ventral oral posterior nuclei) in 26 patients undergoing stereoelectroencephalography (SEEG), with concurrent sampling of cortical and subcortical regions.We first identified hodologically organized thalamocortical fibers connecting these nuclei to individual seizure onset zones (SOZs) via neuroimaging and electrophysiological techniques. Further, analysis of 216 spontaneous seizures revealed the critical role of matched thalamic nuclei in seizure development and termination. Importantly, electrical stimulation of hodologically matched thalamic nuclei immediately suppressed intracortical interictal epileptiform discharges, contrasting with ineffective outcomes from stimulation of unmatched targets. Finally, we chronically implanted two patients with a hodologically-matched neurostimulation system, which led to a clinically relevant reduction (>95%) in seizure frequency.Our results underscore the potential of hodological targeting to modulate epileptiform activity in specific cortical regions, highlighting the promise of precision medicine in thalamic neuromodulation for focal refractory epilepsy, suggesting novel avenues for clinical targeting and therapeutic strategies.

Disclosures: A. Damiani: None. **J. Ho:** None. **S.V. Sarma:** None. **E. Pirondini:** None. **J.A. González-Martínez:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.068/LBA132

Topic: B.08. Epilepsy

Title: Machine learning algorithm for predicting seizure control after temporal lobe resection using peri-ictal electroencephalography

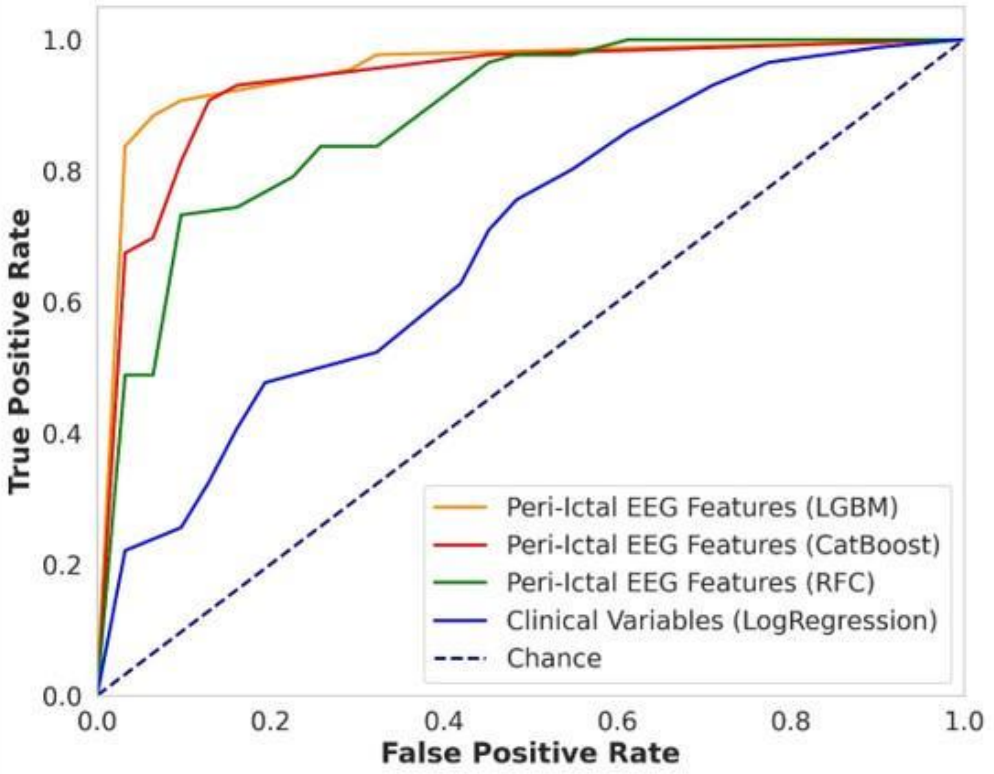
Authors: *S. R. SHEIKH[1], S. GHOSN[2], K.-S. JEONG[3], C. Y. SAAB[4];
[1]Neurosrugery, Cleveland Clin., CLEVELAND, OH; [2]Cleveland Clin., Cleveland, OH; [3]Brown Univ., Providence, RI; [4]Biomed. Engin., Cleveland Clin. / Case Wester/ Brown, Cleveland, OH

Abstract: 30-50% of patients who undergo brain resection for drug resistant epilepsy (DRE) fail to achieve sustained seizure freedom; accurate outcome prediction tools are necessary. We hypothesized that "peri-ictal" EEG (i.e. minutes immediately before and after a seizure) may be optimal for creating an EEG-based surgical outcome prediction framework.

We analyzed data from 294 patients who had undergone temporal lobe resection for DRE with preoperative video EEG evaluation. We captured 5 minutes of "peri-ictal" EEG from a single pre-operative seizure for each patient. A validated machine-learning (ML) artifact detector was applied to raw EEG data. Artifact-free data were then transformed into the frequency domain (Fourier transformation) and power-spectral density (PSD) was calculated across a range of physiological frequencies (1-40Hz). Iterative ML model-building experiments were conducted to find classifier algorithms to predict post-operative seizure control.

Of the 294 patients, 170 were seizure-free at last follow-up, average age was 37.3 years, mean follow-up was 3.4 years, and 78% had abnormal MRI. We were able to build multiple machine learning models that could predict seizure outcome on the basis of peri-ictal EEG features, underscoring the value of peri-ictal data in this context (Figure). The winning model was a Light Gradient Boost Machine (LGBM) classifier; when tested on a hold-out dataset, accuracy was 91.9% (AUC 0.977). The winning model was constructed with 34 EEG features: 70% of features were from the pre-ictal period, 62% from temporal electrodes, 56% from the beta band.

Prior efforts to create surgical outcome prediction frameworks have relied on clinical variables with limited accuracy or data inputs that are invasive (intra-cranial EEG) or absent in routine clinical care (connectomics). We demonstrate that using machine learning methods, 5 minutes of peri-ictal scalp EEG can yield accuracies >90%. Once validated on a multicenter dataset, this approach will be implementable for all temporal DRE patients using data that is captured in routine clinical care.



Model Features	Candidate Model	Accuracy	Precision	Recall	AUC of ROC
Peri-ictal scalp EEG features only	LGBM, 34 EEG features	91.9	95.1	90.7	0.977
Peri-ictal scalp EEG features only	CatBoost, 28 EEG features	90.5	89.1	95.3	0.988
Peri-ictal scalp EEG features only	RFC (with PCA, 57 features)	81.1	79.6	90.7	0.901
Clinical variables from prevailing nomogram	Logistic Regression	62.1	67.4	67.4	0.642

Disclosures: S.R. Sheikh: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on Provisional Patent filing. **S. ghosn:** None. **K. Jeong:** None. **C.Y. Saab:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on Provisional Patent filing.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.069/LBA133

Topic: B.08. Epilepsy

Support: National Institutes of Health [R01-NS094399]

Title: Separating physiological from pathological epileptic High Frequency Oscillations using machine learning approaches

Authors: *J. LIN[1], S. V. GLISKE[4], M. R. ZOCHOWSKI[2], W. C. STACEY[3];
[2]Dept. of Physics and Biophysics Program, [1]Univ. of Michigan, Ann Arbor, MI; [3]Neurol., Univ. of Michigan, Saline, MI; [4]Neurosurg., Univ. of Nebraska Med. Center, Dept. of Neurosurg., Omaha, NE

Abstract: For decades, high frequency oscillations (HFO) have been touted as a promising electrographic biomarker of epileptic tissue. However, the advancement of HFO research has been limited by the lack of a reliable way to differentiate pathological from physiological HFOs, which has been difficult given the lack of a 'gold standard' comparison. HFO recordings are thus a mix of normal activity (physiological HFOs), epileptic activity (pathological HFOs), and false HFOs due to noise. Without a method to distinguish these events, HFO analyses have been inconsistent. We tackled this problem through a multi-faceted approach: 1) supervised classification of HFOs using expert-selected signal features, 2) supervised classification of pre-processed HFO signals and, 3) unsupervised clustering of pre-processed HFO signal. The purposes of these different approaches were not only to distinguish pathological from physiological HFOs, but also to characterize the morphological differences between them. Statistical rigor was achieved by employing our sizeable dataset consisting of millions of HFOs collected from continuous, multi-day recordings of patients from the University of Michigan. We designated physiological and pathological HFOs with surrogate labels of HFOs originating from resected seizure onset zones channels and HFOs originating from non-resected channels. We showed that all of our supervised classifiers provided a good separability between pathological and physiological HFOs. Likewise, the unsupervised clustering also showed a difference between pathological and physiological HFOs. These results suggest a way of distinguishing pathological and physiological HFOs which can be used to increase the specificity of epileptic HFO datasets for more reliable and consistent analyses.

Disclosures: J. Lin: None. **S.V. Gliske:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Natus Medical, Inc. **M.R. Zochowski:** None. **W.C. Stacey:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Natus Medical, Inc.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.070/Web Only

Topic: B.08. Epilepsy

Support: NSFC

Title: Detect epileptic seizure and localize seizure onset zone using interictal SEEG's PSD aperiodic components

Authors: *Y. ZHENG[1,2,3], T.-P. JUNG[2], X. TIAN[3];
[1]Sch. of Sci. and Engin., The Chinese Univ. of Hong Kong, Shenzhen, Shenzhen, China; [2]Swartz Ctr. for Computat. Neurosci., Inst. for Neural Computation, La Jolla, CA; [3]Neural and Cognitive Sci., New York Univ. Shanghai, Shanghai, China

Abstract: Epilepsy is one of the most common neurological diseases impacting about 70 million people in the world. A minimum of thirty percent of individuals with epilepsy develop drug resistance, making them suitable candidates for neuromodulation therapy. The management of drug-resistant epilepsy requires precise identification and localization of seizure onset zones (SOZs). While stereoelectroencephalography (SEEG) provides direct insights into brain activity, traditional analyses have focused predominantly on the periodic components of the power spectral density (PSD), often neglecting the informative potential of its aperiodic components. This study aims to harness these aperiodic components to improve the detection and localization of seizures, addressing significant gaps in the current understanding of epilepsy. In collaboration with a medical institution in Guangzhou, China, long-term SEEG data were collected from 8 patients diagnosed with drug-resistant epilepsy. Each patient had between 6 to 18 electrodes implanted, encompassing over 100 channels distributed across various brain regions. We computed the PSD of each segment using FFT based on Welch's method and utilized the Fitting Oscillations and One-Over F (FOOOF) parametric method to extract the aperiodic components of the PSD, such as offset, exponent, and knee. We then applied machine learning models including K-nearest neighbors (KNN), random forest, support vector machine (SVM), and decision trees to classify states of epileptic and non-epileptic activity based on aperiodic features. Our results demonstrate the high discriminatory capability of the aperiodic components within the PSD. The random forest model outperformed others, achieving an average accuracy of 89.91%, with the best case reaching up to 97.11%. Further analysis at the channel level revealed that between 3 to 12 channels per patient achieved perfect classification accuracy (100%), accurately reflecting the epileptic activity. These channels were predominantly located in brain regions identified as SOZs through concurrent MRI and CT, validating the effectiveness of our approach. Additional tests on previously untrained long-term data confirmed the model's robustness, with detection accuracies approaching 99.95%. This investigation highlights the critical but previously underappreciated role of aperiodic components in SEEG data analysis. By emphasizing these components, our study not only enhances the predictive accuracy for seizure events but also refines the localization of seizure onset zones, offering substantial benefits for surgical planning and therapeutic interventions in epilepsy care.

Disclosures: Y. Zheng: None. **T. Jung:** None. **X. Tian:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.071/LBA134

Topic: B.09. Glial Mechanisms

Title: Midbrain PAG astrocytes modulate mouse defensive and panic-like behaviors

Authors: *S. LEE;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Defensive behaviors against threatening situations are crucial for survival, and maladaptation of neural functions involved in defensive behavior may result in panic-like behavior. Therefore, defensive behaviors must be optimized for animals to efficiently avoid danger and maximize their chance of survival. The midbrain periaqueductal gray (PAG) controls defensive behaviors. However, the underlying substrate of dysregulated panic-like defensive responses is still unknown. Using *in vivo* calcium recordings in mice, we found that PAG astrocytes are activated during threatening situations and trigger defensive behaviors. Using astrocyte optogenetic activation and pharmacologic ablation, we provide evidence that PAG astrocyte activation and subsequent ATP release are required for the manifestation of optimal defensive behavior; therefore, aberrant activation of PAG astrocytes leads to maladaptive defensive behavior that resembles panic-like behavior. Our results suggest that PAG astrocytes are one of the neurobiological substrates underlying defensive dysregulation and might be an important cue in panic-related behaviors via a distinct increase in calcium activity and ATP release.

Disclosures: S. Lee: None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Program #/Poster #: LBA002.072/LBA135

Topic: B.09. Glial Mechanisms

Support: MOST 109-2320-B-182A-004-MY3

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Independent Research Fund Denmark 0134-00107B
CMRPG8M0731-33

Title: Butyrate reduction & HDAC4 increase underlie maternal high fructose-induced metabolic dysfunction in hippocampal astrocytes in female rat

Authors: *C.-W. WU[1], K. L.-H. WU[2], H. HIRASE[3];
[1]Dept. of Electronic Engin., Natl. Kaohsiung Univ. of Sci. and Technol., Kaohsiung City, Taiwan; [2]Inst. for Translational Res. in Biomedicine, Chang Gung Mem. Hosp., Kaohsiung City, Taiwan; [3]Ctr. for Translational Neuromedicine, Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Maternal nutrient intake influences the health of the offspring via microenvironmental systems in digestion and absorption. Maternal high fructose diet (HFD) impairs hippocampus-dependent memory in adult female rat offspring. However, the underlying mechanisms remain largely unclear. Maternal HFD causes microbiota dysbiosis. In this study, we find that the plasma level of butyrate, a major metabolite of microbiota, is significantly decreased in the adult female maternal HFD offspring. In these rats, GPR43, a butyrate receptor was downregulated in the hippocampus. Moreover, the expressions of mitochondrial transcription factor A (TFAM), and peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) were downregulated in the hippocampus. The decreases of these functional proteins were reversed by fructooligosaccharides (FOS, a probiotic) treatment in adulthood. Astrocytes are critical for energy metabolism in the brain. Primary astrocyte culture from female maternal HFD offspring indicated that GPR43 and the mitochondrial biogenesis were significantly suppressed, which was reversed by supplemental butyrate incubation. The oxygen consumption rate (OCR) was reduced in the HFD group and rescued by butyrate. Intriguingly, the nuclear histone deacetylase 4 (HDAC4) was enhanced in the HFD group, suggesting an inhibitory role of butyrate on histone deacetylase activity. Inhibition of HDAC4 effectively restored the OCR, bioenergetics, and biogenesis of mitochondria. Together, these results suggested that the impaired butyrate signaling by maternal HFD could underlie the reduced mitochondrial functions in the hippocampus via HDAC4-mediated epigenetic changes.

Disclosures: C. Wu: None. **K.L. Wu:** None. **H. Hirase:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.073/LBA136

Topic: B.09. Glial Mechanisms

Support: National Institute of Neurological Disorders and Stroke,RO1NS116059

Career Accelerator Fund
Undergraduate Research Scholarship
Undergraduate Research Apprenticeship Program

Title: Mechanism Underlying Astrocytic Uptake of Sulforhodamine 101 (SR101)

Authors: *X. LIU[1], S. TIMSINA[2], M. MCNABB[3], Y. LUO[5], Z. LI[4], Y. DU[6], M. ZHOU[3]; [1]Neurosci., The Ohio State Univ., Columbus, OH; [2]The Ohio State Univ., Pataskala, United Arab Emirates; [3]The Ohio State Univ., Columbus, OH; [4]The Ohio State Univ., Rome, OH; [5]Brain and Cognitive Sci., Univ. of Rochester, Rochester, NY; [6]Dept. of Neurosciences, Univ. of California - San Diego, La Jolla, CA

Abstract: Sulforhodamine 101 (SR101) is a commonly used chemical marker for astrocytes and is particularly useful in functional in vivo and in situ studies. However, the mechanism underlying the astrocytic uptake of SR101 remains elusive. Serendipitously, we found that SR101 uptake can be fully inhibited by meclofenamic acid (MFA). The MFA-mediated SR101 uptake inhibition is characterized by a non-competitive binding of MFA to the SR101 uptake pathway, a rapid inhibitory time course (T50, 0.4925 min), and high efficacy (IC50, 4.428 µM). Therefore, MFA emerges as a useful inhibitor to further explore the mechanism of SR101 uptake in astrocytes. In a transcriptome study, the slco1c1 mRNAs, a gene encoding L-thyroxine (T4) transporter (OATP1C1), showed high astrocyte expression. To explore slco1c1 as a potential SR101 uptake pathway, we pre-incubated acute hippocampal slices with 10 µM T4 for 20 min. This resulted in a 95% inhibition of SR101 uptake. Inhibition of OATP1C1 should lead to a buildup of ambient T4. To examine if T4 could affect neuronal excitability, we examine the electrophysiological responses of CA1 pyramidal neurons to 10 µM T4. Elevated ambient T4 appeared to attenuate the excitability of CA1 pyramidal neurons. Thus, our study has identified MFA as a potent SR101 uptake inhibitor in astrocytes. Additionally, we show that L-thyroxine competitively inhibits SR101 uptake in astrocytes, implying that slco1c1 is likely the transporter that mediates the SR101 uptake in astrocytes. Potentially, inhibition of OATP1C1 has an inhibitory impact on the excitability of CA1 pyramidal neurons.

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Late-Breaking Poster

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Program #/Poster #: LBA002.074/LBA137

Topic: B.09. Glial Mechanisms

Support: ANR-20-CE37-0024

FRM AJE20181039590

Title: Local sources of monoamines in the cerebellar cortex.

Authors: *S. MACH, W. NIU, J. ROYER, X. LI, O. CHAIKOVSKA, M. GALANTE, G. DALLERAC;
Inst. des Neurosciences Paris-Saclay, NeuroPSI, Saclay, France

Abstract: **Rational:** The cerebellum is classically associated with coordination and motor learning. Yet, a growing body of evidence now indicates that the cerebellum also contributes to cognitive aspects including social behavior and navigation skills. Although monoamines such as norepinephrine (NE) and dopamine (DA) are key neuromodulators implicated in these cognitive functions, the *modus operandi* of monoaminergic systems and their relevance to cerebellar functioning remains poorly understood. Interestingly, our preliminary data show that, while in this brain region monoaminergic innervations are sparse, the main vesicular transporter of monoamines VMAT2 is expressed in both Bergmann glial (BGC) cells, specialized radial astrocytes, and Purkinje neurons (PN), the neuronal output of the cerebellar cortex. Our study thus aims at investigating the role of BGCs and PNs in the control of monoaminergic transmission. **Methods:** We characterized the monoaminergic system in the cerebellar cortex using immunohistochemistry experiments targeted against proteins involved in the synthesis, uptake, and transport of DA and NE. To investigate the implication of BGCs and PNs in monoamines transmission, we performed 2-photons imaging of spontaneous DA and NE releases using genetically encoded DA and NE fluorescent sensors ($GRAB_{DA2h}$ and $GRAB_{NE2h}$) in acute cerebellar slices. DA and NE releases were examined under conditions of BGCs or PNs chemogenetic activations as well as in mice knocked-down for VMAT2 in BGCs (aVMAT2cKO mice). Finally, we studied the impact of monoaminergic modulation by BGCs on PNs synaptic transmission via BGC chemogenetic activation during patch-clamp experiments. Experiments were all performed in both males and females mice. **Results:** We found that both PNs and BGCs express proteins of the monoaminergic system, such as TH, DBH, NET and VMAT2 (n=5). Importantly, specific activation of PNs and BGCs respectively increases spontaneous releases of DA and NE (n=10 per group). In aVMAT2cKO mice, BGCs chemogenetic activation however shows no effect on NE release events, suggesting vesicular release of NE from BGCs (n=10 per group). Finally, we found that BGCs chemogenetic activation enhances excitatory synaptic transmission (n=5). **Conclusion:** Together, these results strongly suggest that both BGCs and PNs markedly contribute to monoamine transmission in the cerebellar cortex.

Disclosures: S. Mach: None. **W. Niu:** None. **J. Royer:** None. **X. Li:** None. **O. Chaikovska:** None. **M. Galante:** None. **G. Dallerac:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.075/LBA138

Topic: B.09. Glial Mechanisms

Support: NIH Grant R01NS120746

Title: Trkb.t1 deficient astrocytes display aberrant transcriptional maturation and contribute to excessive cortical spinogenesis

Authors: *X. WEI[1], Y. PAN[2], J. BROWNING[3], K. NOEL[2], M. L. OLSEN[1];
[1]Virginia Tech. Neurosci. PhD Program, Blacksburg, VA; [3]Neurosci., [2]Virginia Tech., Blacksburg, VA

Abstract: Brain derived neurotrophic factor (BDNF) is a critical trophic factor in the central nervous system (CNS), and its truncated tropomyosin receptor kinase B (TrkB.T1) is the most highly expressed isoform in the CNS. Although TrkB.T1 is predominantly expressed in astrocytes, limited studies evaluated its function in astrocytes. Here, we investigated the role of TrkB.T1 in cortical astrocyte developmental processes and astrocyte function during early postnatal development (postnatal day (P) 8, P14, P28 and P60). RNA sequencing of TrkB.T1 deficient astrocytes isolated at these timepoints revealed aberrant gene expression in astrocyte maturation, while pathway analysis indicated disruptions in synapse organization, neurotransmitter transport and exocytotic processes. Subsequent functional secretory proteomics highlighted disruptions in metabolism and lipid regulation, particularly cholesterol transport, suggesting potential implications for synapse formation. We observed dysregulated spine density in the motor and somatosensory cortices from TrkB.T1-deficient astrocytes relative to control astrocytes. These findings suggest that TrkB.T1 deficiency adversely affects normal astrocyte development, which in turn affects neuronal synapse development. This study provides new insights into the role of BDNF/TrkB.T1 signaling in CNS development and lays the groundwork for evaluating astrocyte BDNF/TrkB.T1 signaling in neurological diseases.

Disclosures: X. Wei: None. **Y. Pan:** None. **J. Browning:** None. **K. Noel:** None. **M.L. Olsen:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.076/LBA139

Topic: B.09. Glial Mechanisms

Support: NIH Grant R01NS116059

Title: Closure of the astrocytic syncytium elevates extracellular potassium to suppress synaptic transmission in the mouse hippocampal CA1 region

Authors: *Z. LI[1], Y. DU[2], M. ZHOU[3];
[1]Neurosci., The Ohio State Univ., Columbus, OH; [2]Dept. of Neurosciences, Univ. of California - San Diego, La Jolla, CA; [3]Dept. of Neurosci., Ohio State Univ., Columbus, OH

Abstract: Syncytial Isopotentiality is a glial mechanism crucial for homeostatic regulation of ions and neurotransmitters in the CNS. We show that pharmacological and chemogenetic decoupling of the astrocyte syncytium results in fluctuations and increase in extracellular potassium concentration $[K^+]_e$. We further show that elevated $[K^+]_e$ does not significantly alter the excitability of pyramidal neurons within the physiological range, 3.5 mM - 5.0 mM. In contrast, the excitability of interneurons in the stratum radiatum show rather diverse responses to the increase in $[K^+]_e$, with an overall graded increase in excitability. Specifically, 31% (43/138) of interneurons fire action potentials spontaneously on an average of 8.7 Hz, presumably reflecting the basal inhibitory synaptic activity in this subregion, and their firing increase with elevated $[K^+]_e$ within the physiological range, i.e., 3.5 mM - 5.0 mM, and beyond. In another 69% (95/138) of nonspontaneous firing interneurons, 50% responded to physiological increase in $[K^+]_e$ with increased firing, while another 50% remained silent until 10.0 mM $[K^+]_e$ and beyond. This suggests that increase in $[K^+]_e$ can alter the excitation-inhibition balance. To explore this possibility, we recorded the change in field excitatory post-synaptic potential (fEPSP) from the hippocampal CA1 region following a graded increase in $[K^+]_e$. Indeed, we found that extracellular K^+ concentration-dependently suppressed fEPSPs in the CA1 region. Thus, the $[K^+]_e$ dynamic is regulated by astrocyte syncytium and has a differential impact on glutamatergic and diverse GABAergic neurons to alter the neural circuit function and synaptic transmission.

Disclosures: Z. Li: None. **Y. Du:** None. **M. Zhou:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Program #/Poster #: LBA002.077/LBA140

Topic: B.09. Glial Mechanisms

Support: Fondecyt regular 1221508

Title: Release of glutamate from hypothalamic astrocytes is stimulated by metabolic lactate from tanycytes

Authors: *S. LOPEZ[1], V. AZÓCAR[1], R. C. ARANEDA[2], R. ELIZONDO[1], M. GARCIA ROBLES[1];

[1]Biología Celular, Univ. de Concepción, Concepcion, Chile; [2]Biol., Univ. of Maryland, Col. Park Neurosci. and Cognitive Sci. Program, College Park, MD

Abstract: The arcuate nucleus (AN) of the hypothalamus is one of the primary integrators of local and peripheral signals that convey information about the body's energy level. This integration of signals is carried out by metabolic sensing by a diverse population of cells, including orexigenic and anorexigenic neurons and glial cells such as astrocytes and tanycytes. Still, this process's underlying metabolic and molecular mechanisms are not fully understood. Recently, we showed that activation of the lactate receptor (HCAR1) by L-lactate increases the electrical activity of anorexigenic pro-opiomelanocortin (POMC) neurons in the AN. Surprisingly, immunocytochemistry studies showed that HCAR1 is not expressed in POMC neurons or tanycytes, but instead is expressed in hypothalamic astrocytes. Thus, we hypothesize that tanycyte-derived lactate activates HCAR1 in astrocytes, mediating the activation POMC neurons. To test this possibility, we examined the responses of cultured hypothalamic astrocytes to conditioned media from tanycytes in which lactate production was enhanced or reduced using adenoviral (Ad) transduction of glycolytic activators or inhibitors. Conditioned media from tanycytes containing high concentrations of L-lactate (8 mM, 3 min) produces a significant increase in ((Ca2+)i) in astrocytes (DF/Fo=0.216+-0.012 14 of 44 cells; n=4). Interestingly, the application of the HCAR1-specific agonist, 3Cl-HBA (40 uM), 15 min, increased the release of glutamate from astrocytes (control 2.54+-0.25 nM; 3Cl-HBA, 105.10+-6.32 nM). In a similar way, the application of tanycyte's conditioned media also increased glutamate release from astrocytes, but this effect was abolished when astrocytes were treated with siRNA for HCAR1 (siRNA-control, 35.99+-2.51 nM; siRNA-HCAR1 2.67+-0.17 nM; n=4). Furthermore, the application of L-lactate or 3-Cl-HBA produced an increase in ((Ca2+)i) in astrocytes expressing GCaMP6f in AN brain slices. Together, these results suggest that L-lactate released from tanycytes as a glycolytic product activates HCAR1 in astrocytes, leading to the release of glutamate.

Disclosures: S. Lopez: None. **V. Azócar:** None. **R.C. Araneda:** None. **R. Elizondo:** None. **M. Garcia Robles:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.078/LBA141

Topic: B.09. Glial Mechanisms

Support: RO1NS116059

Title: Astrocyte Syncytial Isopotentiality Sustains the Basal Excitability of Neurons and Synaptic Transmission in the Mouse Hippocampal CA1 Region

Authors: *S. TIMSINA[1], *S. TIMSINA[2], Y. DU[3], Z. LI[2], M. ZHOU[4];
[1]The Ohio State Univ., Pataskala, OH; [2]The Ohio State Univ., Columbus, OH; [3]Dept. of Neurosciences, Univ. of California - San Diego, La Jolla, CA; [4]Dept. of Neurosci., Ohio State Univ., Columbus, OH

Abstract: A strong gap junctional coupling confers an isopotentiality to the astrocyte syncytium across the brain. Further, Syncytial Isopotentiality emerges as a newly appreciated glial mechanism crucial for the homeostatic regulation of ions and neurotransmitters in the CNS. However, how this glial mechanism plays a role in subserving neural circuit function remains to be determined. In the present study, we hypothesized that astrocyte syncytial coupling is required for basal neuron excitability. To experimentally test this hypothesis, we decoupled the astrocyte syncytium pharmacologically with a gap junction inhibitor, Meclofenamic Acid (MFA), as well as high intracellular Ca^{2+} through activation of Gq-DREADDs in astrocytes by 10 nM Clozapine. Attenuation of the evoked pyramidal neuron and a majority of interneurons were observed with both, pharmacological and chemogenetic approaches. The decoupling of the astrocyte syncytium resulted in an increase in the spontaneous excitability in a subset of interneurons: 16/57 (28.07%) in MFA, and 4/14 (28.57%) in 10 nM Clozapine, respectively. At the level of synaptic transmission, we show that both MFA and Gq-DREADD activation-mediated decoupling resulted in a reversible suppression of the field excitatory postsynaptic potential (fEPSP) in the hippocampus CA1 region. Thus, the state of astrocyte syncytial isopotentiality is crucial for the basal excitability of both glutamatergic pyramidal neurons and interneurons, and consequently the strength of synaptic transmission in the mouse hippocampus CA1 region.

Disclosures: S. Timsina: None. **S. Timsina:** None. **Y. Du:** None. **Z. Li:** None. **M. Zhou:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.079/LBA142

Topic: B.09. Glial Mechanisms

Support: NIH NIMH R01 grant (R01 MH132556)
NIH Director's New Innovator Award (DP2 NS136871D)
Whitehall Foundation research grant to X.Y.
Brain and Behavior Research Foundation NARSAD Young Investigator grant to X.Y.
Brain Research Foundation grant to X.Y.

Title: Cell specific proteomes reveal molecular mechanisms mediating astrocyte-neuron interaction

Authors: *H. DU[1], Y. TAN[2], E. KIM[4], J. V. SWEEDLER[5], X. YU[3];
[1]UIUC, Urbana, IL; [2]Dept. of Chem., [3]Univ. of Illinois, Urbana-Champaign, Urbana, IL; [4]Univ. of Illinois Urbana-Champaign, Urbana, IL; [5]Dept Chem., Univ. of Illinois at Chicago Dept. of Chem., Urbana, IL

Abstract: As one of the most abundant resident cells tiling the entire central nervous system, astrocytes form intimate associations with neurons. In the mature brain, astrocytes express numerous transporters, channels and receptors that are essential to monitor, integrate and maintain neuronal activity. Recent studies have shown that abnormalities in astrocytes are associated with many central nervous system (CNS) related diseases. However, the molecular mechanisms involved in signaling pathways related to astrocyte function and astrocyte-neuron interactions remain largely unknown. A thorough elucidation of the protein components involved in astrocyte signaling and astrocyte-neuron interactions is essential for understanding CNS function and the underlying mechanisms of related diseases. Here we developed two proteomic approaches that allow us to profile the protein compositions within astrocytes and at astrocyte-neuron interface in a cell type- and circuit- specific manner with proximity biotinylation approaches using TurboID enzyme. We profiled the astrocyte cytosolic proteomes and astrocyte-neuron interface proteomes in the medial prefrontal cortex (mPFC). The proteomic data indicated cell-specific changes of protein expression in mPFC astrocytes as well as at the astrocyte-neuron interface upon suppressing astrocyte calcium activity. Excitatory neuron proteins and inhibitory neuron proteins were identified at astrocyte-neuron interface and exhibited heterogeneous alteration. We also identified many disease-associated proteins and genetic risk factors in our proteomics analysis. Together our data provides new insight on astrocyte cell-autonomous and non-cell-autonomous mechanisms mediating neuronal activity.

Disclosures: H. Du: None. **Y. Tan:** None. **E. Kim:** None. **J.V. Sweedler:** None. **X. Yu:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.080/LBA143

Topic: B.09. Glial Mechanisms

Support: Human Technopole Early Career Fellowship

Title: Varicose-projection astrocytes: from evolution to neuroinflammation

Authors: *C. FALCONE;
SISSA, Trieste, Italy

Abstract: Understanding the mechanisms underlying neuroinflammation remains a significant challenge in neurobiology. Historically, neuroinflammation research has focused primarily on

neurons, overlooking the crucial role of astrocytes. Recent studies have highlighted astrocytes' fundamental involvement in brain physiology and pathology. However, despite extensive research in rodent models, the specific contributions of astrocytes to neuroinflammation in mice are still ambiguous and not easily translatable to humans. Evidence points to a hominoid-specific astrocyte subtype, Varicose-Projection astrocytes (VP-As), hypothesized to appear under certain brain conditions.
VP-As, first described in 2009, are characterized by their GFAP-positive markers, soma location in deep brain layers (V, VI, and white matter), and distinctive long processes with evenly distributed varicosities. VP-As have only been identified in humans and great apes, exhibiting individual-specific presence and absence in neonatal brains. These features, coupled with their association with Interlaminar astrocytes' varicosities, suggest a potential link to specific brain conditions, such as brain inflammation and injury. Activation of the STAT3 pathway in reactive astrocytes, leading to protein degradation and varicosities, supports the hypothesis that VP-As may represent a specific inflammatory response in the human brain. Our research aims to provide a proof of principle regarding the function of VP-As in brain inflammation, emphasizing the unique role of astrocytes in neuroinflammatory conditions specific to humans.
Data from our lab demonstrate that human-induced pluripotent stem cell (hiPSC)-derived astrocytes develop VP-A-like characteristics when treated with pro-inflammatory factors (TNFα and IL1β). These treatments induce astrogliosis and increase GFAP expression, with varicosities appearing predominantly under TNFα exposure, either alone or in combination with IL1β. These findings suggest a specific molecular pathway activated by TNFα is responsible for varicosity formation. In conclusion, our study seeks to demonstrate that VP-As are a morphological adaptation of astrocytes to inflammatory conditions and to elucidate the molecular mechanisms underlying this transformation. This research will advance our understanding of human-specific astrocyte roles in neuroinflammation, potentially revealing new therapeutic targets for neuroinflammatory diseases.

Disclosures: C. Falcone: None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.081/LBA144

Topic: B.09. Glial Mechanisms

Support: RO1AG084473

Title: Microglia affect the modulation of astrocytic glucose transport by proinflammatory cytokines

Authors: *N. BEGUM[1], S. W. BARGER[2];
[1]Univ. of Arkansas for Med. Sci., LITTLE ROCK, AR; [2]Univ. of Arkansas for Med. Sci., Little Rock, AR

Abstract: Astrocytes play crucial roles in energy homeostasis in the central nervous system (CNS), particularly in delivery of glucose and glucose-derived lactate to neurons. Impairment of astrocytic glucose transport has been implicated in several neurodegenerative diseases such as Alzheimer's disease (AD), amyotrophic lateral sclerosis, and Parkinson's disease, all of which are accompanied by neuroinflammation. Microglia mediate innate immunity in the CNS and respond to stimuli such as amyloid β-peptide (Aβ) with potent production of cytokines. We previously reported an aberration in the translocation of glucose transporter 1 (GLUT1) to the plasma membrane in brains of humans with AD and mice which accumulate Aβ. This was replicated in primary astrocyte cultures treated with Aβ or proinflammatory cytokines. These cultures retained modest levels of microglia which may have contributed to the effects of Aβ and/or proinflammatory cytokines on glucose uptake by astrocytes. To address the role of microglia in glucose transport, we depleted them from astrocyte cultures more thoroughly via a combined treatment with cytosine arabinoside and L-leucine methyl ester. These relatively pure astrocyte cultures were compared to those with retained microglia in glucose uptake assays. We also tested the roles of various proteins implicated in regulation of GLUT1 transport, namely glucose regulated protein (GRP78) and thioredoxin-interacting protein (TXNIP), using pharmacological inhibitors and siRNA. While glucose uptake was diminished by interleukin-1β and tumor necrosis factor in astrocyte/microglia cocultures, it was elevated by these cytokines in pure astrocyte cultures. The GRP78 inhibitor HA-15 significantly increased glucose uptake in the astrocyte cultures containing microglia, whereas it decreased uptake in cultures without microglia. The TXNIP inhibitor SRI-37330 had no effect on glucose uptake. Here we showed that presence of microglia in primary astrocyte cultures alters the impact of proinflammatory cytokines on glucose utilization. This observation highlights the importance of considering interactions between cell types in the complex millieu of the CNS and may inform strategies for therapeutic interventions for improving astrocyte glucose metabolism in neurogenerative diseases.

Disclosures: N. Begum: None. **S.W. Barger:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.082/LBA145

Topic: B.09. Glial Mechanisms

Support: FRM grant AJE20181039590
IReSP grant 20II134-00

FRC grant

Title: Development of astroglial dopaminergic functions is essential in the critical period of prefrontal cognition.

Authors: *X. LI[1], W. NIU[1], S. MACH[1], J. ROYER[1], P. BEZZI[2], M. GALANTE[1], G. DALLERAC[1];
[1]Inst. des Neurosciences Paris-Saclay, NeuroPSI, Saclay, France; [2]Univ. de Lausanne, Lausanne, Switzerland

Abstract: Background: The prefrontal cortex (PFC) is crucial for online cognitive functions such as decision making, planning, and working memory, and is strongly influenced by dopamine (DA). Recent studies suggest that the vesicular DA transporter VMAT2 in astrocytes markedly contribute to DAergic homeostasis in the PFC. We hypothesized that astrocytes regulate tonic DA levels via astroglial release. Our study thus ascertains the role of astrocytes in regulating tonic DA levels via astroglial release and explores the role of this DAergic function in the postnatal critical period of PFC development. **Methods:** To this end, we employed, in both male and female mice, ex vivo 2-photon imaging of DA release using the genetically encoded fluorescent sensor GRAB-DA in acute PFC slices. Calcium-dependent spontaneous release was examined under conditions of action potential blockade, and chemogenetic or pharmacological activation of astrocytes. Additionally, we used mice knockdown for VMAT2 in astrocytes (aVMAT2cKO mice) to assess astroglial contribution to PFC tonic DA release. Ex vivo electrophysiological recordings were conducted to test whether DA applied within the astroglial network modulates synaptic transmission. Finally, we investigated the effects of post-weaning social isolation (PWSI) on PFC astrocytic DA function during the critical period of adolescence (postnatal day 21 to 51) using ex vivo DA imaging and behavioral tests. **Results:** Our findings demonstrate calcium-dependent tonic releases of DA (n=6), unaffected by action potential blockade (n=8) but enhanced by chemogenetic (n=9) or pharmacological (n=8) activation of astrocytes. aVMAT2cKO mice exhibit a drastic reduction in DA release (WT n=14 vs aVMAT2cKO n=31), highlighting the essential role of astrocytes in regulating PFC tonic DA levels. Electrophysiological recordings of PFC slices during dialysis of the astroglial network with DA reveal a significant upregulation of synaptic transmission (n=8). In addition, PWSI results in a reduced astroglial VMAT2 expression (n=8 control vs 8 PWSI) and spontaneous DA release by 30 % (n=10 control vs 22 PWSI), corroborating the hypothesis that schizophrenia is associated with PFC hypodopaminergia. Behaviorally PWSI mice show an increased hyperactivity, deficits in pre-pulse inhibition, along with social deficits (control n=30 vs PWSI n=30). Finally, virally-induced tyrosine hydroxylase expression enabling DA synthesis by astrocytes partially reversed these cognitive deficits (control n=6 vs TH n=6). **Conclusion:** Together, these findings unravel the critical role of astroglial DA in the post-natal development of PFC cognitive functions.

Disclosures: X. Li: None. **W. Niu:** None. **S. Mach:** None. **J. Royer:** None. **P. Bezzi:** None. **M. Galante:** None. **G. Dallerac:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.083/LBA146

Topic: B.09. Glial Mechanisms

Support: China Brain Initiative Grants (STI2030-Major Projects 2021ZD0202803)

Title: Astrocytes release ATP and glutamate in flashes via vesicular exocytosis

Authors: *H. LI;
Chinese Inst. for Brain Research, Beijing(CIBR), Beijing, China

Abstract: Astrocytes regulate brain functions through gliotransmitters like ATP and glutamate, but their release patterns and mechanisms remain controversial. Here, we visualized ATP and glutamate response following astrocyte activation and investigated their mechanisms *in vivo*. Employing cOpn5-mediated optogenetic stimulation, genetically encoded fluorescent sensors, and two-photon imaging, we observed ATP released as temporally prolonged and spatially extended flashes that later converted to adenosine. This release occurs via Ca^{2+} and VNUT-dependent vesicular exocytosis and triggers further ATP release from microglia through P2Y12- and VNUT-dependent mechanisms. VNUT in astrocytes and microglia also contributes to ATP release under LPS-induced brain inflammation. Additionally, astrocytes release glutamate in flashes through TeNT-sensitive exocytosis, independent of ATP release and microglial involvement. These findings establish Ca^{2+}-dependent vesicular exocytosis as a key mode of action, reveal intricate astrocyte-microglia interactions, and suggest a role for gliotransmission in brain inflammation. Furthermore, the methodologies may provide valuable tools for deciphering glial physiology and pathophysiology.

Disclosures: H. Li: None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.084/LBA147

Topic: B.09. Glial Mechanisms

Support: NIH Grant RO1NS116059

Title: Small-conductance Ca^{2+}-activated K^+ channel, SK2, is the final missing component of astrocytic passive K^+ conductance

Authors: *M. MCNABB[1,2], Y. DU[3], M. ZHOU[2];
[1]The Ohio State Univ., COLUMBUS, OH; [2]Dept. of Neurosci., The Ohio State Univ., Columbus, OH; [3]Dept. of Neurosciences, Univ. of California - San Diego, La Jolla, CA

Abstract: Across various brain regions and model species, astrocytes exhibit a characteristic ohmic, or "passive", K^+ conductance. However, the full repertoire of leak-type K^+ channels contributing to this intrinsic property of functionally mature astrocytes remains elusive. Inward-rectifying K^+ channels, such as $K_{ir}4.1$, have been shown to contribute to the passive K^+ conductance. The activation kinetics of K_{ir} channels, however, cannot entirely account for an ohmic behavior, specifically the outward-going portion of the passive K^+ conductance. Therefore, an additional leak-type K^+ channel, expected to follow the Goldman-Hodgkin-Katz (GHK) current equation, must be present to account for this unidentified portion of astrocytic K^+ conductance. In single freshly dissociated astrocytes (FIAs) from the hippocampal CA1 region, our quantitative PCR (qPCR) analysis revealed the highest level of mRNA expression from small-conductance Ca^{2+}-activated K^+ channel, SK2. Accordingly, apamin, a highly selective blocker for SK channels, disclosed a significant portion of apamin-sensitive K^+ currents from FIAs and in situ astrocytes decoupled with meclofenamic acid (MFA), a potent gap junction blocker. Specifically, in both FIAs (P21-25, n = 9) and MFA-decoupled astrocytes (P11-15, n = 9), bath application of 300 nM apamin resulted in an ohmic (Rectification Index: FIA = 1.108 ± 0.102, MFA = 0.970 ± 0.020) suppression of passive conductance (FIA: ΔI_{in} = 47.96% ± 7.79, ΔI_{out} = 41.33% ± 8.30, MFA: ΔI_{in} = 16.95% ± 4.58, ΔI_{out} = 17.34% ± 4.17), rather than the predicted GHK outward rectification, and membrane depolarization (FIA: ΔV_m = 6.13 mV ± 1.77, MFA: ΔV_m = 1.34 mV ± 0.52). Co-application of 300 nM apamin and 0.1 mM $BaCl_2$, a selective K_{ir} channel blocker, resulted in a further reduction of passive conductance (FIA: ΔI_{in} = 80.10% ± 1.98, ΔI_{out} = 58.08% ± 2.90, MFA: ΔI_{in} = 88.24% ± 2.38, ΔI_{out} = 61.29% ± 1.10), and a significant increase in input resistance (FIA: ΔR_{in} = 75.27 MΩ ± 10.05, ΔR_{out} = 27.70 MΩ ± 3.27, MFA: ΔR_{in} = 99.11 MΩ ± 29.24, ΔR_{out} = 25.02 MΩ ± 9.50). Complete elimination of leak-type K^+ conductance was further indicated by the separation of the capacitance discharge from the newly emerging voltage-gated outward transient (I_{Ka}) and delayed rectifying (I_{Kd}) K^+ conductances as a result of improved voltage-clamp quality (FIA: n = 15, MFA: n = 6). Therefore, our results support the involvement of an SK channel, likely SK2, as the molecular identity of the long-sought K^+ channel working in concert with $K_{ir}4.1$ to generate the full range of astrocytic passive K^+ conductance.

Disclosures: M. McNabb: None. **Y. Du:** None. **M. Zhou:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.085/LBA148

Topic: B.09. Glial Mechanisms

Support: NIH R01 MH132556
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Whitehall Foundation research grant
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Brain Research Foundation grant

Title: Task- and Cell-Specific Modulation of Prefrontal Astrocytes on Anxiety-Like Behavior

Authors: *E. KIM[1], B. BROWN[2], X. YU[3];
[1]Univ. of Illinois Urbana-Champaign, Urbana, IL; [2]Psychiatry, Carle Illinois Col. of Med., Champaign, IL; [3]Univ. of Illinois, Urbana-Champaign, Urbana, IL

Abstract: Task- and Cell-Specific Modulation of Prefrontal Astrocytes on Anxiety-Like Behavior
AUTHORS ***Eunyoung Kim[1]**, Brandon L. Brown[2], and Xinzhu Yu[1,3]
[1]Neuroscience Program, University of Illinois at Urbana-Champaign, Urbana, IL [2]Carle Illinois College of Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA[3]Department of Molecular and Integrative Physiology, University of Illinois at Urbana-Champaign, Urbana, IL, USA
DISCLOSURES Eunyoung Kim: None. Brandon L. Brown: None. Xinzhu Yu: None.
ABSTRACT Anxiety disorders are one of the most common psychiatric diseases, with a detrimental impact on the quality of life of patients with anxiety disorders. Unfortunately, current anxiolytic medications are ineffective since around half of patients fail to respond to initial treatment. In order to develop novel therapeutic treatments for anxiety disorders, understanding the neurobiological mechanism is crucial. The medial prefrontal cortex (mPFC) enacts an essential role as a central hub of microcircuits that regulate emotions, including anxiety. Numerous clinical and research studies indicate essential neuronal contribution to anxiety in this brain region, yet the mechanisms of non-neuronal cells governing this emotional state remain poorly understood. Astrocytes are one of the most abundant non-neuronal cells in the brain and interact closely with neurons and other glial cells. Dissimilar to neurons, astrocytes utilize intracellular calcium signals rather than electrical signals to interact with other cells. However, the role of astrocytes in mPFC and their effects on anxiety-like behavior are largely unknown. Here, we show that non-neuronal astrocytes in the mPFC encode anxiogenic environmental cues. Silencing mPFC astrocyte Ca^{2+} signaling heightens anxiety-like behavior and disrupts the balance between excitatory and inhibitory neuronal population activity. Moreover, this effect is differentially pronounced across behaviorally tuned neuronal subpopulations on single-cell and network levels. Collectively, our findings suggest a novel homeostatic plasticity mechanism by which prefrontal astrocytes regulate discrete neuronal populations related to anxiety, offering insights into the pathophysiology and potential therapeutic interventions for emotional disorders.
KEYWORDSAstrocytes, neurons, medial prefrontal cortex, anxiety-like behavior, excitatory, inhibitory, Ca^{2+} imaging

Disclosures: E. Kim: None. **B. Brown:** None. **X. Yu:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

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Topic: B.09. Glial Mechanisms

Support: This work was supported by the Ministry of Health & Welfare and Ministry of Science and ICT (HU22C0115) through the Korea Health Industry Development Institute and Korea Dementia Research Center.

Title: Chronic Glucocorticoids impairing Astrocytic Neuroprotection via NIX-Mitophagy

Authors: *K. V. DO, Female[1,2], M. TRAN[5,2,1], T. HUYNH[6,2], C. HEO[3,2,4], H. CHO[7,2,1]; [1]Dept. of Intelligent Precision Healthcare Convergence, Inst. of Quantum Biophysics, [2]Inst. of Quantum Biophysics, [3]Dept. of Biophysics, [4]Ctr. for Integrated Nanostructure Physics (CINAP), Inst. for Basic Sci. (IBS),, Sungkyunkwan Univ., Suwon, Korea, Republic of; [5]Dept. of Biophysics, Sungkwunkwan Univ., Suwon, Korea, Republic of; [6]Dept. of Biophysics, Sungkwunkwan Univ., Suwon-si, Korea, Republic of; [7]Biophysics, Sungkwunkwan Univ., Suwon, Korea, Republic of

Abstract: Introduction: Prolong Exposure to Chronic Hypercortisolism (HCM) or excess Glucocorticoids (GCs) hormone levels has been associated with atrophy of the hippocampus, cognitive deficits, and increased risk for neurodegenerative disease (NDD), potentially due to negative impacts on mitophagy processes. However, the cellular mechanisms that precipitate the mitochondrial dysfunction and neurotoxicity in the NDD brain cell system have not been fully understood. Here, we investigate the intracellular mechanisms of how chronic HCM induces BNIP3L/NIX-mediated mitophagy impairment in neurons and glial cells, contributing to NDD. **Methods:** This study uses a 1 to 9-week-long human mini-brain on a chip to delve into how glucocorticoids heighten NDD markers by altering mitophagy activities, considering cortisol hypersecretion common in AD patients. Focusing on NDD specifics and broader aging brain responses, we scrutinized the dysfunction of NIX-mediated mitophagy and the consequential aggregation of damaged mitochondria, significant increase in mitochondrial ROS(mROS), p-tau, and fostering brain degradation. **Results:** Our primary findings demonstrate that sustained HCM induces the accumulation of damaged mitochondria in neurons by inhibiting NIX-driven mitophagy, subsequently causing a decrease in ATP production and synaptic transmission loss (NeuN, synapsin), along with the onset of tau pathology. Secondly, distinct from the short-term treatment function of astrocytes in anti-inflammation cytokine, neuroprotective soluble factors (IL10, IGF-1), and supplying ATP to neurons. Long-term co-culturing of astrocytes and neurons with HCM leads to a dip in NIX-regulated mitophagy and damaged mitochondria accumulation,

enhanced neuroinflammation evident with disruption of Ca^{2+} homeostasis, and activated GFAP, STAT3, and C3 activity. Thirdly, Chronic HCM inflicts dysfunctional mitochondria in microglia while initially reducing proinflammatory markers (CD86), however, over time with astrogliosis, this can lead to a dysregulation of inflammatory responses (iNOS, IL-1β, IL6, TNF-α), chemokines (MIP-1a, MCP-1), impairing phagocytic action (TREM2), and resulting in Aβ plate accumulation in the brain. Finally, inhibiting the corticosteroid receptor in our tri-model altered GCs-mediated regulation of mitophagy, reduced the inflammation in Glial cells, and recovered neuronal function. **Conclusions**: In summary, Chronic HCM obstructs NIX-mediated mitophagy in neuronal and glial cells as a risk factor in NDD This research highlights the critical need for research on developing therapies targeting mitochondrial efficacy in healthy aging.

Disclosures: K.V. Do: A. Employment/Salary (full or part-time):; Graduate student Scholarship, full time. 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 the Ministry of Health & Welfare and Ministry of Science and ICT (HU22C0115) through the Korea Health Industry Development Institute and Korea Dementia Research Center.. **M. Tran:** None. **T. Huynh:** None. **C. Heo:** None. **H. Cho:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.087/LBA150

Topic: B.09. Glial Mechanisms

Title: Sleep fragmentation alters microglial function leading to lethal neuroinflammation during sepsis like inflammation

Authors: *A. WANI;
St. Jude Children's Res. Hosp., Memphis, TN

Abstract: It is well established that infection can promote slow wave sleep, but the functional importance of this phenomenon remains unclear. In this study, we utilized sleep fragmentation, i.e., intermittent disruption of sleep throughout the day, to explore the relationships between sleep and inflammatory disease. We found that sub-lethal injection of a bacterial lipopolysaccharide (LPS), prior to sleep fragmentation (SF) invariably resulted in dramatically increased mortality compared to LPS only or SF only controls, highlighting the importance of sleep following an inflammatory challenge. Further investigation revealed hyperactivation of microglia in the hypothalamus and other brain areas in mice subjected to LPS plus sleep fragmentation. As Toll-like receptor-4 (TLR4) is crucial for responses to LPS, we examined animals with microglia-specific deletion of TLR4 and found that it completely protected mice

from the combination treatment. To further explore the role of sleep, we generated Dec2 (BHLHE41) mutant mice that display decreased sleep and found that these animals are protected from low dose LPS plus SF. We are currently extending our results to bacterial infection.

Disclosures: A. Wani: None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.088/LBA151

Topic: B.09. Glial Mechanisms

Support: NIH Grant R01DA052618

Title: Repeated fentanyl abstinence intensifies opioid withdrawal and induces a proinflammatory state in striatal microglia

Authors: *D. BERGKAMP[1,3], A. DAWKINS[4], J. F. NEUMAIER[2,3];
[1]Pharmacol., [2]Psychiatry, Univ. of Washington, Seattle, WA; [3]VISN 20 Mental Illness Research, Educ. and Clin. Ctr., VA Puget Sound Hlth. Care Syst., Seattle, WA; [4]Neurobio., Harvard Univ., Boston, MA

Abstract: Opioid withdrawal is a serious obstacle to abstinence for individuals that want to reduce their consumption or stop using altogether. Fentanyl and highly potent new opioid analogues in particular make for difficult withdrawal experiences that can be precipitated by contemporary treatments, such as buprenorphine. Furthermore, anecdotal evidence suggests that previous experiences of opioid withdrawal may exacerbate the severity upon opioid discontinuation. To study the impact of repeated opioid withdrawal compared to a single withdrawal episode, we compared male and female mice after one versus five cycles of withdrawal experiences. We focused on microglia as well by selectively expressing HA-tagged ribosomes in microglia of transgenic mice (Ribotag $Rpl22^{-HA}$ x $Cx3c1\text{-}Cre^{ERT2}$) to allow us to sequence the microglial translatome and compare it to the whole striatal transcriptome in each mouse. For animals in the one cycle group, we administered saline or fentanyl twice daily for five days by ip injections, doubling the dose of fentanyl each day. Following the final injection, the animals entered spontaneous withdrawal and we collected the striatum for extraction of mRNAs undergoing translation at 16 hours into the withdrawal. For animals in the five-cycle groups, we repeated the saline or fentanyl injections another four times, with four days of home cage abstinence between injection cycles, then collected the striatum at 16 hours into the final withdrawal. Our results from RNA sequencing showed no effects of sex, but massive effects of cycle and drug treatment. Fentanyl five animals had increased expression of microglial homeostasis markers (such as *Tmem119, P2ry12, Hexb*) as well as increased expression of

disease associated genes (such as *Lyz*, *Ctss*, *Ctsb*) and interferon response related genes (such as *Tlr7*, *Irf7*, *Myd88*) compared to animals in the fentanyl one group. Morphological analyses of microglia from cage mate mice, not expressing the HA-tagged ribosomes, also showed an effect of repeated fentanyl withdrawal, reducing the average ramification index which suggests a more reactive, proinflammatory state. Finally, five cycles of fentanyl withdrawal induced more severe behavioral withdrawal signs. Together these results suggest that the mouse striatal microglia initiate an inflammatory response following five but not one opioid withdrawal experiences and suggest that drug therapies targeting this process may mitigate the severe withdrawal associated with repeated opioid tolerance and withdrawal.

Disclosures: D. Bergkamp: None. **A. Dawkins:** None. **J.F. Neumaier:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

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Topic: B.09. Glial Mechanisms

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Takeda Science Foundation
JSPS Kakenhi Grant-in-Aid for Scientific Research (C)
Kakenhi Grant-in-Aid for Scientific Research (B)
JSPS WISE program "The Graduate Program for Medical Innovation (MIP)"

Title: Maternal immune activation and peripubertal stress synergistically disrupt cerebellar plasticity integration and impair motor coordination learning.

Authors: *M. HIKOSAKA[1], N. HOSOI[3], G. OHTSUKI[2];
[1]Grad. Sch. of Med., [2]Dept. of Drug Discovery Med., Kyoto Univ., Kyoto, Japan; [3]Dept. of Neurophysiol. and Neural Repair, Gunma Univ. Grad. Sch. of Med., Maebashi, Japan

Abstract: Prenatal and early life stress disrupts neural network functioning, cumulatively increasing the risk for neuropsychiatric disorders later in life. However, how developmental stress impairs cognition and learning remains elusive. Here, we investigated cerebellar synaptic connectivity, plasticity, and learning using translational model mice that received both maternal immune activation and peripubertal social defeat stress (i.e., 2HIT) in both sexes. These mice exhibited impairments of motor coordination learning, except for the resilient females. In the cerebellum, we found an increase in microglial contact, a reduction of Purkinje-cell spine density and parallel-fiber synaptic responsiveness in 2HIT. Metabotropic glutamate receptor-mediated and climbing fiber-mediated responses were both diminished. Furthermore, multiple forms of Purkinje cell plasticity were dysregulated, including polarity reversal of parallel-fiber long-term depression and failure of intrinsic plasticity. Notably, cerebellar microglia replacement

ameliorated those phenotypic impairments. Our findings suggest that stress-associated microglia impede neural circuit formation and cause disorganized plasticity, leading to cerebellar learning deficits.

Disclosures: M. Hikosaka: None. **N. Hosoi:** None. **G. Ohtsuki:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.090/LBA153

Topic: B.09. Glial Mechanisms

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JSPS WISE program "The Graduate Program for Medical Innovation (MIP)"

Title: Maternal immune activation and peripubertal stress synergistically produce reactive microglia and confine cerebellar cognitive function.

Authors: *G. OHTSUKI, M. HIKOSAKA;
Dept. of Drug Discovery Med., Kyoto Univ., Kyoto, Japan

Abstract: The functional alteration of microglia emerges in the brains exposed to extrinsic stress insults during early development. Pathophysiological findings of psychiatric disorders such as schizophrenia and autism implied a localized deficit of the cerebellum. However, the link between microglia reactivity and cerebellar dysfunction is missing. Here, we investigated the developmental immune environment of translational mouse models that combine two risk factors: maternal infection and repeated social defeat stress (*i.e.*, 2HIT). We found synergy of inflammatory stress insults produced reactive microglia, specifically in the cerebellum in both sexes. The microglial proliferation correlated with the Purkinje neuron loss in 2HIT mice. Highly multiplexed imaging-mass-cytometry demonstrated a TREM2-positive population of stress-associated microglia in the cerebellum. Single-cell-proteomic clustering revealed IL-6- and TGFβ-signaling association with microglial cell transition. Purkinje cells reduced excitability, cerebellum-involved brain-wide functional dysconnectivity, and behavioral anomalies underpin the cerebellar cognitive dysfunctions in 2HIT animals, ameliorated by cerebellum-specific microglia replacement.

Disclosures: G. Ohtsuki: None. **M. Hikosaka:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.091/LBA154

Topic: B.09. Glial Mechanisms

Support: NIH Diversity Supplement R01MH123093W1
NRSA T-32 grant

Title: Gut Microbiota-Mediated Celecoxib Treatment in a Preclinical Model of Stress-Induced Depression

Authors: *K. C. NNAH[1], Z. HAGE[2], M. MADEIRA[2], A. KOKKOSIS[3], S.-A. E. TSIRKA[4]; [1]Neurobio. and Behavior, Stony Brook University, Program in Neurosci., Stony Brook, NY; [2]Pharmacol. Sci., Stony Brook Univ., Stony Brook, NY; [3]Velocigene, Regeneron Pharmaceuticals, NYACK, NY; [4]Pharmacol. Sci., Univ. Med. Center, Stony Brook, Stony Brook, NY

Abstract: Major Depressive Disorder (MDD) is a multifactorial heterogeneous psychiatric disorder that affects more than 350 million people worldwide, yearly. The pathophysiology behind MDD is full of ubiquitous symptoms and heterogeneous biology, whereby some individuals may display similar symptoms (anhedonia, low mood, physical ailments, cognitive impairment amongst others) but the underlying pathophysiology may be completely different. Most studies in the field of depression investigate neuronal (monoaminergic and glutamatergic) dysfunction but in a subset of individuals, depression may involve chronic neuroinflammation and gastrointestinal (GI) dysbiosis. It has been shown that the cytokines commonly secreted by over-reactive microglia induce changes that negatively regulate neuronal plasticity and synaptic elements. Researchers have begun to delve into the role of the gut microbiome and specifically microbiota, in the establishment or exacerbation of depression, however it has been challenging to narrow down the vast and complex contributing mechanisms. Gut microbiota have a direct effect on myeloid cells, as bacterial metabolites influence the inflammatory responses elicited by them, both in the periphery (monocytes/macrophages) and in the central nervous system (microglia). Both microbiota and microglia converge on the cycooxygenase-2/prostaglandin E2 (COX-2/PGE2) signaling pathway, providing some insight into inflammatory mechanisms behind depression. Widely used as an anti inflammatory treatment, celecoxib is a specific COX-2 inhibitor that also has been reported to have antidepressant effects. Through the inhibition of COX-2, not only does celecoxib result in decrease of inflammation, but the treatment also decreases gastrointestinal side effects that have been observed with other nonselective NSAIDs. While there have been studies that examine how gut microbiota metabolize NSAIDs, not many have looked into celecoxib specifically. The objective of this work is to characterize the neuronal and GI changes under inflammatory conditions within a mouse model of chronic stress and then relate behavioral changes to differences in gut microbiota composition and GI function. My

essential question is whether celecoxib leads to attenuation of major depressive disorder symptoms through gut microbiota metabolism. The results obtained will provide new knowledge in a fast-growing field and uncover novel treatments for MDD.

Disclosures: K.C. Nnah: None. **Z. Hage:** None. **M. Madeira:** None. **A. Kokkosis:** None. **S.E. Tsirka:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.092/LBA155

Topic: B.09. Glial Mechanisms

Support: K01AT010984
R56MH135895

Title: A Novel Approach to Depression Treatment: Targeting Microglial Glutaminase in Chronic Stress Model

Authors: *Y. LI[1], M. HUANG[3], A. G. THOMAS[3], W. LIYANAGE[2], N. HIN[4], K. M. RANGARAMANUJAM[2], T. TSUKAMOTO[3], R. RAIS[3], B. S. SLUSHER[3], X. ZHU[1];
[1]Dept. of Psychiatry and Behavioral Sci., [2]Dept. of Ophthalmology, Johns Hopkins Univ., Baltimore, MD; [3]Dept. of Neurol., [4]Dept. of Medicinal Chem., Johns Hopkins Drug Discovery, Baltimore, MD

Abstract: Major depressive disorder (MDD) is a common and debilitating psychiatric disorder with a high lifetime prevalence, imposing a severe economic burden on society. Despite several clinically effective treatments for MDD, many patients exhibit resistance to current antidepressants. Thus, novel interventions based on pathological mechanisms of MDD are needed. Our previous research found that glutaminase (GLS1), the enzyme that catalyzes the hydrolysis of glutamine to glutamate, is significantly upregulated in activated microglia in the brain of mice subject to Chronic Social Defeat Stress (CSDS), a well-established rodent model used to study stress-induced mood disorders, including depression.
In this study, we developed hydroxyl-terminated poly(amidoamine) (PAMAM) dendrimer nanoparticle delivery systems designed to target microglial GLS1 specifically. We synthesized two novel dendrimer-GLS1 inhibitors, Dendrimer-TTM020 (D-TTM020) and Dendrimer-JHU29 (D-JHU29). Using the CSDS model, we evaluated the target engagement and efficacy of these inhibitors through various assays, including glutaminase enzymatic activity assays, immunohistochemistry, histopathology, and a comprehensive battery of behavioral tests, including the social interaction test.
Using a Cy5 fluorescently labeled hydroxyl-terminated dendrimer (D-Cy5), we tested its brain

penetration in mice after CSDS and found that D-Cy5 was selectively engulfed by activated microglia in mice after CSDS. Both D-TTM020 and D-JHU29 significantly reduced microglial GLS1 activity in two brain regions: the prefrontal cortex and the hippocampus. Furthermore, these conjugates enhanced sociability in the CSDS murine model, without exhibiting undesirable side effects, specifically no gastrointestinal-related toxicities, indicating their potential as effective treatments for chronic stress-associated depression.
The development of microglial-targeted glutaminase inhibitors, particularly dendrimer-based conjugates, represents a novel therapeutic approach for chronic stress-associated depression. Our study shows these inhibitors significantly reduce microglial glutaminase activity and enhance sociability in a chronic stress murine model, highlighting their potential as effective and safe treatments for depression.

Disclosures: Y. Li: None. **M. Huang:** None. **A.G. Thomas:** None. **W. Liyanage:** None. **N. Hin:** None. **K.M. Rangaramanujam:** None. **T. Tsukamoto:** None. **R. Rais:** None. **B.S. Slusher:** None. **X. Zhu:** None.

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LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.093/LBA156

Topic: B.09. Glial Mechanisms

Title: Microglia-mediated loss of hippocampal perineuronal nets in mild respiratory COVID

Authors: C. STEIFMAN[1], O. LAGASSE[1], **C. CHAPON**[1], *M. T. TONG[2];
[1]Macalester Col., St Paul, MN; [2]Biol., Macalester Col., Saint Paul, MN

Abstract: Post-acute sequelae of SARS-CoV-2 infection, or “long COVID,” is characterized by ongoing respiratory and cognitive symptoms. “Brain fog” is common amongst long COVID sufferers who report many cognitive deficits, including memory impairments, that impact their daily lives. Previous research using COVID mouse models have found cellular and molecular differences in critical memory regions, like the hippocampus. In this study, we investigate the effects of mild COVID on perineuronal nets (PNNs) in the hippocampus. PNNs are condensed extracellular matrix structures that have been shown to control plasticity and thus may play a role in COVID-related memory symptoms. We used a mouse (CD-1 males) model of mild SARS-CoV-2 infection limited to the respiratory system where infection clears within 1 week. Seven weeks post-infection, brain tissue from infected and control mice were harvested for extensive histological analysis to assess microglia activation (CD68+/Iba1+) and PNNs (WFA+) across hippocampal subregions dentate gyrus (DG), CA1, and CA2/3. Our preliminary findings showed that mice with mild COVID have a higher density of activated microglia that were closely associated with and engulfing PNNs in the DG and CA1, but not CA2/3. This interestingly

corresponds to higher PNN density in CA2/3 of COVID mice, but no differences in DG and CA1. These findings suggest that microglia-mediated regulation of PNNs in the hippocampus occurs in respiratory SARS-CoV-2 infection and may provide an explanation for the memory impairments experienced by long COVID sufferers.

Disclosures: C. Steifman: None. **O. Lagasse:** None. **C. Chapon:** None. **M.T. Tong:** None.

Late-Breaking Poster

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.094/LBA157

Topic: B.09. Glial Mechanisms

Support: Ciencia de frontera CF-2023-G-243

Title: Chronic acoustic stress stimulate oligodendrocite proliferation in the adult male mice brain

Authors: *M. A. MALDONADO MUÑOZ[1,3], L. CRUZ MENDOZA[5], M. S. LUQUIN DE ANDA[7], Y. RUVALCABA DELGADILLO[6], D. REBOLLEDO-SOLLEIRO[4], F. JÁUREGUI[2]; [1]Univ. Nacional Autonoma de Mexico, Cancún, Mexico; [2]Fisiologia, Univ. Nacional Autonoma de Mexico, Ciudad de México, Mexico; [3]Univ. Anáhuac Cancún, Cancún, Mexico; [4]Univ. Anáhuac Cancún, CANCUN, Mexico; [5]Neurociencias, Univ. De Guadalajara, Guadalajara, Mexico; [6]Neurosci., Univ. De Guadalajara, Zapopan, Mexico; [7]Univ. de Guadalajara, Guadalajara, Mexico

Abstract: The hippocampus (HP), lateral ventricles (LV), and corpus callosum (CC) are crucial brain regions known for their sensitivity to environmental changes and high rates of cellular proliferation and adaptation. Despite the prevalence of environmental noise as a stressor, its effects on the proliferation and differentiation of the primary cellular phenotypes in these regions remain largely unknown. This study investigates the impact of acoustic stress on the proliferation and differentiation rates in the HP, LV, and CC of adult male mice. Using an experimental model of chronic noise exposure (21 days), urban sounds at intensities ranging from 90 to 105 decibels were simulated according to the mouse audiogram. Histological sections from each region were analyzed for proliferation (BrdU+ immunolabeling) and cell differentiation (BrdU+ co-labeled with NeuN+, Olig2+, GFAP+, and Iba1+). Our findings indicate that chronic noise exposure reduces cellular proliferation in all evaluated areas. Although this antiproliferative effect impacts most cell lineages, cell differentiation analysis revealed a notable increase in oligodendrocyte proliferation, particularly in the corpus callosum. These results confirm that chronic environmental stressors exert an antiproliferative effect but also suggest that oligodendrocytes may respond to acoustic stress by increasing their presence in exposed brains.

Disclosures: M.A. Maldonado Muñoz: None. **L. Cruz Mendoza:** None. **M.S. Luquin de Anda:** None. **Y. Ruvalcaba Delgadillo:** None. **D. Rebolledo-Solleiro:** None. **F. Jáuregui:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.095/LBA158

Topic: B.09. Glial Mechanisms

Support: PAPIIT-UNAM-México No. IN205822
CONAHCYTCF-319740

Title: Positive allosteric modulators of GABAAreceptors expressed in oligodendroglial cells promote their survival in vitro

Authors: *A. G. CARDENAS-PEREZ[1,2], E. GARAY[2], A. CISNEROS-MEJORADO[2], R. O. ARELLANO[2];
[1]Neurobiología Celular y Molecular, Inst. de Neurobiología, UNAM, Campus Juriquilla, Univ. Nacional Autonoma de Mexico, Querétaro, Mexico; [2]Inst. de Neurobiología, Univ. Nacional Autónoma de México, Queretaro, Mexico

Abstract: Oligodendrocytes (OLs) and neurons establish GABAergic communication that have important effects on the functions of both cell types, although the functional consequences of this cellular interaction are still not fully understood. Expression of functional GABA type A receptors ($GABA_AR$) in OLs is controlled by their contact with neurons since their precursor cell (OPCs) stage. This suggested a role for GABAergic signaling in the establishment of the OPCs-neuron dialogue and their differentiation towards mature OLs. Here, in OLs maintained *in vitro* the GABAAR activity was potentiated using ganaxolone (GX) and N-butyl-β-carboline-3-carboxylate (β-CCB) two allosteric positive modulators of the receptor and studied their effects on cell survival to obtain information related with the mechanisms involved. OLs were isolated from rat (P11) optic nerve and maintained *in culture* in proliferation medium (PM). In control conditions, cells were mainly O4+, and their survival decreased strongly with the time in culture. However, both allosteric modulators, either GX (1 μM) or β-CCB (10 μM) added to the PM significantly increased cell survival. The O4+ pattern was not different for the cells in the presence of either GX or β-CCB. The survival increase caused by GX or β-CCB was eliminated in the presence of either gabazine (150 μM) or bicuculline (30 μM), specific $GABA_AR$ antagonists. Thus, our results indicated that both Gx and β-CCB promoted the survival of oligodendroglial cells through the activation of the $GABA_AR$. This would explain at least in part, the positive effects that $GABA_AR$ positive modulators such as β-CCB have on myelination process observed *in vivo*.

Disclosures: A.G. Cardenas-Perez: None. **E. Garay:** None. **A. Cisneros-Mejorado:** None. **R.O. Arellano:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.096/LBA159

Topic: B.09. Glial Mechanisms

Support: CONACyT CF-2023-G-1190

Title: Acute activation of the rat dorsal root ganglion nociceptive cells by the serum of patients suffering from fibromyalgia

Authors: *A. ALMANZA-GUTIERREZ[1], P. SEGURA[2], L. MARTÍNEZ MARTÍNEZ[3], M. MARTINEZ-LAVIN[3], F. MERCADO[1];
[1]Inst. Nacional de Psiquiatria Ramon de la Fuente Muñiz, Ciudad de México, Mexico; [2]CONAHCyT, Investigador por México, Ciudad de México, Mexico; [3]Inst. Nacional de Cardiología Ignacio Chávez, Ciudad de México, Mexico

Abstract: Background/Purpose. A consistent line of investigation proposes fibromyalgia as a stress-evoked sympathetically maintained neuropathic pain syndrome. DRG house the soma of the somatosensory neurons filtering to the brain painful stimuli arising from most parts of the body and internal organs. Each individual neuronal nucleus tightly interacts with its enveloping immune-competent satellite glial cells (SGCs). Different mediators activate SGCs inducing cytokine release and stronger SGCs-nociceptive neuron coupling, leading to chronic pain. Little is known about the acute effect of human serum on cultured murine DRG nociceptive cell physiology. IgG from fibromyalgia patients induce hyperalgesia in mice by binding to SGCs. Objectives: To define if human serum can acutely activate murine DRG pro-nociceptive cells. To find out if the serum of women suffering from fibromyalgia induces more pronounced acute stimulation of DRG neurons and/or their SGCs when compared to serum from healthy women.
Methods. Serum from 6 women suffering from fibromyalgia and 6 matched healthy controls were tested on Wistar rat DRG neurons and their SGCs. The serum and the following activating substances; capsaicin 1 µM, ATP 10 µM and K^+ 60 mM, were sequentially perfused onto primary DRG cell cultures. Fluo-4 was used as intracellular calcium concentration reporter. Researchers were blinded to the serum provenance.
Results. 1477 DRG neurons were studied, of these 625 were activated by human serum. The intensity of neuronal activation in response to patients' serum was not different from controls. The percentage of neurons activated by patients serum (43%) also, was not different from controls. 558 DRG SGCs were activated by human serum. A higher proportion of SGCs were activated by patients' serum compared to controls' serum. Finally, patients' serum induced

greater calcium influx into SGCs.
Conclusion. Human serum is able to acutely activate murine DRG pro-nociceptive cells. When compared to serum collected from healthy women, serum derived from fibromyalgia sufferers induces more intense and widespread stimulation on ATP unresponsive DRG SGCs, suggesting the presence of potentially identifiable pro-nociceptive substance(s) in the circulation. SGCs hyperstimulation appears to be independent of P2X7 signaling. DRG SGCs may play an important role in the pathogenesis of fibromyalgia.

Disclosures: A. Almanza-Gutierrez: None. **P. Segura:** None. **L. Martínez Martínez:** None. **M. Martinez-Lavin:** None. **F. Mercado:** None.

Late-Breaking Poster

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

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Topic: B.09. Glial Mechanisms

Support: NIH Grant R35 NS122260
NIH Grant R01 NS111719
NIH Grant R21 NS115492

Title: Endothelin B receptor inhibition rescues aging-dependent neuronal regenerative decline

Authors: R. FENG[1], ***S. F. ROSEN**[1], I. ANSARI[1], S. JOHN[1], M. B. THOMSEN[2], C. G. GEOFFROY[3], V. CAVALLI[1];
[1]Washington Univ. Sch. of Med., Saint Louis, MO; [2]CS27 LLC, Springboro, OH; [3]Dept. of Neurosci. and Exptl. Therapeut., Texas A&M Univ. Sch. of Med., Bryan, TX

Abstract: Peripheral nerve injuries have a major impact on patient's functioning and quality of life. Peripheral sensory neurons regenerate their axons after injury to regain function, but this ability declines with age, contributing to increases in healthcare costs and the risk of long-term disability. The mechanisms behind this decline are not fully understood. Excessive production of endothelin 1 (ET-1), a potent vasoconstrictor, is linked to many diseases that increase with age. However, the role of ET-1 and its receptors in axon regeneration is unknown. Using a single cell RNAseq approach, we reveal that in dorsal root ganglia (DRG), satellite glial cells (SGCs), which completely envelop the sensory neuron soma, express the endothelin B receptor (ETBR), while ET-1 is expressed by endothelial cells. Inhibition of ETBR *ex-vivo* in DRG explant cultures improves axon growth in both adult and aged conditions in both sexes. Additionally, *in vivo* treatment with the FDA- approved compound, Bosentan, improves axon regeneration and reverses the age-dependent decrease in axonal regenerative capacity. Bosentan treatment *in vivo* also enhances the expression of connexin 43 in SGCs after injury in adult and aged mice. These

results reveal that inhibition of ETBR function enhances axon regeneration and rescues the age-dependent decrease in axonal regenerative capacity, providing a potential avenue for future therapies. Future studies will examine whether Bosentan treatment rescues sensory dysfunction that occurs during aging, and its mechanism for increasing axonal regenerative capacity.

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Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

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Topic: B.09. Glial Mechanisms

Support: This work is supported by the Merkin Peripheral Nerve and Regeneration Center at JHU and Dr. Miriam and Sheldon G. Adelson Medical Research Foundation.

Title: Mapping the temporal pattern of the mRNA expression profile following denervation in humans and rats

Authors: *M. A. KHAN[1,2], X. HU[2,1], S. H. TUFFAHA[3,1], A. J. BELZBERG[4,1], S. THOMAS[2,1], R. KAWAGUCHI[5], A. HOKE[2,1];
[2]Departments of Neurosci. and Neurol., [3]Dept. of Plastic and Reconstructive Surgery, [4]Dept. of Neurosurg., [1]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [5]Dept. of Neurol., David Geffen Sch. of Medicine, Univ. of California, Los Angeles, Los Angeles, CA

Abstract: Background
Rodent models are typically used to investigate the cellular pathways following nerve injury. However, delayed coaptation for as little as 8 weeks in rodents significantly impairs recovery, whereas humans can withstand longer durations of denervation. Hence, little is known about how the gene expression profile of rodents following denervation maps temporally onto humans. Here, we compared mRNA expression in denervated humans (RNA-seq) and rats (microarrays).
Methods
Humans: Seventy-three patients underwent peripheral nerve surgery at Johns Hopkins Hospital (duration of denervation: control, 3mo, 6-8mo, 12mo-5yr) and distal nerve samples were analysed using RNA-seq.
Rats: the sciatic nerve was transected (duration of denervation: control, 1d, 3d, 7d, 14d, 1mo, 3mo, 6mo) and distal sciatic nerve samples were analysed using DNA microarrays and qPCR.
Results
In human denervation, RUV analysis revealed a triphasic temporal pattern of RNA expression. The 3mo denervation group showed an increased innate immune response and reduced energy

production, whereas 6-8mo denervation had an increased adaptive immune response. Finally, 12mo-5yr denervation showed somewhat reversion to the original state, with increased energy production, but reduced neurogenesis.
Gene ontology pathway analysis revealed persistent downregulation of biosynthetic pathways involved in cholesterol, lipid, secondary alcohol and acetyl coenzyme A metabolism in both humans and rats. In rats, cellular proliferation and immune signalling were upregulated between days 1 and 14 of denervation, with ficolin-1 RNA upregulated between day 1 and 7, whilst pyroptosis was upregulated at day 14.
Overlap analysis showed 3 months of denervation in humans corresponded most significantly to 3-7 days of denervation in rats. Six months of human denervation corresponded to 7-14 days rat denervation, and 12mo-5yrs of human denervation corresponded to 6 months in rats.
Discussion
Denervation induces a differential RNA expression profile that maps temporally between humans and rodents. We will now perform RNA-seq on chronically denervated rat models to further characterise these changes.

Disclosures: M.A. Khan: None. **X. Hu:** None. **S.H. Tuffaha:** None. **A.J. Belzberg:** None. **S. Thomas:** None. **R. Kawaguchi:** None. **A. Hoke:** None.

Late-Breaking Poster

LBA002: Theme B Late-Breaking Posters

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA002.099/LBA162

Topic: B.10. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH-NINDS: 5K00NS125815

Title: Fatigue and cognition differences in their relationship with social and biological markers of stress in Black and White patients with Multiple Sclerosis

Authors: *S. N. MOODY[1], D. DEVIER[3], B. J. COPELAND[2], M. MANUEL[4], J. LOVERA[5], **C. L. MUSE**[6];
[2]Neurol., [1]LSU Hlth. Sci. Ctr., New Orleans, LA; [3]LSU Hlth. Sci. Ctr. Cell Biol. & Anat., New Orleans, LA; [4]Cell. Biol. and Anat., Augusta Univ., Augusta, GA; [5]Neurol., LSU Hlth. Sci. Ctr. - New Orleans, New Orleans, LA; [6]Xavier Univ., New Orleans, LA

Abstract: Background: High fatigue is reported by patients with Multiple Sclerosis (MS) and associated with the HPA-axis. There are racial differences in both MS and fatigue. Cortisol, a biomarker associated with the stress response system, also often differs between racial groups and is dysregulated in patients with MS. There is a dearth of knowledge on the relationship between race, stress, and fatigue in patients with MS.

Objective: To examine the relationship of race, perceived stress, cumulative cortisol, and depression with reported fatigue and cognition (Symbol Digit Modality Test- SDMT).
Methods/Patients: Eighty-three adults diagnosed with MS (77% Female; 49% Black) and 43 healthy controls (72% Female; 26% Black) were selected from a cohort of participants taking part in a study designed to validate a novel cognitive measure in patients with neurodegenerative disorders. Self-reported fatigue, depression, and stress were collected. Cognition was measured using the oral SDMT and hair samples were assayed to gauge cumulative hair cortisol.
Results: Participants with MS reported higher total, psychological and physiological fatigue than healthy controls. All regression models controlled for age, education and residualized depression. Higher levels of total fatigue were associated with perceived stress B; = 0.79, (61) = 3.65, p; < .001 and MS B; = 10.87, (61) = 2.95, p; < .005. Higher cognitive fatigue was only associated with higher reported perceived stress B;=0.44, (61) =3.77, p;<.001 but not MS. Higher cortisol B; = −2.00, (61) = −2.47, p;=.016, patients with MS B;= −8.72, (61)=−3.10, p;=.003, and Black participants B;= −7.33, t;(61)= −2.79, p;=.007 were associated with lower SDMT scores.
Conclusion: Self-reported perceived stress captured reports of fatigue in both MS and control groups. Higher cumulative cortisol, MS, and being Black, corresponded with worse cognition. While this points to a relationship between biomarkers of stress and cognition in patients with MS, self-reports and not biological markers of stress may better capture patient fatigue.

Disclosures: S.N. Moody: None. **D. Devier:** None. **B.J. Copeland:** None. **M. Manuel:** None. **J. Lovera:** None. **C.L. Muse:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.001/LBA1

Topic: C.01. Brain Wellness and Aging

Support: National Institute on Aging Intramural Research Program

Title: A comprehensive view of age-related neuroinflammation revealed by spatial transcriptomics studies in murine brain

Authors: *L. WANG;
Natl. Inst. on Aging/NIH, Baltimore, MD

Abstract: To systematically understand age-induced molecular changes, we performed spatial transcriptomics on a total of 36 coronal brain sections from both male and female mice across young, middle-aged, and geriatric age groups. We identified seven transcriptionally distinct regions that coincided with known brain anatomy. All regions exhibited age-associated upregulation of inflammatory mRNAs and downregulation of mRNAs related to synaptic

function. Notably, aging white matter fiber tracts showed the most prominent changes with pronounced effects in females. The inflammatory signatures indicated major ongoing events: microglia activation, astrogliosis, complement activation, and myeloid cell infiltration. Immunofluorescence and quantitative MRI analyses confirmed the physical interaction of activated microglia with the fiber tract and concomitant reduction of myelin in old mice. Additionally, a small subset of RNAs associated with cellular senescence was also found to be upregulated in the vicinity of the aging fiber tracts. Machine learning algorithms identified candidate transcription factors driving these changes which we independently validated by CUT&RUN. Our study provides a resourceful dataset of spatially resolved transcriptomic features in the naturally aging murine brain encompassing three age groups and both sexes. The results link previous disjointed findings and provide a comprehensive overview of brain aging identifying fiber tracts as a focal point of inflammation with a strong sex-bias towards females. Our findings further imply a potential molecular/cellular mechanism for age-related neuroinflammation and identify potential targets for further investigation.

Disclosures: L. Wang: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.002/LBA2

Topic: C.01. Brain Wellness and Aging

Support: AI164769
AG076949
MH133561
AG080790
We thank Stefano Marenco and the Human Brain Collection Core at the National Institute of Mental Health for providing some of the postmortem human brain tissue samples.
We thank the families for donating the brain tissue used in this study.

Title: Single-nucleus and spatial characterization of human hippocampus reveal dysregulated gene expression with aging and Alzheimer's disease

Authors: *L. POLIZZI[1,2], Z. ZHANG[8], M. MARIANI[2,9], C. SISSOKO[2,9], A. RAMNAUTH[2,9], M. REZAEI[2,9], Y. LIU[2,3], Y.-Y. HUANG[2,9], A. J. DWORK[2,4,9,10], G. ROSOKLIJA[2,4,10], V. ARANGO[2,9], R. HEN[2,9,5,6], J. MANN[2,9,7], H. GALFALVY[2,9], M. BOLDRINI[2,9];
[1]Univ. of Trento, Trento, Italy; [2]Psychiatry, [3]Biostatistics, [4]Pathology and Cell Biol., [5]Neurosci., [6]Pharmacol., [7]Radiology, Columbia Univ., New York, NY; [8]Mental Hlth. and Data Sci., [9]Mol.

Imaging and Neuropathology, New York State Psychiatric Inst., New York, NY; [10]Macedonian Acad. of Sci. & Arts, Skopje, North Macedonia, The Republic of

Abstract: The U.S. population aged 65 and over is expected to reach 84 million by 2050, increasing the incidence of age-related illness, like Alzheimer's disease (AD), and highlighting the need for new therapeutic targets and a deeper understanding of disease mechanisms. Cognitive decline with aging includes impairments in episodic memory, with the dentate gyrus (DG) and adult hippocampal neurogenesis (AHN) being implicated in these functions. In normal aging (NA) humans, there is a decrease in the multipotent progenitor stem cell pool, reduced angiogenesis, and reduced neuroplasticity, though neural progenitor and immature granule neuron (GN) numbers do not show significant age-related decline. AD involves loss of neuronal tissue in the hippocampus and entorhinal cortex. Post-mortem analysis of AD hippocampus tissue revealed a decrease in immature GN and overall cell numbers compared to NA. If this is due to reduced stem cell proliferation and neurogenesis or reduced apoptosis remains unknown. Here, we investigate cellular lineages, molecular regulators, and pathway disruptions in the human neurogenic niche in NA and AD hippocampus, using single-nucleus RNA and ATAC sequencing and spatial transcriptomics. Single-Cell Multiome and Visium Spatial Transcriptomics (10X Genomics) were employed to profile gene expression and chromatin accessibility in the hippocampus proper of 12 NA (all males, age 14-74) and 9 AD subjects (4 females, 5 males, age 79-89+). Libraries were sequenced on NovaSeq 6000 Sequencer (Illumina), and datasets were preprocessed using standard quality control metrics. Unsupervised clustering identified all hippocampal cell types including sub-clusters of mature GNs, excitatory and inhibitory neurons, astrocytes, microglia, oligodendrocytes, vasculature, ependyma and choroid plexus cells. Logistic mixed effect models were used to examine age effects on gene expression in NA, using subject as a random effect. All models were adjusted for post-mortem interval. We identified 11 genes with significant positive (B&H adjusted p-value < 0.05) association with aging in GN. These genes include CNTNAP3B and CNTNAP4 involved in cell adhesion and neuronal function, PDE3A which regulates cyclic nucleotide levels, and is involved in neurodevelopment and cognitive processes, SLC7A11, which has a role in neurotransmitter balance and neurodegenerative processes, GML and NUTM2A-AS1 which are associated with cancer and cellular stress responses. Dysregulation of these genes may be involved in altered synaptic connectivity, impairment of synaptic plasticity, and elevated DNA damage response and apoptosis associated with aging.

Disclosures: L. Polizzi: None. **Z. Zhang:** None. **M. Mariani:** None. **C. Sissoko:** None. **A. Ramnauth:** None. **M. Rezaei:** None. **Y. Liu:** None. **Y. Huang:** None. **A.J. Dwork:** None. **G. Rosoklija:** None. **V. Arango:** A. Employment/Salary (full or part-time):; Work by VA related to this paper were completed when she was employed at Columbia and the New York State Psychiatric Institute; the opinions expressed in this abstract are the author’s own. **R. Hen:** None. **J. Mann:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); JJM receives royalties for commercial use of the C-SSRS from the Research Foundation of Mental Hygiene. **H. Galfalvy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); HG and her family own stocks in Illumina, Inc.. **M. Boldrini:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.003/LBA3

Topic: C.01. Brain Wellness and Aging

Support: NIH R01MH124997 to S.F.
NIH R01AG077783 to Z.Y.

Title: Elevating neuronal MCU levels in the hippocampus increases mitochondrial calcium uptake and respiration

Authors: M. CAWLEY[1], R. MONTALVO[1], Z. YAN[1], *S. FARRIS[2];
[1]Fralin Biomed. Res. Inst., [2]Virginia Tech., Roanoke, VA

Abstract: Neurons sustain energy demands via mitochondrial oxidative phosphorylation as the major source of ATP. However, the mechanisms coupling changes in neuronal activity to ATP output are not well understood. The mitochondrial calcium uniporter (MCU) complex is proposed to fulfill this role by sensing activity-induced increases in cytosolic calcium and transporting it into the mitochondrial matrix, which induces calcium-dependent activation of enzymes that promote ATP generation. However, different regions of the brain express different amounts of the main pore forming subunit, MCU, including a 4-fold enrichment of MCU in hippocampal subregion CA2 compared to neighboring CA1. The functional significance of MCU enrichment on mitochondrial and neuron function remains unclear. To address this, we first tested the impact of increasing MCU levels on mitochondrial calcium dynamics and mitochondrial respiration. We hypothesized that more MCU would increase the rate of mitochondrial Ca^{2+}-uptake, resulting in accelerated enzymatic activity and a greater capacity for ATP production via oxidative phosphorylation. We used adeno-associated viral vectors to overexpress MCU, or GFP as a control, in the hippocampus of adult male and female wildtype mice. We measured mitochondrial calcium kinetics in isolated mitochondria challenged with 5 µm calcium boluses (20 µm total) using a calcium-sensitive indicator and fluorometry. Preliminarily, in mice with MCU overexpression, we found an increase in the calcium retention capacity (average fold change compared to control ± sem: 1.51 ± 0.41, N=4 mice/group) and the rate of mitochondrial calcium uptake after each calcium bolus compared to the paired control mice (bolus (b)1= 1.45 ± 0.31; b2= 1.72 ± 0.67; b3= 1.62 ± 0.56; b4= 1.19 ± 0.07). In a subset of these mice (N=2 pairs), we simultaneously measured the rate of oxygen consumption and efficiency of oxidative phosphorylation using high-resolution respirometry. In mice with MCU overexpression, we found a small but consistent increase in state II (ave. fold change ± sem: 1.13 ± 0.06), maximal respiration (1.08 ± 0.005), and respiratory conductance (1.17 ± 0.07) compared to the paired control mice. Additional biological replicates are underway to verify these findings. Collectively, these studies suggest that modulating neuronal MCU expression alone can enhance

the capacity and the rate of mitochondrial calcium uptake to boost energy production. Further, the data are consistent with the idea that neuronal mitochondria enriched with MCU, such as in hippocampal CA2 neurons, may modulate the kinetics of mitochondrial Ca^{2+}-uptake to support circuit-specific energy demands.

Disclosures: M. Cawley: None. **R. Montalvo:** None. **Z. Yan:** None. **S. Farris:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.004/LBA4

Topic: C.01. Brain Wellness and Aging

Title: Identification of a small molecule novel compound in reducing mitochondrial dysfunction in age-related cellular models.

Authors: *K. L. JOYCE, A. BOOMINATHAN;
MitoSENS, SENS Res. Fndn., Mountain View, CA

Abstract: Throughout many neurodegenerative diseases and aging, mitochondrial decline from functional to dysfunctional is commonplace. Many mechanisms, including protein aggregation, inflammation, and reactive oxygen species, cause this. The loss of ATP production and increase in ROS and debris reduces the function of the neurons and eventually leads to neuronal death. Attempts to increase mitochondrial function such as NRF2 activation, CoQ10 supplement, and mitochondrial transfer have failed to create significant and lasting effects. As we age mitochondrial DNA accumulates mutations due to its proximity to ROS and lack of repair mechanisms. Therefore, we have investigated compounds related to mitophagy activation to clear damaged and low-functioning mitochondria. We have identified SRF-1 as a lead to reduce mtDNA mutation burden on cells and increase mitochondrial ATP production in two models of mtDNA disease and aging. In cells with the common deletion mutation, a 5kb removal of 8 protein-coding genes, after 28 days on compound cells had ~22% decrease in the mutation load. Prolonged incubations in the compound (for 42 days total) yielded ~60% reduction in the mutation load compared to control cells (SEM ± 3.56%). Simultaneously, there was an increase in COX3, a gene found in the deleted region by 150% compared to control cells (SEM ± 18.5%) indicating that cells are removing mitochondria with the highest levels of mtDNA damage and maintaining wildtype integrity. Functional assays showed that mitochondrial ATP production returned to levels similar to wild type cells. In cells that harbor the Leigh's Syndrome mutation 8993T to G, there is an 89% (SEM ± 3.34%) reduction of the point mutation after 42 days on the compound with a 197% increase in the wildtype ATP6 gene (SEM ± 17.3%) however, recovery of mitochondrial function is nonsignificant presumably because of the mutation severity. These data prove the utility and potential of this compound as a therapy for many diseases related to

mitochondrial function including mtDNA diseases, aging, and neurodegenerative disorders. Omics analysis will determine the mechanism of action and pathways associated with the compound and target identification.

Disclosures: K.L. Joyce: A. Employment/Salary (full or part-time):; SENS Research Foundation. **A. Boominathan:** A. Employment/Salary (full or part-time):; SENS Research Foundation.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.005/LBA5

Topic: C.01. Brain Wellness and Aging

Support: NIH R01-AG078181
Johns Hopkins Merkin PNNR center 90093312
R01-AG068130
R01-NS093416

Title: Targeting GCPII to promote remyelination in aging peripheral nerve injuries

Authors: *Y. SU[1,2,3], M. HUANG[1,2,3], A. G. THOMAS[2], M. H. FARAH[3], B. S. SLUSHER[1,2,3]; [2]Johns Hopkins Drug Discovery, [3]Neurol., [1]Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Peripheral nerve injuries (PNIs) represent a significant clinical challenge, especially with aging when axonal remyelination and regeneration are compromised. This study explores the therapeutic potential of inhibiting glutamate carboxypeptidase II (GCPII), a neuropeptidase involved in glutamate signaling, for promoting remyelination following PNI. GCPII activity was significantly upregulated following PNI, but was normalized with the selective GCPII inhibitor 2-(phosphonomethyl)-pentanedioic acid (2-PMPA) treatment (7464 ± 626 vs. 10,047 ± 440 vs. 1504 ± 89 fmol/mg/h; $p < 0.05$, $n = 3$). Immunostaining confirmed that the elevation of GCPII was predominantly in activated macrophages and repair Schwann cells. In vitro, 2-PMPA treatment enhanced myelination in dorsal root ganglion (DRG) explants, with a significant increase in myelin segments (17.67 ± 3.48 vs. 72.67 ± 4.37; $p < 0.05$, $n = 3$). In vivo, using a sciatic nerve crush injury model in aged mice, 2-PMPA significantly accelerated remyelination, as evidenced by a decreased g-ratio (0.90 ± 0.01 vs. 0.73 ± 0.05; $p < 0.05$, $n = 3$) and a higher percentage of remyelinated axons (28.1 ± 2.1 vs. 82.5 ± 7.2%; $p < 0.05$, $n = 3$). Further, we targeted GCPII inhibition specifically on macrophages and Schwann cells using dendrimer-conjugated 2-PMPA. Electrophysiological assessments of nerve conduction speed via compound muscle action potential (CMAP) recordings demonstrated a significant decrease in CMAP latency after 10 weeks of GCPII inhibition in aged PNI mice (4.04 ± 0.11 vs. 3.23 ± 0.13 ms; $p <$

0.01, n = 5). These findings suggest that GCPII inhibition is a promising therapeutic strategy to enhance remyelination following PNI, particularly in elderly patients where this process is compromised.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.006/LBA6

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant T32MH020016

Title: Age, sex, and disease modify brain barrier permeability to hundreds of proteins

Authors: *A. FARINAS[1], J. RUTLEDGE[2], V. A. BOT[1], J. TIMSINA[3], C. CRUCHAGA[3], T. WYSS-CORAY[1];
[1]Stanford Univ., Stanford, CA; [2]The Amaranth Fndn., New York, NY; [3]Washington Univ. in St. Louis, Saint Louis, MO

Abstract: The brain barriers prevent the unrestricted exchange of factors between the blood and the brain, yet a comprehensive understanding of how barrier function changes with aging and disease is still lacking. To address this, we used the SomaScan assay to measure thousands of proteins in paired human cerebrospinal fluid (CSF) and plasma samples from three cohorts comprising 767 people, including healthy elderly individuals and those with sporadic or familial Alzheimer's disease. Using RNA sequencing data from 21 organs across the body, we identified 742 proteins specifically produced in the peripheral organs and calculated their CSF/plasma ratios to identify changes in their transport into the brain. Many, but not all, peripheral proteins had elevated CSF/plasma ratios with healthy aging, indicating that the permeability of the blood-CSF barrier increases with age only for specific subsets of proteins, such as those involved in stress response and coagulation pathways. Surprisingly, increased brain uptake of specific peripheral proteins was associated with the maintenance of normal cognitive function in old age, suggesting a protective role for certain peripheral factors in the aging brain. Correlation network analysis revealed clusters of peripheral proteins whose CSF/plasma ratios changed together; these modules were enriched for specific protein domains which could act as molecular handles facilitating their transport into the brain. Our approach represents a novel method for identifying putative molecular features involved in transport of substrates across the brain barriers, a longstanding challenge in the development of therapeutics for neurological disorders. Additionally, this work provides the largest-scale substrate-specific readout to date of brain

barrier permeability in living humans, contributing to our understanding of the diverse changes to brain barrier function that occur with healthy aging and neurodegenerative disease.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.007/LBA7

Topic: C.01. Brain Wellness and Aging

Support: NIH NINDS/NIA R01 NS127284-03

Title: Learning and memory impairment during perimenopause: effects of accelerated ovarian failure in a model of vascular dementia

Authors: *R. L. KALISH[1], A. SHEHRYAR[1], B. DENG[1], G. M. DEMARCO[1], E. J. BAUMOEL[2], A. C. CHAPMAN[2];
[2]Psychology, [1]Binghamton Univ. - SUNY, Binghamton, NY

Abstract: Vascular dementia (VaD) is a result of cerebrovascular disease commonly caused by chronic hypertension. Cerebrovascular disease is more prevalent in men until menopause occurs, after which women are more affected. Perimenopause is the natural transition to non-reproductive status and is associated with impaired memory. However, the combined effects of chronic hypertension and perimenopause on cognition remain unclear. We hypothesized learning and memory would be impaired during perimenopause and to a greater extent during chronic hypertension. We used five-month-old female spontaneously hypertensive rats (SHR) as a model of VaD and normotensive Wistar (Wis) rats. Rats received daily injections of 4-vinylcyclohexene diepoxide (VCD; 160 mg/kg s.c., 15 days) to induce ovarian failure or vehicle (n=6/group). Two months later, learning and memory were tested using a Morris water maze task: four consecutive days of four 120 sec swim trials during which escape latency was measured. On day five, memory was probed: the platform was removed and latency to and crossings through the platform zone quantified. Data are mean±SEM. Comparisons were made via a 2-way ANOVA with a post-hoc Tukey test. There was a main effect of hypertension on escape latency, with SHR finding the platform faster than Wis groups on training days 1 ($F_{(1,20)}$=11.99; $p<0.01$) and 2 ($F_{(1,20)}$=18.99; $p<0.01$). However, all rats had a similar escape latency by day 4 (Fig 1). During the probe, both VCD groups trended towards slower latencies to the platform zone (Wis: 33.3±16.2 sec; SHR: 34.8±15.2 sec), taking ~3 times longer than control groups (Wis: 12.7±5.8 sec; SHR: 10.3±5.5 sec; $F_{(1,20)}$=3.64; $p=0.07$). VCD groups also trended toward fewer crossings through the platform zone ($F_{(1,20)}$=3.26; $p=0.08$). These data suggest

long-term memory may be impaired in the perimenopausal period. While we found no compounding effect of chronic hypertension as hypothesized, deficits may develop/progress over time. These findings highlight the importance of furthering our understanding of how the menopause transition may contribute to VaD.

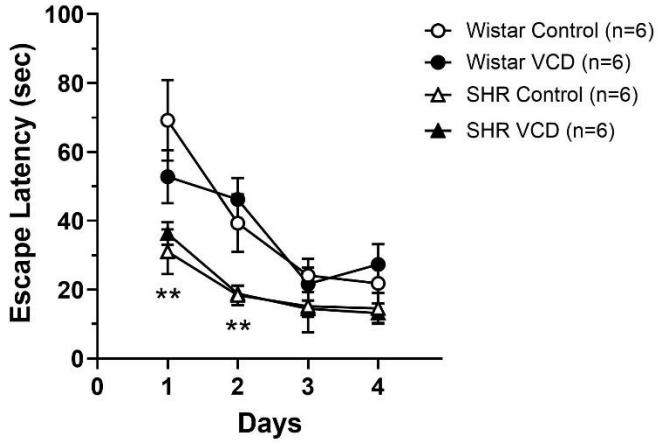


Fig 1. The time it took for rats to find the hidden platform (escape latency) across four training days of Morris water maze for Wistar and SHR rats that were either vehicle controls or had accelerated ovarian failure via VCD injections.

Disclosures: R.L. Kalish: None. **A. Shehryar:** None. **B. Deng:** None. **G.M. DeMarco:** None. **E.J. Baumoel:** None. **A.C. Chapman:** None.
Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.008/LBA8

Topic: C.01. Brain Wellness and Aging

Support: NRF Grant 2017M3C7A1029484

Title: Spatiotemporal characteristics of cerebral activity reflecting cognitive function improvement after dopaminergic treatment in restless legs syndrome patients

Authors: *H. KIM[1], K. KIM[2];
[2]Dept. of Biomed. Engin., [1]Yonsei Univ., Wonju, Korea, Republic of

Abstract: Introduction: Restless legs syndrome (RLS) is a neurological condition causing uncomfortable sensations, mainly in the legs, due to dopamine system dysfunction from brain iron deficiency. It causes cognitive impairments like attention and working memory deficits, linked to abnormal prefrontal cortex activity. Dopamine agonist treatment improves both RLS symptoms and cognitive function, but underlying brain activity changes remain uninvestigated. This study aims to reveal cortical activity features reflecting cognitive improvement using event-related potentials during a working memory task, based on machine learning analysis. **Methods**:

We recorded 19-channel EEGs from 9 drug-naive RLS patients and 13 controls during the Sternberg working memory task. Cortical source activities were reconstructed using sLORETA. For each retrieval stimulus in the Sternberg task, activities were averaged in 50 ms windows from 0-800 ms post-stimulus and projected onto 2D Mollweide maps. Input data comprised 120×120×16 3D volumes (2D space×time). A CNN-based classifier was trained to discriminate between RLS patients and controls. For evaluation, the classifier predicted output class (patients or controls) from treated RLS patients' data. Spatiotemporal characteristics of cortical activity in the treated patients were identified using layer-wise relevance propagation (LRP) analysis. A feature visualization method examined feature distributions of treated patients, visualizing 2D feature vectors from the classifier's last fully connected layer. **Results**: The CNN classifier successfully discriminated between RLS patients and controls with 99.62 ± 0.81% test accuracy. It predicted over 70% of single-trial EEG data as 'normal control' for all treated patients except one. LRP analysis showed that left caudal middle and superior frontal cortex activities at 350-400 ms were most important for prediction. Feature distribution for treated patients was closer to that of controls. **Discussion**: The results demonstrate that the cortical activities of treated RLS patients were restored to close to those of normal controls, with prefrontal activity crucial for cognitive improvement. This outcome stems from the CNN classifier's ability to discriminate between RLS patients' and controls' cortical activities. The study suggests a potential link between prefrontal cortex activity changes and cognitive improvement following dopaminergic treatment in RLS patients.

Disclosures: H. Kim: None. **K. Kim:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.009/LBA9

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

Support: NIH/NIGMS R25GM130437
NIA K01 AG066747
NRSA (T32 GM148752)
AARG-21-846012
NIA 3P30 AG013319-25S1

Title: Phenotypic Analysis of PLCG2 Variants Within Novel Late-onset Alzheimer’s Disease Mouse Model

Authors: *J. GARCIA ROGERS[1], S. SMITH[1], S. FERNANDEZ[1], S. G[1], M. N. MITHAIWALA[2], J. P. PALAVICINI[3], S. C. HOPP[4];
[1]Univ. of Texas Hlth. Sci. Ctr. San Antonio, San Antonio, TX; [2]Pharmacol., Univ. of Texas Hlth.

Sci. Center, San Antonio, San Antonio, TX; [3]Univ. of Texas Hlth. Sci. Ctr. At San A, San Antonio, TX; [4]Biggs Inst. for Alzheimer's and Neurodegenerative Dis., UT Hlth. San Antonio, San Antonio, TX

Abstract: Recent studies have linked PLCG2, the gene that codes for phospholipase C γ2 (PLCγ2), to late-onset Alzheimer's Disease (LOAD). PLCG2 polymorphisms were associated with reduced (P522R) and increased (M28L) risk for LOAD. Additionally, the P522R variant has been associated with increased longevity. The aim of our study is to compare difference in behavioral, biochemical, and histological phenotypes between PLCγ2 variants in a novel LOAD mouse model (LOAD2) with humanized Aβ, TREM2*R47H, and ApoE4. Males and female LOAD2 mice expressing wild type (WT), P522R, or M28L PLCγ2 were tested in the Barnes Maze task for spatial memory at 12 months, frailty analysis for aging phenotypes at 15 and 19 months, open field and novel object recognition for anxiety, locomotion, and recognition memory at 18 months, and fear conditioning for associative fear learning and memory at 21 months. Mice were euthanized at 23 months for brain histological and biochemical analyses, including lipidomics. M28L mice made significantly more errors during Barnes Maze training and both M28L and P522R mice had significant deficits compared to LOAD2 mice during the memory-testing probe trial. Frailty testing revealed that in females only, M28L mice had higher Frailty Index scores than WT mice and P522R mice. Open Field and Novel Object Recognition testing showed no deficits in locomotion, anxiety, or recognition memory for any PLCγ2 genotype. When frailty was reassessed, there was an increase in the overall scores of all genotypes , with M28L still displaying the highest scores. There were no differences in associative fear learning or memory in these mice. Brain lipidomic analyses indicated that there are differences in myelin related lipids between PLCγ2 genotypes and sex, with male P522R mice having a greater abundance of N-cerebrosides and N-sulfatides compared to their M28L and WT counterparts. In summary, mice expressing M28L and P522R PLCγ2 displayed minor but statistically significant deficits in learning and memory, sex-specific increases in frailty index scores and myelin associated lipid abundance, suggesting these variants may play a role in altering various phenotypes relevant to aging and LOAD. Future research will examine histological markers for various microglia, myelin, synaptic, and immune-cell markers in these mice, as well as explore sex differences seen in our results.

Disclosures: J. Garcia Rogers: None. **S. Smith:** None. **S. Fernandez:** None. **S. G:** None. **M.N. Mithaiwala:** None. **J.P. Palavicini:** None. **S.C. Hopp:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.010/LBA10

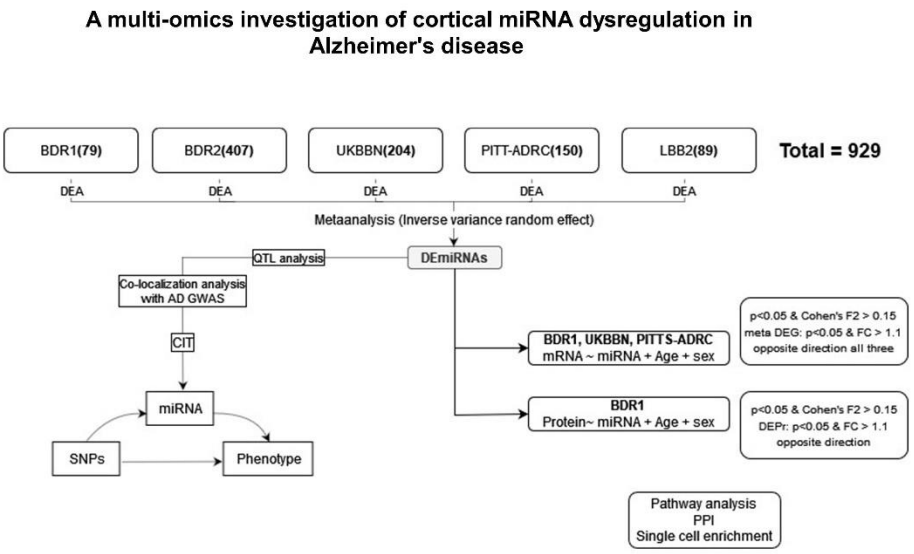
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant: R01AG067015
Alzheimer's Society grant: AS-PG-14-038
Medical Research Council grant: MR/S011625/1
ZonMw Memorabel/Alzheimer Nederland grant: 733050516
Alzheimer's Society grant: AS-PG-16b-012
Alzheimer's Research UK: ARUK-PPG2017B-021

Title: A large-scale meta-analysis of miRNA-sequencing in Alzheimer's disease cortex, with multi-omics integration.

Authors: E. PISHVA[1], ***K. LUNNON**[2];
[1]Maastricht Univ., Maastricht, Netherlands; [2]Univ. of Exeter, Exeter, United Kingdom

Abstract: MicroRNAs (miRNAs) are a species of small non-coding RNAs that regulate gene expression by mediating the degradation or repressing the translation of target messenger RNAs (mRNAs). As a single miRNA can target numerous mRNAs and as a given mRNA could be regulated by several miRNAs, understanding the contribution of miRNAs to dysfunctional gene expression networks in AD is complicated. We have performed a meta-analysis of miRNA expression in association with tau pathology, utilizing small RNA sequencing data we have generated in five independent cortical datasets (N = 929 unique samples), with subsequent integration of matched genetic, transcriptomic and proteomic data to identify miRNA-mediated dysregulated molecular signatures in disease. We have identified 26 Bonferroni significant miRNAs that are differentially expressed with respect to Braak neurofibrillary tangle (NFT) stage (as a quantitative measure of tau pathology), of which 18 showed a significant reverse correlation with their target mRNA, and 12 showed a significant correlation with the protein product of that transcript. Expression weighted cell type enrichment (EWCE) demonstrated that the target genes were enriched in neurons and oligodendrocytes. By overexpressing our most significant miRNA, miR-132-3p, in iPSC neurons, microglia and oligodendrocytes, we observed decreased expression of several mRNA targets we had found in our postmortem analysis. Finally, our miRNA quantitative trait loci (miQTL) analysis showed a significant trans-miQTL for miR-132 and the *APOE* region, which was observed across all four cohorts assessed. This study represents the largest and most comprehensive analysis of miRNAs in AD post-mortem brain tissue. As miRNA-based therapeutics is an emerging area of drug development in other disorders, this is an avenue that could be explored for the treatment of AD.



Disclosures: E. Pishva: None. **K. Lunnon:** None.
Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.100/LBA96

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: EME-REEM Grant COGNIPROG
Fundación Francisco Soria Melguizo Grant Ayudas2021FFSM
Carlos III Health Institute RICORS RD21/0002/0063

Title: Exploring plasma microRNAs as prognostic biomarkers for cognitive impariment and progression in Multiple Sclerosis

Authors: *J. HUERTAS PONS[1,2], A. MIGUELA BENAVIDES[1], C. COLL MARTINEZ[1,2], A. GIFREU FRAIXINÓ[1,3], G. ÁLVAREZ-BRAVO[1,3,4], L. RAMIÓ-TORRENTÀ[1,4,5], A. QUIROGA[1,2];
[1]Neurodegeneration and Neuroinflam. Res. Group, Girona Biomed. Res. Inst. (IDIBGI), Girona, Spain; [2](ricors, rd21/0002/0063), Carlos III Hlth. Inst., Madrid, Spain; [3]Neurol. Dept., Dr. Josep Trueta Univ. Hosp. and Santa Caterina Hospital, Girona Neuroimmunology and Multiple Sclerosis Unit, Griona-Salt, Spain; [4]Med. Sci. Dept., Univ. of Girona, Girona, Spain; [5]Med. Director, Fundació Hosp. d'Olot i Comarcal de la Garrotxa, Olot, Spain

Abstract: Introduction: Multiple sclerosis (MS) is an autoimmune disease that causes demyelination and neuroaxonal damage in the central nervous system, leading to a range of unpredictable and variable symptoms. Cognitive impairment is a significant concern in MS, impacting patients' quality of life. MicroRNAs (miRNAs) are emerging as crucial regulators of gene expression and cellular processes linked to neurodegeneration and cognitive function. As circulating biomarkers, miRNAs have potential for monitoring cognitive changes over time in MS patients. **Objectives:** To investigate changes in miRNA levels over five years in MS patients and evaluate their prognostic potential as biomarkers for cognitive outcomes, particularly in relation to Symbol Digit Modalities Test (SDMT) scores, which most accurately reflect cognitive processing speed and attention, commonly affected in MS. **Methods:** Blood samples from 20 MS patients were collected at diagnosis and after five years, using EDTA polypropylene tubes, centrifuged and stored at -80ºC. Concurrently, SDMT was administered to assess cognitive function. miRNA profiles were analyzed using 384-well Taqman Gene Expression Array Cards targeting 31 unique miRNAs. Statistical analyses included T-tests for comparing miRNA levels over time and partial correlations with SDMT, adjusted for age and Expanded Disability Status Scale (EDSS) scores. **Results:** Only significant increases were observed in the levels of hsa-miR-124-3p, hsa-miR-16-5p, hsa-miR-20a-5p, and hsa-miR-423-3p at the five-year follow-up compared to baseline (p-values: 0.04, 0.01, 0.027, and 0.008, respectively). A significant positive correlation was observed between miR-20a-5p and miR-16-5p levels and baseline SDMT scores ($r = 0.577$, $p = 0.039$; $r = 0.481$, $p = 0.051$ respectively), indicating that higher levels of these miRNAs are associated with better cognitive performance at baseline. Similarly, miR-423-3p levels showed a near-significant positive correlation ($r = 0.442$, $p = 0.076$), indicating a trend towards better cognitive performance with higher miR-423-3p levels. **Conclusions:** Our findings reveal the overexpression of four plasma miRNAs involved in cellular regulation, differentiation, synaptic function, and apoptosis. Notably, hsa-miR-20a-5p and hsa-miR-16-5p are positively correlated with baseline cognitive performance, highlighting their potential as valuable biomarkers for monitoring cognitive progression in MS. Further research is needed to validate these biomarkers and explore their therapeutic potential.

Disclosures: J. Huertas Pons: A. Employment/Salary (full or part-time):; Carlos III Health Institute (RICORS, RD21/0002/0063). C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Novartis, Sandoz. **A. Miguela Benavides:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Novartis, Horizon, Biogen, Sanofi. **C. Coll Martinez:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Bristol-Myers-Squibb, Merck, Sanofi. **A. Gifreu Fraixinó:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); UCB Pharma, Bial Pharmaceutical, Angelini Pharma, Merck, Bristol-Myers-Squibb, Biogen, Janssen. **G. Álvarez-Bravo:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); TEVA, Merck, Sanofi, Biogen, Novartis. **L. Ramió-torrentà:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Biogen, Novartis, TEVA, Merck, Bayer, Genzyme, Roche, Bristol-Myers-Squibb, Almirall, Jansen, Sanofi. **A. Quiroga:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Novartis, Merck, Horizon.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.101/LBA97

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Title: Enhanced vulnerability to trauma induced neurodegeneration in a Drosophila model of human tauopathy

Authors: *K. LOHR;
Washington and Jefferson Col., Washington, PA

Abstract: Deposition of the microtubule-associated protein tau is a hallmark pathology of the family of neurodegenerative diseases known as tauopathies, including Alzheimer's disease, frontotemporal dementia, and chronic traumatic encephalopathy. Ongoing work on mechanisms of tau-mediated neurodegeneration suggest that genetic contributions interact with peripheral or environmental factors to contribute to disease onset and severity. Head trauma is an established modifier of brain health and function in human, rodent, and invertebrate models. Using an established impact injury model known as HIT, we have examined the effect of traumatic injury on behavior and neurodegenerative markers in transgenic Drosophila expressing human tau in neurons. Tau transgenic flies show worsened outcomes compared to their non-transgenic controls as shown by both locomotor activity and tissue histology. To expand upon this work, we are examining other neurodegenerative models in the HIT paradigm as well as other biochemical markers of cell death. These data suggest that tau transgenic flies have an increased vulnerability to traumatic injury in this Drosophila model of human tauopathy.

Disclosures: K. Lohr: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.102/LBA98

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: James Scholar at UICOM-R

Title: Ptau/tau as a biomarker to evaluate the therapeutic effects of drp1 inhibitors for hereditary spastic paraplegias

Authors: *C. SAGARTZ[1], X.-J. LI[2];
[1]Univ. of Illinois Col. of Med., Rockford, IL; [2]Dept. of Biomed. Sci., Univ. of Illinois, Rockford, IL

Abstract: **Background** Hereditary spastic paraplegia (HSP) is a neurodegenerative disease that affects motor neurons, causing patients to develop progressive muscle weakness. SPG11 is the most common autosomal recessive form of HSPs, which is caused by mutations in the *SPG11* gene. This mutation can be studied in the lab using induced pluripotent stem cells (iPSCs), which are reprogrammed from patient fibroblasts by being transfected with pluripotent factors. These stem cells can then be differentiated into cortical neurons, providing an effective tool to investigate biomarkers to screen for SPG11. One potential biomarkers for SPG11 is the pTau or Tau proteins. The pTau levels and the pTau to Tau ratio (pTau:Tau) demonstrated a significant increase when measured in a phenotypic screen in the iPSC derived neurons from patients with other neurodegenerative disease, such as Alzheimer's disease (AD). The pTau:Tau biomarker can be tested furthermore with the introduction of Drp inhibitors like P110, which have demonstrated therapeutic potential in past studies in SPG11. **Hypothesis** The specific aim of this project was to determine whether SPG11 mutation increased the pTau levels and the pTau:Tau ratio in cortical neurons. Another aim of this project was to determine the effect of P110 on pTau and Tau. **Methods** SPG11 and control iPSCs were differentiated into cortical neurons using our established protocol, followed by the collection of lysates from these neurons. Biological triplicate independent samples were studied. The concentrations of pTau and Tau were measured in the samples using the respective ELISA kits and quantified using a standard curve. The statistical significance of mean values of pTau, Tau, and pTau:Tau were analyzed using a one-way ANOVA followed by Dunnett's test. **Results** There were statistically significant increases in both pTau concentrations and pTau:Tau in SPG11 neurons compared to the control neurons ($p<0.05$). The differences in Tau levels between the samples were not statistically significant. Moreover, P110 treatment showed a trend in reducing the pTau expression level in SPG11 neurons. **Conclusions** pTau has been used as a biomarker in neurodegenerative diseases, and the significant increase in pTau and pTau:Tau from our study shows promise for the use of pTau as a biomarker for SPG11. This potential is further supported by the lack of significant alteration in total Tau alone, illustrating that pTau is a more specific change that occurs due to the disease process.In the future, another ELISA kit can be utilized to measure pTau with a different phosphorylation site, and neurofilament, another potential biomarker for SPG11, can be tested in SPG11 neurons.

Disclosures: C. Sagartz: None. **X. Li:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.103/LBA99

Topic: C.06. Neuromuscular Diseases

Support: NIGMS T32 Trainee 1T32GM145470-01
Sami Barmada R01 NS097543
Rackham Conference Travel Grant
Live Like Lou Foundation Conference Travel Grant
Bok Choy Senior Individualized Project Fund for Biochemistry
Diebold Fund
Kalamazoo College Fund for Student Off-Campus Educational Experiences

Title: Connecting RNA Methylation to TDP43 Pathology in ALS/FTD

Authors: *V. SCHMIDT[1,2], C. HSIEH[2,3], E. M. TANK[2], S. J. BARMADA[2];
[1]Dept. of Biol., Kalamazoo Col., Kalamazoo, MI; [2]Dept. of Neurol., [3]Cell. and Mol. Biol. Grad. Program, Univ. of Michigan, Ann Arbor, MI

Abstract: Amyotrophic lateral sclerosis (ALS) is a debilitating disease characterized by the progressive loss of upper and lower motor neurons, leading to muscle atrophy, paralysis, and eventually death. ALS patients often develop cognitive and behavioral changes seen in frontotemporal dementia (FTD), for which, like ALS, there are few effective therapies. The dysregulation of TDP43, an essential RNA-binding protein crucial for RNA processing, is a key pathological feature of both conditions. We previously reported pervasive RNA destabilization in ALS/FTD patient-derived induced pluripotent stem cells (iPSCs) and control iPSCs in which TDP43 was overexpressed. We also detected methylation at the nitrogen-6 position of adenosine (m6A) — a co-transcriptional modification linked with RNA decay — in >95% of TDP43 target transcripts. Several of these substrates were hypermethylated in ALS patient spinal cord, implying m6A-mediated degradation of TDP43 substrates. Even so, the connection between RNA methylation, RNA destabilization, and TDP43 mislocalization remain poorly understood. TDP43 localization is strongly influenced by RNA binding, undergoing cytoplasmic redistribution in the presence of high affinity, GU-rich mRNAs. Our preliminary data show a similar phenomenon with addition of m6A-modified, but not unmodified mRNA, suggesting a key role for methylation in TDP43 binding and function. Furthermore, we find that m6A-RNA colocalizes with cytoplasmic TDP43 aggregates in ALS spinal motor neurons. Based on these collective findings, we hypothesize that disease-associated hypermethylation contributes to the mislocalization and dysregulation of TDP43. To test this hypothesis, we are evaluating the impact of RNA methylation on TDP43 mislocalization using inhibitors of m6A methyltransferases (“writers”) and demethylases (“erasers”) in human iPSC-derived motor neurons. Additionally, we are investigating the influence of m6A on TDP43-mediated RNA splicing and stabilization. We and others identified m6A sites within *TARDBP* (the transcript encoding TDP43) in a region important for autoregulation, a process by which TDP43 binds and regulates its own expression. Our preliminary findings suggest that bidirectional deviation from physiological m6A levels disrupts TDP43 autoregulation. Ultimately, these studies may uncover

novel mechanisms of neurodegeneration in ALS/FTD and provide new therapeutic directions to recover RNA homeostasis in these disorders.

Disclosures: V. Schmidt: None. **C. Hsieh:** None. **E.M. Tank:** None. **S.J. Barmada:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.104/LBA100

Topic: C.06. Neuromuscular Diseases

Support: RF1NS127407
Cullen Young Investigator Award
Mussallem Transformative Scholars Award

Title: AP2A1 downregulation causes TDP-43 misregulation and neurodegeneration

Authors: *A. HELD[1], P. SENARATNE[2], S. POWLEY[1], C. LAGIER-TOURENNE[1], B. WAINGER[2];
[2]Neurol., [1]Massachusetts Gen. Hosp., Charlestown, MA

Abstract: TDP-43 aggregates are a hallmark of almost all amyotrophic lateral sclerosis (ALS) cases and half of Alzheimer's disease (AD) cases, but the mechanisms underlying their formation and contribution to neurodegeneration remain unclear. We have found that *AP2A1* is downregulated in ALS and AD postmortem tissue, and that its downregulation causes TDP-43 cytoplasmic localization, insoluble cleaved TDP-43, and neuronal death. AP2A1 is a subunit of the AP2 complex, and knocking down other AP2 complex members yields similar phenotypes, suggesting that AP2 complex function is necessary to prevent TDP-43 accumulation. Furthermore, downregulating AP2 components also increases neurodegeneration caused by Aβ42 and Tau, suggesting that AP2 function may be more generally implicated in clearing toxic proteins. The primary function of the AP2 complex is clathrin-mediated endocytosis, but it also interacts with the autophagy protein LC3. Knocking down LC3, but not clathrin, enhances neurodegeneration caused by TDP-43, suggesting that AP2 may regulate TDP-43 through LC3. We then performed a screen of endocytosis and autophagy genes related to TDP-43 and found that several genes that mediate LC3 processing also enhance neurodegeneration caused by TDP-43. Finally, we also identified three genes related to autophagy and endocytosis that alleviate neurodegeneration caused by TDP-43.

Disclosures: A. Held: None. **P. Senaratne:** None. **S. Powley:** None. **C. Lagier-Tourenne:** None. **B. Wainger:** F. Consulting Fees (e.g., advisory boards); Quralis.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.105/LBA101

Topic: C.06. Neuromuscular Diseases

Support: NIA, 5T32AG000255
American Epilepsy Society 2023 - 2024 seed grant
NIA, 1R01AG075276

Title: DREADDs modulation of TDP-43 pathology formation after hippocampal FTLD-TDP extract injection in CamKIIa-NLS4 mice

Authors: *E. JIA, W. RODEMER, K. HOXHA, T. BAFFIC, I. RA, J. GUJRAL, S. PORTA, V. M. LEE;
Dept Pathol & Lab. Med., Univ. Pennsylvania Sch. Med., Philadelphia, PA

Abstract: Neuronal hyperexcitability is a hallmark of amyotrophic lateral sclerosis (ALS) yet its relationship to the TDP-43 inclusions that comprise the predominant pathology in over 90% of ALS cases remains unclear. Emerging evidence in cell and animal models suggest that TDP-43 pathology induces neuronal hyperexcitability. As neuronal activity has been shown to promote intercellular alpha-synuclein and tau transmission, we hypothesized that activity may likewise promote TDP-43 pathology propagation. To test this hypothesis we performed unilateral hippocampus co-injection (2.5µL total volume) of human-derived FTLD-TDP extract (1.1ng TDP-43) and AAV (1.15×10^{10} vg) encoding either the excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs, hM3Dq-mCherry) or AAV-mCherry control in CamKIIa-NLS4 mice (2.5µL total injection volume; n = 8 mice per group, approximately equal numbers males and females). All mice received Clozapine N-oxide (CNO) eyedrops (1mg/kg) thrice weekly for 3 months post-injection (mpi). Behavior (Y maze, elevated zero maze, and accl. rotarod) was assessed at 1 and 3 mpi. Histological examination was performed at 3 mpi. No difference in behavioral phenotype was observed at either timepoint between DREADDs and mCherry cohorts. At 3 mpi, *de novo* p409/410 TDP-43 pathology was clearly observed in the hippocampus and cortex of injected mice. As expected, histological analysis revealed much greater pathology formation in the hippocampus ipsilateral to the injection site relative to the contralateral side (~5-fold difference, $p<0.001$). Surprisingly, within the ipsilateral hippocampus, we observed a modest reduction in TDP-43 pathology in the DREADDs injected mice relative to mCherry controls ($p<0.05$). No differences were observed on the contralateral side. While we did not observe an increase in TDP-43 pathology with DREADDs modulation of neuronal activity, it is possible that the DREADDs co-injection and their repeated activation may have exacerbated cell loss. Future studies will employ orthogonal approaches, such as optogenetics, to address these limitations.

Disclosures: E. Jia: None. **W. Rodemer:** None. **K. Hoxha:** None. **T. Baffic:** None. **I. Ra:** None. **J. Gujral:** None. **S. Porta:** None. **V.M. Lee:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.106/LBA102

Topic: C.06. Neuromuscular Diseases

Title: Artificial Intelligence Powered Approach to Enhance the Development of Splice Switching Oligonucleotides Targeting Novel Alternative Splicing Isoforms for the Treatment of Amyotrophic Lateral Sclerosis

Authors: *B. J. JURGIELEWICZ, B. DA SILVA, T. LANTIN, R. LUTHER, A. D. FRONK, S. STANTON, K. ANDERSON, M. ACKERMAN, G. ARUN;
Envisagenics, Long Island City, NY

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a late onset, highly progressive, and ultimately fatal neurodegenerative disease. Therapeutic options and novel target identification remain limited as the majority of ALS cases are sporadic (sALS), having no clear etiology. Thus, there is an urgent need for the identification of novel targets and subsequent development of therapeutics. Alternative Splicing (AS) is a pervasive phenomenon in ALS. At least 8 out of the 10 top causative mutations in neurodegenerative diseases are in genes encoding RNA Binding Proteins (RBPs) that regulate AS, which are highly dysregulated in ALS and may give rise to toxic RNA isoforms. We have developed a suite of AI/ML-based algorithms to uncover these targets, ascertain functionality, druggability, and identify efficient therapeutic splice switching oligonucleotides (SSOs) to correct the observed potentially pathogenic splicing changes. Using this approach, we identified 15 novel alternative splicing RNA isoforms that are enriched in a significant portion of sALS patients using ALS patients and healthy tissue RNA-seq data. These AS events were validated in vitro, using human ALS patient derived induced pluripotent stem cells (iPSCs) differentiated into mature motor neurons from both sporadic and familial etiologies. Using our AI/ML algorithm, SpliceLearn, we have also identified high efficiency SSOs that can perform splicing switching activity of our top 2 AS-derived targets that are prevalent in minimum 10% of sALS patients. In preliminary functional assays, the SSOs targeting the AS events have shown to mitigate TDP43 mis-localization and decrease DNA damage in sALS and fALS motor neuron cell lines, suggesting a functional association of the identified novel targets in the pathophysiology of ALS.
To summarize, our computational and experimental approach supports novel AS-derived target discovery and therapeutic development, combining sophisticated RNA analytics on patient RNA-seq data with extensive experimental validation methods, enabling the development of

potential therapeutics for both sporadic and familial ALS patients who are in critical need of effective treatments.

Disclosures: B.J. Jurgielewicz: A. Employment/Salary (full or part-time):; Envisagenics. **B. da Silva:** A. Employment/Salary (full or part-time):; Envisagenics. **T. Lantin:** A. Employment/Salary (full or part-time):; Envisagenics. **R. Luther:** A. Employment/Salary (full or part-time):; Envisagenics. **A.D. Fronk:** A. Employment/Salary (full or part-time):; Envisagenics. **S. Stanton:** A. Employment/Salary (full or part-time):; Envisagenics. **K. Anderson:** A. Employment/Salary (full or part-time):; Envisagenics. **M. Ackerman:** A. Employment/Salary (full or part-time):; Envisagenics. **G. Arun:** A. Employment/Salary (full or part-time):; Envisagenics.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.107/LBA103

Topic: C.06. Neuromuscular Diseases

Support: FAPESP # 2018/05006-0
CNPq # 303050/2021-7

Title: Anti-inflammatory and neuroprotective effects of TNF-alpha inactivation in spinal motor neurons of Duchenne muscular dystrophy (DMD) mice

Authors: A. OLLER BONANI, V. L. MATHEUS, A. MIDORI ROSSI TOMIYAMA, *A. OLIVEIRA;
Univ. of Campinas - Lab. of Nerve Regeneration, Campinas, Brazil

Abstract: Duchenne muscular dystrophy (DMD) is a severe neuromuscular disease caused by the absence of functional dystrophin protein, resulting in muscle degeneration, inflammation, and retrograde changes in the central nervous system (CNS). Inflammation in DMD results in increased glial activation and production of tumor necrosis factor-alpha (TNF-α), an inflammatory molecule that contributes to the degradation of dystrophic myofibers. Therefore, we investigated the anti-inflammatory and neuroprotective effects of the drug etanercept (a chimeric protein blocking the TNF-α receptor) in the spinal cord microenvironment of MDX mice. For this purpose, adult male isogenic MDX mice (n=5/group) and C57BL/10Unib control mice (n=5/group) were divided into 4 groups; G1 received vehicle, while the other groups received etanercept at doses of 3 (G2), 6 (G3), and 12 mg/kg (G4), administered every 72 h (i.p.). Daily walking track test (CatWalk system) and muscle strength measurement by grip strength test were performed. At the end of the second week of treatment, after euthanasia, lumbar spinal cord and tibialis anterior and soleus muscles were harvested for flow cytometry

analysis, immunofluorescence (synaptophysin, GAD65, VGLUT1, IBA-1, GFAP) and H&E staining. The procedures were approved by the Institutional Animal Ethics Committee (CEUA/IB/UNICAMP/Brazil, protocol number 6340-1/2023). Results showed that Etanercept at 12mg/kg was able to attenuate astrogliosis by 30% (vehicle vs. Etanercept -12mg; $p<0.0001$) and microglial activation by 50% (vehicle vs. Etanercept -12mg; $p<0.0001$) in MDX animals compared to vehicle MDX. In addition, etanercept effectively upregulated the expression of synaptophysin (vehicle MDX vs. 6mg/kg MDX - 80% increase; vehicle MDX vs. 12mg MDX - 80% increase; $p<0.0001$), GAD65 (vehicle MDX vs. 6mg MDX - 40% increase; $p<0.01$; vehicle MDX vs. 12mg MDX - 40% increase; $p<0.001$) and VGLUT-1 was downregulated in MDX (vehicle BL10 vs. vehicle MDX - 35% decrease; $p<0.01$) and increased with treatment (vehicle BL10 vs. 12mg MDX - 25% decrease; $p<0.05$). The downregulation of pro-inflammatory cytokines such as TNF-α reached 30% when comparing vehicle MDX to MDX treated with etanercept (12mg/Kg; $p<0.05$). Similar results were obtained for Th1 polarization (vehicle MDX vs. 12 mg MDX - 30% decrease; $p<0.05$). These regulatory effects were reflected in functional outcomes with gains in muscle strength and improvement in the Sciatic Functional Index ($p<0.05$). Overall, etanercept therapy showed excellent anti-inflammatory and synaptic effects in the spinal cord of MDX mice, suggesting that it may be an effective clinical intervention for DMD.

Disclosures: A. Oller Bonani: None. **V.L. Matheus:** None. **A. Midori Rossi Tomiyama:** None. **A. Oliveira:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.108/LBA104

Topic: C.06. Neuromuscular Diseases

Title: Emerging mechanisms and therapies in Charcot - Marie Tooth Disease : A Meta Analysis.

Authors: *S. FEROZ;
Aga kha university and hospital, Karachi, Pakistan

Abstract: Background: Charcot-Marie-Tooth (CMT) disease is an inherited neuropathy that causes progressive motor and sensory deficits in individuals. Molecular mechanisms interventions ruling out the major cause of CMT remains unknown. Our meta-analysis aims to evaluate recent studies of mitochondrial dysfunction, non-coding RNAs and genetic defects in CMT.**Methods:** For Meta analysis, literature resources used were Embase, PubMed and Cochrane Library between 2011 till June 2024. Our inclusion criteria included reviews, original research articles and clinical trials on genetic analysis, mitochondrial dysfunction, and Non-coding RNA (lncRNA and miRNA) replacement and effect.**Results:** In the 55 studies reviewed,

findings suggest Mitochondrial dysfunction in CMT patients with AR-CMT2 and CMT4A are dominant and are also the recessive form of CMT2K. Also in CMT patients,MFN2 catalytic activity gets impaired due to mitochondrial fusion and diminished neuronal transport, seen mostly in Charcot-Marie-Tooth type 2A. Overall motility of the MFN2 protein can be one of the culprits in CMT disease. Genetic analysis depicted, manipulating genes such as GDAP1or silencing genes like CMT1A and PMP22 and co expressing genes such as GJB1 in the CMT1A gene, and modulation of HDAC or UPR enzymes could create progressive differentiation for CMT models. In Japan researchers identified novel causative genes for CMT namely, MME and COA7. In non-coding RNAs (lncRNA and miRNA), studies detected lncRNA CR18854 and lncRNA CR43467 effectively interact with dFIG4 gene and reduce length of synaptic branches and the ratio of boutons at neuromuscular junctions. Studies also inferred lncRNA CR43467 to be the genetic network that works together with CMT causing genes. These non-coding RNA hold the potential to interrelate and create a cure CMT disease as therapeutic targets or biomarkers.**Conclusion:** The meta-analysis gives us insight into the major causes of Charcot-Marie-Tooth disease, where emphasis can be on mitochondrial dysfunction, genetic mutations and non-coding RNAs. Mitochondrial dysfunction is predominant in CMT4, CMT2K and AR-CMT2A with a defect in the MFN2 protein, suggesting that therapies targeting mitochondrial aberrations could be valuable. Genetic manipulation like controlling GDAP1, silencing PMP22, CMT1, MME, COA7 and co expression of GJB1 can help identify solutions for developing gene-based therapies. Interaction of lncRNA CR18854 and CR 43467 with dFIG4 gene could create novel biomarkers. Collectively new therapeutic avenues, that include iPSC models and gene therapy can be essential for creating novel and effective treatments for patients with CMT.

Disclosures: S. Feroz: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.109/LBA105

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Neuroprotective effect of Gymnemic acid in SH-SY5Y cells

Authors: *S. KAPSE[1], M. M. MIGLIORE[2];
[1]Sch. of Pharm., MCPHS Univ., Boston, MA; [2]Sch. of Pharm., MCPHS Univ., Malden, MA

Abstract: Impairment of glucose metabolism and elevated reactive oxygen species (ROS) are closely associated with neurodegeneration. In-vitro models of neurodegeneration were generated using streptozotocin (STZ) and 6-hydroxydopamine (6-OHDA) in SH-SY5Y cells. STZ enters cells via the glucose transporter 2 (GLUT2), causing DNA alkylation, while 6-OHDA) inhibits mitochondrial complex I and IV depleting ATP stores of the cell, and increasing ROS

production. These toxins lead to cell death in dose dependent manner. The STZ-induced glucose metabolism impairment model in SH-SY5Y cells provides a valuable link between neurodegeneration and altered glucose levels as seen in Type 2 diabetes. Gymnemic acid (GA1), a triterpenoid derived from the herb Gymnema sylvestre, is widely used in Eastern medicine for its anti-diabetic properties, though its precise mechanism of action remains unclear. We hypothesize that GA1 will protect neuronal cells from the cellular damage caused by 6-OHDA and STZ by maintaining their metabolic activity, altering glucose utilization, and reducing oxidative stress. Our data demonstrates that GA1 increases cell viability by over 20% following STZ or 6-OHDA exposure. Through a combination of ATP quantification and protein carbonyl measurement, we established that GA1 treatment for 24 and 48 hours confers neuroproective potential after STZ and 6-OHDA insult. ATP levels in the 6-OHDA model increased from 25nM to 350nM post GA1 treatment, indicating that the cells were more metabolically active. To elucidate the signaling mechanisms underlying GA1's protective effect, we assessed the levels of AKT/pAKT and PI3K/pPI3K proteins in these cells. Alterations in AKT and PI3K levels suggest that GA1 influences cell survival and growth pathways in neuronal cells. Our preliminary findings indicate that GA1exerts neuroprotective effects by reducing oxidative stress and maintaining metabolic activity. GA1 appears to modulate cellular growth and proliferation pathways, enhancing cell survival under conditions of elevated oxidative stress and impaired glucose metabolism.

Disclosures: S. Kapse: None. **M.M. Migliore:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.011/LBA11

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

Support: R01AG074082
R01AG079223
P30AG10161
P30AG72975
R01AG015819
R01AG017917
U01AG61356

Title: Transcriptomics of post-mortem choroid plexus reveals dysfunction in Alzheimer’s disease

Authors: *T. PHILIPPE[1], N. KEARNS[1], D. SAUNDERS[1], D. AVEY[2], S. DE TISSERA[1], H. VYAS[1], D. A. BENNETT[3], Y. WANG[4];

[1]Rush Univ., Chicago, IL; [3]Rush Alzheimer's Dis. Ctr., [4]RADC, [2]Rush Univ. Med. Ctr., Chicago, IL

Abstract: Background: The choroid plexus (ChP) is a physical and immunological barrier that protects the brain and maintains homeostasis. Imaging, biomarker, and animal studies highlight the importance of this structure in Alzheimer's Disease (AD) development and pathogenesis. Understanding ChP molecular dysfunction during AD progression will indicate novel avenues for therapeutic intervention. Recent single-cell RNA sequencing studies have begun to reveal the transcriptional diversity of ChP cells in mouse brains. However, to date there is no comprehensive study that charts the molecular properties of cell types within human ChP and their changes during AD progression. **Method:** We performed single-nuclei RNA-sequencing (snRNA-Seq) on ChP from 81 ROSMAP participants with no cognitive impairment (NCI), mild cognitive impairment (MCI), or Alzheimer's Dementia (AD(d)). To examine protein expression changes, we also conducted proteomics on a subset of postmortem CSF and ChP tissue samples. **Result:** We identified 15 major cell types from over a million ChP nuclei, including four types of epithelial cells, four types of fibroblasts, four types of border-associated macrophages (BAMs), one type of T cells, and two types of vascular cells. We mapped the spatial distribution of specific cell types using the CosMx Spatial Molecular Imager and RNAscope. In the Ad(d) but not the MCI group, we observed proportionally elevated BAM_2 cells expressing higher levels of stress response genes. CellChat analysis inferred stronger interactions between BAMs and other cell types via the CD45, SPP1, and VISFATIN pathways in AD(d). Differential gene expression (DEG) analysis of epithelial subtypes revealed decreased expression of genes essential for cilia formation and movement in participants with AD(d) but not MCI. In fibroblasts and epithelial cells, we observed changes in genes and genetic pathways related to cell adhesion, ion transport, cell metabolism, and pro-inflammatory response in AD(d) and MCI. Postmortem CSF and ChP tissue protein changes corroborate DEGs, indicating multifaceted disease ChP pathophysiology in AD. **Conclusion:** We provide a comprehensive spatial single-cell transcriptomic atlas of the human ChP and chart the differentially expressed genes, pathways, and intercellular communications related to cognitive impairment. Our results indicate a spectrum of cellular and molecular dysfunctions in ChP during AD development, with cilia dysfunction and BAM_2 abundance correlated with the severity of cognitive impairment.

Disclosures: T. Philippe: None. **N. Kearns:** None. **D. Saunders:** None. **D. Avey:** None. **S. De Tissera:** None. **H. Vyas:** None. **D.A. Bennett:** None. **Y. Wang:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.110/Web Only

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACYT grant A1-S-21433 to PDM

Title: Effect of quinolinic acid administration on autophagy, apoptosis and necroptosis pathways.

Authors: *A. D. ENCISO-OCEGUERA[1], P. MALDONADO[2], J. PEDRAZA CHAVERRI[3], C. A. SILVA-ISLAS[4];
[1]Inst. Nacional de Neurología y Neurocirugía, Mexico City, Mexico; [2]Pharmacol., Univ. Nacional Autónoma de México, Mexico City, Mexico; [3]Facultad de Química, Univ. Nacional Autónoma de México, Universidad Nacional Autonoma de México, Mexico; [4]Patología Vascular Cerebral, Inst. Nacional De Neurología Y Neurocirugía, Ciudad De México, Mexico

Abstract: Neurodegenerative diseases are characterized by the progressive loss of the neuronal population in specific regions of the brain due to different factors such as toxic metabolic disorders. In these diseases there are different biochemical mechanisms that play an important role in cellular and tissue damage, among which excitotoxicity is an important event in cell damage. Excitotoxicity is a mechanism of neuronal death caused by the overactivation of glutamate amino acid receptors, particularly those of the N-methyl-D-Aspartate (NMDA) subtype, causing the massive entry of Ca^{2+} through the plasma membrane, generating the deregulation of important pathways in the maintenance of cellular homeostasis such as autophagy. Autophagy is a degradative pathway that maintains cellular homeostasis through the degradation and recycling of cellular components. It has been observed that the administration of quinolinic acid (QUIN), an excitotoxic molecule, increases activation of autophagy and at the same time blocks the flow of autophagy (last stage of this pathway), in addition to the activation of different types of regulated cell death mechanisms such as apoptosis and necroptosis. In the present work we evaluated, under an excitotoxic model of quinolinic acid, the different cell death pathways: autophagy, apoptosis and necroptosis. Male Wistar rats (260-300 g) were administered 1 μL of isotonic saline solution or 1 μL of QUIN equivalent to 120 and 240 nmol in the right striatum, then the cortex tissue was extracted 48 hours after QUIN administration. Finally, the proteins of apoptosis caspase-3 and Bax; autophagy p62 and cathepsin D; and necroptosis MLKL and RIP1 were quantified by Western Blot. The results show that after 48 hours of QUIN administration, the levels of caspase-3 and Bax in cortex tend to increase with 240 nmol, however this increase is not statistically significant. On the other hand, Cathepsin D and p62 show a decrease in its levels following both doses of QUIN administration. Additionally, in the necroptosis pathway, we only observed an increase in RIP1 with 120 nmol of QUIN. In conclusion these results suggest that striatal QUIN administration promotes alteration in autophagy pathway in the cortex at 48 h.

Disclosures: A.D. Enciso-Oceguera: None. **P. Maldonado:** None. **J. Pedraza Chaverri:** None. **C.A. Silva-Islas:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.111/LBA106

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: AHA predoctoral fellowship 24PRE1188417

Title: Mitochondrial NMNAT3 is essential in the absence of cytosolic NAD+ synthesis by NMNAT2

Authors: *L. BARBAR[1], A. STRICKLAND[2], J. BLOOM[2], Y. SASAKI[5], J. D. MILBRANDT[3], A. DIANTONIO[4];
[1]Washington Univ. Sch. of Med., St Louis, MO; [3]Dept. of Genet., [4]Dept Developmental Biol., [2]Washington Univ. Sch. of Med., St. Louis, MO; [5]Genet., Washington Univ. St. Louis, Saint Louis, MO

Abstract: Loss of nicotinamide adenine dinucleotide (NAD+) is a hallmark of axon degeneration and neurodegenerative disease. NAD+ is an essential metabolite, necessary for fundamental cellular functions including ATP synthesis. NAD+ pools are compartmentalized into the nucleus, cytosol, and mitochondria, with different roles in each compartment. Loss of cytosolic NMNAT2, the major NAD+-synthesizing enzyme in axons, leads to the activation of SARM1, an NAD+-cleaving enzyme, which results in catastrophic NAD+ depletion and axon loss. Knockout of *Nmnat2* in mice shows widespread axonopathy and perinatal lethality. In the absence of SARM1, mice lacking NMNAT2 live a normal lifespan with no overt phenotype, indicating that cellular and metabolic processes are maintained despite the lack of cytosolic NAD+ synthesis by NMNAT2. Given the central role of NAD+ in cellular and metabolic processes, this suggests that other subcellular compartments contribute to the cytosolic NAD+ pool. Mitochondria hold the largest NAD+ pool in neurons. While NAD+ transporters facilitating mitochondrial import in mammalian cells were recently identified, the possibility of mitochondrial NAD+ export to the cytoplasm remains unexplored. We find that partial loss of mitochondrial NAD+-synthesizing NMNAT3, in Nmnat2:Sarm1 double knockout mice, leads to nerve conduction deficits and paralysis, suggesting the presence of a mechanism for mitochondrial NAD+ export to the cytosol. We are currently investigating NAD+ exchange between mitochondria and cytosol as a candidate mechanism for axon resilience.

Disclosures: L. Barbar: None. **A. Strickland:** None. **J. Bloom:** None. **Y. Sasaki:** None. **J.D. Milbrandt:** None. **A. DiAntonio:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.112/LBA107

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Fundação Carlos Chagas Filho de Amparo a Pesquisa do Estado do Rio de Janeiro (FAPERJ)
Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNpq)
Instituto Nacional de Neurociencia Translacional (INNT)
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)

Title: Trophic activity of leukotrienes on mouse dorsal root ganglia and regenerating peripheral nerve

Authors: *C. SPINELI-CARVALHO[1], M. S. CHICHIERCHIO[2], V. RIBEIRO-RESENDE[3]; [1]Carlos Chagas Filho Inst. of Biophysics, Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [2]Univ. Federal Do Rio De Janeiro, Rio DE Janeiro, Brazil; [3]Inst. de Biofísica Carlos Chagas Filho, Univ. Federal do Rio do Janeiro, Rio de Janeiro, Brazil

Abstract: Leukotrienes (LTs) are lipid mediators of the inflammatory eicosanoid family, synthesized from the metabolism of arachidonic acid by the enzyme 5-lipoxygenase (5-LO). LTs are divided into two groups: cysteinyl-LTs (LTC_4, LTD_4 and LTE_4) and (LTB_4), which have different biological effects when they activate their receptors (CysLTs and BLTs). 5-LO and other enzymes responsible for LT synthesis as well as its receptors are expressed in various cell types of the central nervous system. It is known that 5-LO interferes with neuritogenesis and that LTs may be released during development and regeneration of the peripheral nervous system. Therefore, we evaluated basic functional and morphological parameters in the dorsal root ganglion (neuritogenesis and cell migration *in vitro*) and sciatic nerve (thickness, cell and axonal density, macrophage and neutrophil labelling, and vascularization *in vivo*) in adult 129svev mice. We also assessed the regenerative capacity of the peripheral nerve after crush-induced injury. Treatment with LTs resulted in different effects: in which LTB_4 increased the area and density of migrating cells, while LTD_4 treatment only increased the density of neurites in culture. Ganglia treatment with zileuton, a 5-LO pharmacological inhibitor, did not affect the parameters studied, but treatment potentiated with NGF-induced neuritogenesis. In $5\text{-}LO^{-/-}$ mice with sciatic nerve injury, increased thickness and cell density were observed, although there was no significant difference in axons compared to the control group, suggesting no possible regenerative properties. Taken together, our data suggest that 5-LO activity is important for both development and neurite outgrowth in culture. These data suggest an intrinsic relationship between the products of the enzyme and the biology of peripheral neural tissue.

Disclosures: C. Spineli-Carvalho: None. **M.S. Chichierchio:** None. **V. Ribeiro-Resende:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.113/LBA108

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: UNE Office of Sponsored Research, School of Molecular and Physical Sciences, College of Arts and Sciences,
UNE Minigrant to DJS and DJM
Kahn Family Foundation Undergraduate Summer Research Scholarship to MED

Title: Genetic Loss of Fibroblast Growth Factor 1a Increases susceptibility of Embryonic Zebrafish to the Detrimental Effects of the Dopaminergic Neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

Authors: M. E. DOW[1], *D. J. MOKLER[2], D. SMALL[3];
[1]Sch. of Biol. Sci., [2]Biomed. Sci., [3]Sch. of Mol. and Physical Sci., Univ. of New England, Biddeford, ME

Abstract: Fibroblast Growth Factor 1 (FGF1) is a neurotrophic cytokine expressed in embryonic and adult vertebrate central nervous systems. Interactions between FGF1 ligands and FGF receptor tyrosine kinases (FGFRs) regulate neural progenitor cell proliferation and differentiation. FGF1 is also induced in neurons and other CNS cell populations after exposure to oxidative stress-inducing neurotoxic chemicals. FGF1's neuroprotective activity includes activation of the transcription factor Nrf2 and the subsequent transcriptional increase in antioxidant gene expression. However, the effects of decreased endogenous fgf1 expression on neuron survival/function including thosethat produce dopamine after neurotoxin challenge are not reported. In this study, control (dateGFP) and loss-of-function fgf1a (dat-eGFP fgf1a) zebrafish (Danio rerio) strains expressing a green fluorescent protein marker in dopaminergic neurons were used to test the hypothesis that FGF1 is required to protect dopaminergic (DA) neurons from dysfunction and death caused byneurotoxic chemical exposure. Zebrafish are a well-recognized toxicological vertebrate model for examining chemical effects on neuron development, regeneration, and survival. Unlike mammals, zebrafish express two similar, but structurally distinct fgf1 genes (fgf1a and fgf1b). Physiological, behavioral, and biochemical/molecular analyses were conducted on embryonic control and fgf1a-deficient zebrafish exposed from three days post fertilization (3dpf) for 12 to 72 hours to the DA neuron poison 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Survival of dat-eGFP fgf1a mu mu embryos was significantly reduced at 50 uM and higher doses of MPTP after48 hours compared to dat-eGFP larvae (n = 50 each cohort). Expression of nrf2 in fgf1a-deficient strains was less than 50% of control at 100 uM MPTP (n=3 RNA samples) as determined by Quantitative Reverse Transcriptase Polymerase Chain Reaction (RT-qPCR). Double-blinded immunofluorescence studies revealed a reduction in DA number and morphology (n=6 eachcohort) in dat-eGFP fgf1a animals that corelated with a 50% reduction in dopamine levels. Finally, distinct behavioral responses between dat-eGFP control and dat-eGFP fgf1a mu mu at 50 uM and lower MPTP doses indicated changes in neurological function that were sensitive to fgf1a expression. Collectively, these data suggest that loss of fgf1a increases the sensitivity of zebrafish embryos to detrimental effects of ROS-producing chemicals. These data may provide

insight into gene-environment interactions underlying the pathology of neurodegenerative diseases of aging.

Disclosures: M.E. Dow: None. **D.J. Mokler:** None. **D. Small:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.114/LBA109

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Synaptic and cellular mechanisms involved in the anti epileptic effect of GAO-3-02

Authors: *A. BELMEGUENAI[1,2], L. BEZIN[3,2], J. BODENNEC[3,2], V. MUTEL[2], S. BODENNEC[2];
[1]Lyon Neurosci. Res. Ctr., Univ. Claude Bernard Lyon 1, Bron, France; [2]GAOMA Therapeut., Bron, France; [3]Lyon Neurosci. Res. Ctr., Univ. Claude Bernard Lyon 1, Bron, France

Abstract: We recently reported that GAO-3-02 displayed robust anti-seizure effects across validated seizure and epilepsy models. We have also demonstrated that GAO-3-02 exerts potent anti-neuroinflammatory effects in different in vitro and in vivo models of neuroinflammation. We therefore tested the effect of GAO-3-02 on neuronal excitability in an in vitro model of febrile infection-related epilepsy syndrome (FIRES), a protracted and difficult-to-treat neuroinflammatory condition. We next investigated the potential synaptic and cellular mechanism underlying the antiepileptic activity of GAO-3-02 by characterizing the effects of GAO-3-02 on GABAA-mediated currents in acutely-obtained hippocampal slices from rat lithium-pilocarpine (Pilo) model and slices from lipopolysaccharide (LPS)-treated and non-treated healthy rats. We further examined the possible roles of the cannabinoid receptor 2 (CB2) in the effects produced by GAO-3-02 using pharmacological approaches. Using in vitro model of FIRES, we found that treatment of LPS-exposed slices with GAO-3-02 strongly reduced the excitability in hippocampal CA1 pyramidal cells evoked by neuroinflammation and 0 Mg^{2+}/4-AP. Interestingly, while the bath application of GAO-3-02, significantly increased GABAergic transmission in Pilo and LPS-exposed slices either at room temperature (23-25°C) or at 35°C, it was virtually ineffective in healthy slices. This effect was blocked by a CB2 receptor antagonist (SR144528). Further results demonstrated that bath-application of GAO-3-02 does not change the paired-pulse ratio (PPR) of evoked inhibitory postsynaptic currents (eIPSCs) and increases the amplitude of miniature IPSC (mIPSC) without affecting frequency indicating a postsynaptic mechanism of action in Pilo slices.The present study suggests that GAO-3-02 reduces CA1 pyramidal neuron excitability in an in vitro model of FIRES and enhances GABAergic transmission in Pilo and LPS-exposed slices by activating the postsynaptic CB2 receptor. These data provide new insights into the mechanism of GAO-3-02 in the treatment of

neuroinflammation-related diseases. Therefore, GAO-3-02 may be a potential therapeutic option for FIRES.

Disclosures: A. Belmeguenai: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GAOMA Therapeutics. F. Consulting Fees (e.g., advisory boards); GAOMA Therapeutics. **L. Bezin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GAOMA Therapeutics. F. Consulting Fees (e.g., advisory boards); GAOMA Therapeutics. **J. Bodennec:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GAOMA Therapeutics. F. Consulting Fees (e.g., advisory boards); GAOMA Therapeutics. **V. Mutel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GAOMA Therapeutics. F. Consulting Fees (e.g., advisory boards); GAOMA Therapeutics. **S. Bodennec:** A. Employment/Salary (full or part-time):; GAOMA Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GAOMA Therapeutics.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.115/LBA110

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant #1R15DA045564-01
NIH Grant #5R25MH080661-13/2004445114

Title: Human breast milk-derived exosomes attenuate lipopolysaccharide-induced upregulation of CD40 and NLRP3 in microglia

Authors: *O. AKINDURO[1,2], S. KUMAR[2], Y. CHEN[3], J. OATES[2], B. THOMAS[2], Q. HASSAN[3], B. SIMS[2];
[1]Biol., UAB Neurosci. Grad. Programs, Birmingham, AL; [2]Dept. of Pediatrics/Division of Neonatology, [3]Dept. of Oral and Maxillofacial Surgery, Sch. of Dent., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Microglia mediate the immune response in the central nervous system against insults, including lipopolysaccharide (LPS), a bacterial endotoxin that initiates neuroinflammation in the neonatal population, especially preterm infants. The synthesis of the proinflammatory proteins cluster of differentiation 40 (CD40) and nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) depends on the canonical nuclear factor kappa B (NF-κB) cascade as the

genes encoding *CD40* and *NLRP3* are transcribed by the phosphorylated NF-κB p50/p65 heterodimer in LPS-induced microglia. Exosomes, which are nanosized vesicles (40-150 nm) involved in intercellular communication, are implicated in many pathophysiological processes. Human breast milk, which is rich in exosomes, plays a vital role in neonatal immune system maturation and adaptation. Activated microglia may cause brain-associated injuries or disorders; therefore, we hypothesize that human breast milk-derived exosomes (HBME) attenuate LPS-induced activation of CD40 and NLRP3 by decreasing p38 mitogen-activated protein kinase (MAPK) and NF-κB p50/p65 activation/phosphorylation downstream of toll-like receptor 4 (TLR4) in murine microglia (BV2). We isolated purified HBME and characterized them using nanoparticle tracking analysis and transmission electron microscopy to assess size and concentration. Fluorescence-activated cell sorting and western blots (WB) showed the presence of CD9, CD63, and CD81, which are exosome-specific markers. BV2 microglia were exposed to the four following *in vitro* experimental conditions ($n \geq 3$ per group): 1) PBS (control 1), 2) LPS (exposure group), 3) HBME (control 2), and 4) LPS and HBME simultaneously (treatment group). Analysis of BV2 microglia exposed to LPS and HBME (condition 4) indicated that HBME modulated the expression of signaling molecules in the canonical NF-κB pathway. Treatment increased the protein expression of myeloid differentiation primary response 88 (MyD88) ($P < 0.05$) and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IκBα) ($P < 0.01$), and decreased the activation of proteins p38 MAPK ($P < 0.05$) and NF-κB p65 ($P < 0.01$). Additionally, we observed decreased protein expression of CD40 ($P < 0.05$), NLRP3 ($P < 0.05$), and IL-1β ($P < 0.05$), and increased protein expression of IL-10 ($P < 0.05$). In conclusion, HBME have great potential for attenuating CD40 and the NLPR3 inflammasome signaling in the microglial response to LPS.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.116/LBA111

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: USAMRICD SEED FY2023
Research Participation Program administered by Oak Ridge Institute for Science and Education (ORISE)

Title: Imidazoline receptor targeting as a novel method of seizure control during nerve agent induced status epilepticus in a rat model.

Authors: *K. WAGNON[1], A. N. SANTORO[2], T. WHITTY[4], G. CAPACIO[5], D. CRAIG[6], K. P. WATSON[3], H. S. MCCARREN[7];
[1]United States Army Med. Res. Inst. of Chem. Def., Baltimore, MD; [2]Neurosci., USAMRICD, APG-EA, MD; [3]USAMRICD, USAMRICD, Edgewood, MD; [4]US Army Med. Res. Inst. of Chem. Def. (USAMRICD), Aberdeen, MD; [5]US Army Med. Res. Inst. of Chem. Def. (USAMRICD), Joppa, MD; [6]US Army Med. Res. Inst. of Chem. Def. (USAMRICD), Baltimore, MD; [7]US Army Med. Res. Inst. of Chem. Def. (USAMRICD), Aberdeen Proving Ground, MD

Abstract: Nerve agents are an effective model to induce seizures that rapidly progress to status epilepticus (SE), which is a medical emergency. The longer SE continues, the harder it becomes to stop with traditional antiseizure drugs like benzodiazepines. Persistent SE can cause brain damage that severely impacts quality of life for survivors. Second line antiseizure drugs like levetiracetam, fosphenytoin, and valproate are only effective in approximately half of cases, which underscores a need to develop novel treatments that terminate SE when other options fail. Our lab has previously found that the alpha2-adrenergic agonist dexmedetomidine is highly effective at terminating benzodiazepine-resistant SE in rats, but its efficacy may not be fully attributable to action at its canonical binding partner. Here, we test the hypothesis that activation of dexmedetomidine's secondary targets, imidazoline receptors, will exert antiseizure effects.This project utilized an established rat model of benzodiazepine-resistant nerve agent-induced status epilepticus. Adult male Sprague Dawley rats were implanted with EEG electrodes, followed ~1 week later by induction of SE via subcutaneous administration of soman. Twenty minutes after onset of SE, rats received midazolam and a test treatment (CR4056, 2-BFI, agmatine) or control (saline). EEG activity, blood pressure, and temperature were monitored for four hours, after which rats were humanely euthanized and perfused for evaluation of brain damage with H&E staining.The non-selective imidazoline agonist agmatine controlled seizures in 6/13 rats at 10 mg/kg dosing. Higher doses resulted in similar rates of seizure control (4/11 rats at 30 mg/kg, 6/16 rats at 80 mg/kg). Though agmatine was somewhat effective at controlling SE, 14/40 rats across all dose groups succumbed before the 4 hour endpoint, possibly due to reduced blood pressure mediated through the imidazoline-1 receptor. The imidazoline-2 receptor agonists CR4056 and 2-BFI were less effective at controlling SE, with 10 mg/kg stopping seizures in 4/13 and 2/12 rats respectively. Post-treatment mortality rates for CR4056 and 2-BFI were 2/13 and 3/12 respectively. Future work will include targeted blocking and reversal experiments to determine if imidazoline receptor antagonists can prevent or reverse the ability of dexmedetomidine to control SE.

Disclosures: K. Wagnon: None. **A.N. Santoro:** None. **T. whitty:** None. **G. Capacio:** None. **D. Craig:** None. **K.P. Watson:** None. **H.S. McCarren:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.117/LBA112

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant ES031282

Title: Tamoxifen increases REST (NRSF) via Wnt-β-catenin signaling and genomic ER pathway

Authors: A. DIGMAN, *E.-S. LEE;
Pharmaceut. Sci., Florida A&M Univ., Tallahassee, FL

Abstract: Chronic exposure to elevated levels of manganese (Mn) can lead to a neurological disorder referred to as manganism and is also considered a risk factor for Parkinson's disease (PD). Lower levels of the repressor element-1 silencing transcription factor (REST, aka neuron restrictive silencer factor), have been reported in patients with PD and Alzheimer's disease. Studies have shown that Mn exposure decreases REST levels in mice and neuronal cells, while overexpression of REST provides protection against Mn toxicity. Activation of Wnt signaling increases REST expression and E2 has shown to activate Wnt signaling. However, E2's clinical application is limited due to its adverse peripheral effects and thus, selective estrogen receptor modulators (SERMs) that can increase REST expression without causing peripheral effects could serve as ideal candidates. In this study, Tamoxifen (TX), as a representative SERM, was investigated to determine if it could increase REST levels through Wnt signaling and/or genomic nuclear ER and provide protection against Mn toxicity in CAD neurons and mice. The results showed that TX (1 μM, 24 h) increased REST mRNA/protein levels and parallelly protected neurons against Mn (250 μM) toxicity. TX increased REST promoter activity via both non-genomic Wnt/β-catenin-TCF/LEF signaling and the genomic estrogen receptor (ER) pathway. Among various ER types, ER-α was the primary mediator of TX's action in increasing REST transcription in CAD neurons. We also tested if REST, particularly dopaminergic REST, is critical in TX-induced neuroprotection against Mn toxicity in vivo, using dopaminergic-specific REST-deleted male mice (REST cKO). TX pellets (25 mg/21-d release) were subcutaneously implanted in the back of the neck of mice, followed by exposure to Mn (300 μg, intranasal, daily) for 3 weeks. The results showed that TX induced protection against Mn toxicity in REST cKO mice as it attenuated Mn-induced behavioral dysregulation in locomotor activity and motor coordination, along with the attenuation of Mn-induced dysregulation of Nrf2, SOD2, catalase, TNF-α, COX-2, Bcl-2, and Bax in the striatum of REST cKO mice. Intriguingly, TX increased REST protein levels in the striatum of REST cKO mice. These findings suggest that dopaminergic REST is not the sole factor for TX-induced upregulation of REST and its protective effects against Mn toxicity, since TX increased REST expression in non-dopaminergic neural cells. Taken together, TX could offer protection against Mn toxicity, at least in part, by REST signaling, providing potential therapeutic strategies for developing brain-specific neuroSERMs.

Disclosures: A. Digman: None. **E. Lee:** None.

Late-Breaking Poster

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH RF1AG060769

Title: Rev-erb agonism suppresses age-associated neuroinflammation

Authors: *R. MIRABEL[1], M. E. HAYES[2], T. BURRIS[1];
[2]Pharmacodynamics, [1]Univ. of Florida, Gainesville, FL

Abstract: As the brain ages, it exhibits a proinflammatory state (neuroinflammation) which is associated with cognitive decline and the pathology of neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's diseases (PD). Neuroinflammation and neuronal death are linked to microglia and astrocytes activation. Thus, the transcription regulation of proteins such as the nuclear receptor REV-ERBα, a suppressor of proinflammatory gene expression, could play a pivotal role in regulating neuroinflammation. In this study, we conducted a comprehensive transcriptomic analysis (RNA-seq) of the hippocampus of C57BL/*6J* rodents at various stages of aging. We observed a progressive increase in the expression of genes associated with neuroinflammation as the rodents advanced in age. Comparison of the transcriptomic data between 6-month-old and 18-month-old rodents highlighted a significant upregulation of key proinflammatory genes. For example, lipocalin-2 (Lcn2) and chemotactic cytokine ligand 2 (Ccl2), both of which are known to be upregulated in active astrocytes, exhibited an exceedingly high degree of induction (17.34-fold, p=0.000004 and, 15.34-fold, p=0.001, respectively). Additionally, macrophage metalloelastase (Mmp-12), a marker for reactive microglia, also showed substantial increase in expression as well (25.18-fold, p=0.002). These findings collectively point towards an age-related increase in neuroinflammation. We administered two synthetic REV-ERB agonists derived from distinct chemical scaffolds to 18-month-old mice: SR9009, a STL1267 analog or vehicle. This treatment aimed to assess the effects of activating REV-ERB on the expression of proinflammatory genes that we observed to be substantially increased at 18-months of age. Treatment with SR9009 induced a significant downregulation of gene expression for Lcn2 (18.09-fold, p=0.00003), Ccl2 (3.14-fold, p=0.15), and Mmp-12 (2.21-fold, p=0.44). Similarly, the administration of the STL-1267 analog led to a substantial downregulation of these genes: Lcn2 (3.75-fold, p=0.05), Ccl2 (5.91-fold, p=0.03), and Mmp-12 (3.24-fold, p=0.26). These findings suggest that activation of REV-ERB with synthetic small molecule agonists significantly suppresses proinflammatory gene expression association with age-induced neuroinflammation. Thus, REV-ERB agonists are promising therapeutics for limiting the decline in cognitive function due to age-related neuroinflammation and neurodegenerative disorders.

Disclosures: R. Mirabel: None. **M.E. Hayes:** None. **T. Burris:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.119/LBA114

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: KU Research Sector Grant #Grant # MY01/22.

Title: The inactivation of $GABA_A$ receptor dampens the promyelinating effects of lactation.

Authors: *A. MOUIHATE, S. KALAKH;
Kuwait Univ., Kuwait, Kuwait

Abstract: Introduction: We recently showed that lactation promoted the cell division of oligodendrocyte precursor cells and myelination. The mechanism underlying this beneficial effect is not clear. In the present study, we hypothesized that the neurotransmitter GABA contributes to this neuroprotective effect. **Methods:** After parturition, a group of dams (Sprague Dawley rats) was randomly selected, separated from their pups, and served as a non-lactating rat group (nLact). Another group of dams was kept with their pups to allow lactation (Lact). On the fourth day after parturition, rats were subjected stereotaxically to lysolecithin-induced demyelination in their *corpora callosa*. Each of these two rat groups was randomly split into two subgroups that received daily intraperitoneal injections of either saline or the $GABA_A$ receptor antagonist bicuculline (1mg/Kg) for 7 days. On the 8^{th} day, rat brains were collected and subjected to a series of immunostaining and transmission electron microscopy to monitor the density and cell division of oligodendrocyte precursor cells, microglia, and the myelination in the demyelinated region of the *corpus callosum*. **Results:** Lactating rats exhibited reduced signs of demyelination manifested by a lower number of unmyelinated axons and decreased g-ratio when compared to nLact rats. Blockade of the $GABA_A$ receptor by bicuculline altered these promyelinating effects of lactation. At the cellular level, lactation enhanced the density and the mitosis of $NG2^+$-containing cells (OPC) in the demyelinated area of the *corpus callosum*. Such increases were halted when the $GABA_A$ receptor was blocked. On the other hand, bicuculline led to a significant increase in the density of the phagocytic subset of microglia (Iba+/CD68+) in both nLact and Lact rat groups. **Conclusion:** These data suggest that the neuroprotective effect of lactation in response to a demyelinating lesion operates, at least in part, through the $GABA_A$ receptor. Furthermore, the $GABA_A$ receptor appears to promote the silencing of microglial activity in response to a demyelinating injury. This study paves the way for exploring the $GABA_A$-mediated effects of breastfeeding in alleviating symptoms of demyelinating diseases such as multiple sclerosis.

Disclosures: A. Mouihate: None. **S. Kalakh:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.012/LBA12

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

Support: NIA Grant R01AG074082

Title: Spatial long non-coding RNA expression in human brains of Alzheimer's Disease

Authors: *D. AVEY[1,2], B. NG[2], K. LOPES[2], S. TASAKI[2], R. VIALLE[2], J. XU[2], S. DE TISSERA[2], A. IATROU[3,2], D. A. BENNETT[2], Y. WANG[2];
[2]Rush Alzheimer's Dis. Ctr., [1]Rush Univ. Med. Ctr., Chicago, IL; [3]Div. of Depression and Anxiety Disorders, Harvard Med. Sch., Boston, MA

Abstract: Long non-coding RNAs (lncRNAs) have been shown to regulate gene expression at multiple levels. Compared with coding RNAs, lncRNAs exhibit greater tissue/cell-type specificity. The lncRNAs in the brain often display specific spatial expression patterns and play essential roles in brain development and function. The dysregulation of lncRNA expression has been implicated in aging and many neurological disorders, including Alzheimer's disease (AD). Here, we acquired spatial transcriptomics (ST) data from 78 postmortem brain sections of 21 individuals, covering 258,987 microdomains. We detected layer-specific lncRNAs, most belonging to antisense and lincRNA biotypes. We also built 11 gene networks (one for each cortical layer/subregion), tallying to 273 modules. We found a subset to be lncRNA-enriched and observed modules to be preserved across cortical layers, but to a lesser extent for white matter and meninges. We then compared AD-differential mRNAs and lncRNAs and observed ~2-fold more differentially expressed (DE) mRNAs than lncRNAs. Nonetheless, a greater proportion of AD DE lncRNAs is layer-specific. Gene set enrichment analysis indicates that AD DE lncRNAs are implicated in gene regulation, synaptic signaling, and apoptosis. Notably, we observed minimal overlap between AD DE lncRNAs and A-beta-associated lncRNAs, indicating other pathological factors contributing to AD DE lncRNA expression. We further integrated expression quantitative trait loci (eQTL) derived from single nucleus RNAseq data to infer the genetic circuits and cell types associated with AD DE lncRNAs. For cortical layer and white matter AD DE lncRNAs, the corresponding eQTL SNPs are largely associated with microglial and oligodendrocyte expression, respectively. Our data represent the first high-throughput characterization of lncRNA spatial expression in the context of human brain aging and neurodegeneration. This data will be a valuable resource for future studies investigating the roles of lncRNAs in the human brain.

Disclosures: D. Avey: None. **B. Ng:** None. **K. Lopes:** None. **S. Tasaki:** None. **R. Vialle:** None. **J. Xu:** None. **S. De Tissera:** None. **A. Iatrou:** None. **D.A. Bennett:** None. **Y. Wang:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.120/LBA115

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NINDS U01 NS112008
NIH/NIEHS ES027245 and ES026892

Title: Histones in extracellular vesicles amplify NLRP3-inflammasome activation and alpha-synuclein aggregation in environmentally linked Parkinson's disease

Authors: *A. BARGUES CAROT, M. SAMIDURAI, C. JANARTHANAM, H. JIN, V. ANANTHARAM, A. KANTHASAMY, A. G. KANTHASAMY;
Univ. of Georgia, Athens, GA

Abstract: Emerging evidence indicates that histones can be released into the extracellular space by damaged cells, and these circulating histones act as damage-associated molecular patterns (DAMPs) that augment inflammatory responses. We previously reported that Fyn activates the pathological α-synuclein (α-syn)-induced NLRP3 inflammasome, a multiprotein complex that activates caspase-1 and promotes maturation and secretion of the proinflammatory cytokines IL-1β and IL-18 in microglia. Herein, we report a novel pathological interaction between circulating extracellular vesicles (EV)s containing histones and α-syn in amplifying the neuroinflammatory response in environmentally linked Parkinson's disease (PD). Specifically, we found that exposing dopaminergic neuronal cells to environmental neurotoxicants such as metals and pesticides increases histone 3 (H3) levels released in small EVs. Notably, the EVs isolated from the serum of PD patients and farmers exposed to pesticides, as well as in the MitoPark PD model, showed elevated H3 levels. Interestingly, the serum EVs from PD patients demonstrate increased H3 posttranslational modifications (H3 acetyl and phospho). We then investigated whether H3 plays a role in mediating neuroinflammation by activating the NLRP3 inflammasome via the Fyn kinase pathway. Recombinant (r)H3-treated primary mouse microglia promoted the generation of reactive oxygen and nitrogen species (ROS and RNS), the release of proinflammatory cytokines, and the activation of the NLRP3 inflammasome. Interestingly, rH3 treatment exacerbated α-syn-mediated NLRP3 activation, cytokine release, and RNS generation in mouse primary microglia compared to α-syn treatment alone. The Fyn inhibitor saracatinib, or Fyn knockdown, dampened H3-mediated NLRP3 inflammasome activation, suggesting the involvement of Fyn kinase in this process. Interestingly, we found rH3 interacted with

monomeric α-syn, augmenting its aggregation, suggesting that H3 can serve as a possible co-factor regulating the pathogenic α-syn protein misfolding process. Collectively, these results demonstrate that H3 in EVs may serve as a key pro-inflammatory amplifier of α-syn protein aggregation and neuroinflammation through the activation of NLRP3 inflammasome signaling via Fyn kinase signaling.

Disclosures: A. Bargues Carot: None. **M. Samidurai:** None. **C. Janarthanam:** None. **H. Jin:** None. **V. Anantharam:** None. **A. Kanthasamy:** None. **A.G. Kanthasamy:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.121/LBA116

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Schizophrenia risk gene C4 induces pathological synaptic loss by impairing AMPAR trafficking

Authors: *R. PHADKE[1], A. BRACK[1], L. FOURNIER[1], E. KRUZICH[1], M. SHA[1], C. JOHNSON[2], A. CRUZ-MARTIN[1];
[1]Boston Univ., Boston, MA; [2]Brandeis Univ., WALTHAM, MA

Abstract: Neuroimmune interactions play a significant role in regulating synaptic plasticity in both the healthy and diseased brain. The complement pathway, an extracellular proteolytic cascade, exemplifies these interactions. Its activation triggers microglia-dependent synaptic elimination via the complement receptor 3 (CR3). Current models of pathological complement activity in the brain propose that accelerated synaptic loss resulting from overexpression of C4 (C4-OE), a gene associated with schizophrenia, follows this pathway. Here, we report that C4-mediated cortical hypoconnectivity is CR3-independent. Instead, C4-OE triggers impaired GluR1 trafficking through an intracellular mechanism involving the endosomal protein SNX27, resulting in pathological synaptic loss. Moreover, C4 circuit alterations in the prefrontal cortex, a brain region associated with neuropsychiatric disorders, were rescued by increasing neuronal levels of SNX27, which we identify as an interacting partner of this neuroimmune protein. C4-OE led to reduction in dendritic spine sizes, along with aberrant GluR1 trafficking at the synapse, with reduced association of GluR1 with recycling endosomes. Our results link excessive complement activity to an intracellular endo-lysosomal trafficking pathway altering synaptic plasticity.

Disclosures: R. Phadke: None. **A. Brack:** None. **L. Fournier:** None. **E. Kruzich:** None. **M. Sha:** None. **C. Johnson:** None. **A. Cruz-Martin:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.122/LBA117

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH RF1AG067429
NIH R25AG076396

Title: Effects of chronic vagus nerve stimulation in aging

Authors: *J. I. RODRÍGUEZ[1], J. SEEDANSINGH[2], S. N. BURKE[2], B. SETLOW[3], J. L. BIZON[4];
[1]Neurosci., Univ. of Florida, Newberry, FL; [2]Neurosci., [3]Dept. of Psychiatry, Univ. of Florida, Gainesville, FL; [4]Neurosci., Univ. of Florida Dept. of Neurosci., Gainesville, FL

Abstract: The aging population is at significant risk for cognitive decline, which adversely affects activities of daily living and overall quality of life. This decline is mediated in part via age-related changes in excitatory/inhibitory (E/I) signaling in the brain, as well as increases in inflammation, both of which disrupt cognitive function. Electrical vagus nerve stimulation (VNS), an FDA-approved treatment for epilepsy, shows promise in enhancing neuroplasticity and reducing inflammation, suggesting that it may counteract age-related cognitive deficits. The broad goal of this research program is to address several potential beneficial effects of VNS in aging: first, to investigate whether VNS can remediate age-related impairments in cognitive tasks mediated by the hippocampus and prefrontal cortex (PFC); second, to determine if VNS can attenuate age-associated E/I dysregulation and impaired synaptic function in the hippocampus and PFC; and third, to determine how VNS affects peripheral and brain markers of inflammation in aged rats. Aged male and female FBN rats (24 mo.) were surgically implanted with a cuff electrode around the left vagus nerve and received daily 1-hour sessions of VNS using parameters previously demonstrated to enhance cortical plasticity and various forms of learning (100 stimulus trains/session at 30Hz, 700 µA, 120 µs biphasic pulse width, 0.8 s train duration), or a sham control procedure, for at least 30 sessions, during which experiments were conducted to gather data for the study's objectives. Preliminary data indicate that this VNS regimen significantly improves working memory performance in aged rats, and significantly alters the profile of cytokine expression in aging. These findings, along with published data across species, suggest that VNS may serve as a promising intervention to mitigate cognitive decline and improve overall brain health in the aging population.

Disclosures: J.I. Rodríguez: None. **J. Seedansingh:** None. **S.N. Burke:** None. **B. Setlow:** None. **J.L. Bizon:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.123/LBA118

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Endogenous β-hexosaminidase protein distribution in mouse brain: implications for gene therapy

Authors: *A. GLOVER, Y. LI, Y. GONG, F. EICHLER;
Neurol., Massachusetts Gen. Hosp., Boston, MA

Abstract: The HEXB gene encodes the β-subunit of β-hexosaminidase (β-hex), a lysosomal enzyme that is involved in the hydrolysis of terminal N-acetyl-D-hexosamine residues in glycolipid ganglioside GM2 and other molecules. The reduction of this enzyme results in an accumulation of gangliosides and glycolipids in the central nervous system and peripheral organs, leading to subsequent neuronal cell death and neurodegeneration. Sandhoff's disease is a lysosomal storage disease caused by mutations in HEXB. AAV-mediated gene therapy has shown promise but its biodistribution has been questioned based on residual enzyme activity in juvenile patients who do not tolerate gene therapy well and exhibit symptom aggravation that could be due to altered circuitry. Understanding the distribution of β -hex in wild type mouse brain will shed light on how to optimize gene delivery. The HEXB-/- murine model manifests a phenotype similar to juvenile Sandhoff Disease patients and exhibits motor deficits with a shortened lifespan. In the mouse central nervous system, HEXB expression is enriched in microglia, but the protein localization and its distribution have not been fully characterized. Using immunofluorescence, we found extensive β-hex protein expression across mouse brain with high abundance in the hippocampus, cortex, and thalamus. Co-staining with the microglial marker IBA1 revealed significant expression of β-hex in microglia, which aligns with the HEXB gene expression pattern. Surprisingly, co-staining with the neuronal marker NeuN also revealed neuronal expression of β-hex, particularly in the cortex and hippocampus, despite lower neuronal HEXB mRNA expression. To account for these observations, we propose that neuronal uptake of secreted β-Hex of microglial origin accounts for the increased neuronal β-hex levels. Co-culture experiments are currently underway to test this hypothesis. The proposed cross talk between microglia and neurons can help inform routes of gene-based therapeutic approaches in Sandhoff's disease. Separately, additional experiments in HEXB+/- mice will further complement our understanding of adaptive plasticity in the developing mouse brain and point to directions in optimizing gene delivery for this devastating neurogenetic disease.

Disclosures: A. Glover: None. **Y. Li:** None. **Y. Gong:** None. **F. Eichler:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.124/LBA119

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DOD GWI160086
NIH R01ES031656

Title: Epigenetics of neuroinflammatory response to exposure to organophosphates and glucocorticoids

Authors: *B. C. JONES;
Genetics, Genomics, and Informatics, Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: In 1991, the United States and allies sent nearly 1,000,000 troops to the Middle East to counter actions by Saddam Hussein against Kuwait. Between 25 and 35% of combatants became ill with a multisymptomatic malaise, Gulf War illness or GWI, that included gastrointestinal and neurological symptoms. The neurological signs included general lethargy, memory problems, headaches and insomnia. Collectively, they may be termed “sickness behavior.” The cause of GWI is likely exposure to organophosphate (OP) chemicals including sarin and chlorpyrifos. O’Callaghan and Miller proposed that the sickness behavior was a result of neuroinflammation caused by exposure to the OPs and high circulating cortisol as might be expected during the stress of combat. Thus, they developed an animal model of the exposure experienced by the combatants. This included exposure to corticosterone (the major glucocorticoid in rodents) followed by exposure to diisopropyl- fluorophosphate (DFP), a sarin surrogate. This protocol produces neuroinflammation in rodents and research into the genetics of differential susceptibility has revealed candidate genes underlying acute susceptibility. The major problem about GWI is its chronicity. Many of the GWI veterans are still ill, having suffered for 30+ years. The major issue is to understand the mechanisms of chronicity to identify therapeutic strategies. Chronic GWI likely has epigenetic underpinnings, so our approach was to identify methylation of candidate genes and individual differences. Our experimental approach was to add corticosterone for 7 days to the drinking water of male and female mice from 11 BXD inbred strains. On the 8^{th} day, we administered DFP to mimic the exposure to OPs of Gulf War troops. Forty-two weeks after DFP treatment, we euthanized the mice and harvested the medial prefrontal cortex. The tissues were then examined for genome-wide methylation of individual genes by MBD-seq. In an earlier study, involving the same protocol but with male and female mice from just the two parental strains of the BXD family, C57BL/6J and DBA/2J, using MBD-seq, we identified 4 genes that differed between the strains in response to corticosterone+DFP. The methylated genes were *Ttll7, Akr1c14, Slc44a4,* and *Rusc2,* all related to various GWI symptoms. The 11-strain study revealed another, *Eif2b5,* which is regulated by *Mapkapk2,* a major player in inflammation. Our work demonstrates multiple genes whose expression in the long term is altered by exposure to OPs and glucocorticoids. These genes point to biochemical

mechanisms that may be targets for therapeutic intervention. Supported by grants DOD GWI160086 and USPHS R01ES031656

Disclosures: B.C. Jones: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.125/LBA120

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Research Foundation of Korea (NRF) grant funded by the Korea government (MIST) (RS-2024-00347913)
National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT (RS-2024-00348012)

Title: Substance P-Neurokinin 1 signal in the acute phase of MIA-induced osteoarthritis drives the onset of chronic pain via neuroimmune interaction-mediated pain processing in rats.

Authors: *M. KWON[1,2], E. PARK[3], H. OK[4], H. YOO[1], J. KIM[1,2,4];
[1]Rehabil. Sci. Program, Dept. of Hlth. Sci., Korea Univ., Seoul, Korea, Republic of; [2]Transdisciplinary Major in Learning Hlth. Systems, Dept. of Healthcare Sci., Grad. School, Korea Univ., Seoul, Korea, Republic of; [3]Dept. of Physiol., Col. of Medicine, Korea Univ., Seoul, Korea, Republic of; [4]Dept. of Hlth. and Envrn. Sci., Col. of Hlth. Science, Korea Univ., Seoul, Korea, Republic of

Abstract: Chronic pain is a major symptom in patients with osteoarthritis (OA), which limits daily activity and reduces quality of life. The SP-neurokinin 1 (NK1) signal is known to be involved in neurogenic inflammation, an inflammatory reaction triggered by the nervous system driven by active interaction between the immune system and nociceptor neurons, which substantially influences the chronicity and severity of OA pain. Neuroimmune interactions related to the SP-NK1 signal have been highlighted for their importance in pain processing and the chronicity of OA pain. However, the exact pathological role and related mechanisms remain unclear. In the present study, we aimed to investigate the role of the SP-NK1 signal in the development of chronic OA pain in a preclinical animal model with MIA-induced OA.We examined whether intra-articular inhibition of the SP-NK1 signal during the acute phase of MIA-induced OA, using GR82334 (GR), an NK1 receptor antagonist, can decrease inflammatory pain behaviors and delay the development of secondary hyperalgesia by modulating neuroimmune interactions in the knee joint, dorsal root ganglia (DRG), and spinal dorsal horns (SDHs). Intra-articular injection of 1 and 10 μM GR in pre-GR or post-GR groups showed a significant reduction in the knee joint diameter ratio and knee bending score. Additionally, The pre- and

post-groups of GR prevented the decrease in PWT on day 14 compared to the MIA group. The pre- and post-GR groups showed that pro-inflammatory cytokines (CCL2, TNF-α, IL-1β, and IL-6), pain-related peptides (CGRP and SP), and the activation of M1 macrophages were significantly reduced at 14 day post-MIA in the knee joint and DRGs. Furthermore, the expression of CGRP and SP and the activation of M1 microglia in the SDHs (L3-5) were significantly decreased in these groups.The present data showed the intra-articular inhibition of the SP-NK1 signal using an NK1 receptor antagonist in the acute phase of MIA-induced OA attenuated the primary hyperalgesia and delayed the development of secondary hyperalgesia. Of note, these effects were shown through suppressing neurogenic inflammation in the afferent nerve terminal of the knee joint and inhibiting neuroimmune interaction in DRGs and SDHs. Our findings demonstrated that the SP-NK1 signal involves the development of OA-induced chronic pain via the neuroimmune interaction-mediated pain processing pathway, confirming the potential of NK1 receptor antagonists as a therapeutic approach for chronic OA pain.

Disclosures: M. Kwon: None. **E. Park:** None. **H. Ok:** None. **H. Yoo:** None. **J. Kim:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.126/LBA121

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Harvard Medical School SHURP Program
T32 NS007473-22 NIH
The Reagan Sloane Shanley Scholarship
NS129823-01 NIH NINDS
1F32NS136267-01 NIH
The Pediatric Hydrocephalus Foundation
NIH P50 HD105351

Title: Choroid plexus immune cell infiltration following neuroinflammation during development

Authors: *O. Y. DE PABLO-CRESPO[1,2,4], C. HEHNLY[4,3], M. K. LEHTINEN[4,3];
[1]Río Piedras Campus, Univ. of Puerto Rico, San Juan, Puerto Rico; [2]Summer Honors Undergraduate Res. Program (SHURP), Div. of Med. Sci., [3]Harvard Med. Sch., Boston, MA; [4]Pathology, Boston Children's Hosp., Boston, MA

Abstract: Hydrocephalus is a life-threatening condition denoted by excessive cerebrospinal fluid (CSF) accumulation in the ventricles. One common cause of pediatric hydrocephalus is inflammation in the brain. Most CSF is produced by a unique secretory tissue called the choroid plexus (ChP). The ChP also forms a critical barrier between the brain and the periphery. It has been shown that this tissue can be activated during brain inflammation, where it interacts with

immune cells. However, how this process occurs is not well understood. Although several experimental hydrocephalus models exist, there is currently no inflammatory hydrocephalus model in developing mice. Here, we defined an inflammatory model of hydrocephalus in embryonic and postnatal mice to address this gap. Previously, it was shown in an adult model of inflammatory meningitis/hydrocephalus using a 2.5μg dose of lipopolysaccharide (LPS) intracerebroventricular that neutrophils (24hr) then monocytes (72hr) infiltrate the brain at the ChP. Our study aims to investigate this process in our developmental model of inflammatory hydrocephalus. We confirmed that, similarly to the adults, using a weight-adjusted dose of LPS (0.06μg) in embryos (E14/E15), there was an early increase in infiltrating inflammatory neutrophils and/or undifferentiated monocytes ($CD45^+/S100A9^+/Iba1^-$). At 72 hours, there was an increase in resident macrophages likely differentiated from monocytes ($CD45^+/Iba1^+/S100A9^+$). However, in postnatal mice (P7), a weight-adjusted dose of LPS (0.5-1μg) there was no increase in $CD45^+$ cells. The results of this study will help pave the way for eventual therapies to target the ChP to control brain inflammation and associated hydrocephalus.

Disclosures: O.Y. De Pablo-Crespo: None. **C. Hehnly:** None. **M.K. Lehtinen:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.127/LBA122

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH 1R56NS138437-01

Title: Persistent long-term cognitive impairment, blood-brain barrier permeability and neuroinflammation are associated with reduced cerebrovascular Wnt/β-catenin signaling after severe SARS-CoV-2 infection in mice.

Authors: *R. MARTINS-GONCALVES[1], A. ALMOUSAWI[1], A. SENAPATI[1], A. FOGEL[1], M. ORTIZ[2], S. E. LUTZ[3];
[1]Anat. and Cell Biol., Univ. of Illinois in Chicago, Chicago, IL; [2]Anat. and Cell Biol., Univ. of Illinois Chicago, Chicago, IL; [3]Anat. and Cell Biol., Univ. of Illinois Chicago Col. of Med., Chicago, IL

Abstract: Survivors of both mild and severe SARS-Cov-2 infection can present a variety of persisting symptoms, including fatigue and brain-fog, symptoms that are associated with increased permeability of the blood-brain barrier (BBB). We have previously reported that during acute SARS-CoV-2 infection, BBB permeability and neuroinflammation are associated with suppressed cerebrovascular Wnt/β-catenin signaling, and that delivery of cerebrovascular-targeted Wnt ligands prevents acute BBB permeability, neuroinflammation, and cognitive

impairment. In the current study, we investigate long-term BBB permeability and Wnt/β-catenin pathway activation after severe SARS-Cov-2 respiratory infection in mice. 3-month-old C57BL/6 (50% male) were intranasally infected with $3x10^3$ FFU of the mouse adapted rSARS2-$N501Y_{MA30}$. Survivors were submitted to open field and Novel Object Recognition (NOR) behavioral assessment and euthanized at 30 or 60 days post inoculation (dpi). Brain samples were collected for immunostaining and flow cytometry of isolated/dissociated microvasculature. The infection induced weight loss and 65% mortality. Infected mice displayed reduced distance traveled and increased immobility in open field test, and short-term memory impairment in NOR test, lasting up to 60dpi. Surviving mice also displayed increased BBB permeability up to 60dpi, evidenced by increased infiltration of $CD3^+/CD4^+$ lymphocytes and fibrinogen in the hippocampus. Additionally, elevated expression of CD69 in infiltrating lymphocytes at 30dpi, and increased $Iba1^+/CD68^+$ in hippocampus at both 30 and 60dpi, are evidence for increased lymphocyte and microglial activation in the CNS. This data points to persistence of BBB permeability, neuroinflammation, and cognitive impairment in this mouse model of neurological post-acute sequalae of COVID-19 (neuroPASC, also known as “long COVID”). Mechanistically, we found reduced expression of the Wnt/β-catenin pathway protein WISP1 in the hippocampus up to 60dpi. One way Wnt/β-catenin signaling can protect the BBB is by suppressing Caveolin-1, a protein that contributes to BBB transcytosis. We found increased expression of Caveolin-1 in $CD31^+$ endothelial cells from the brain microvasculature at 30dpi, pointing to reduced Wnt signaling in the CNS as a possible cause of BBB permeability and neuroinflammation in a mouse model of neuroPASC.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.128/LBA123

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Determinning the anti-inflammatory therapeutic index of propofol in a murine modelof neuroinflammation

Authors: *M. HUANG[1,2], Y. SU[2,1], B. S. SLUSHER[1,2,3,4,5];
[1]Johns Hopkins Drug Discovery, [2]Neurol., [3]Psychiatry and Behavioral Sci., [4]Pharmacol. and Mol. Sci., [5]Dept. of Oncology, Johns Hopkins Univ., Baltimore, MD

Abstract: Neuroinflammation has been implicated in various neurological disorders. Propofol, a widely used intravenous anesthetic, has demonstrated robust neuroprotective properties in addition to its sedative effects. We aimed to establish the therapeutic index of propofol in a

lipopolysaccharide (LPS)-induced neuroinflammatory mouse model. We first determined the minimum dose of propofol that does not induce sedation by administering various intraperitoneal doses and assessing locomotor activity and sedation scores. Subsequently, we evaluated the lowest dose of significantly reducing cytokine levels in plasma and brain tissue in LPS-treated mice using a multiplexed protein detection array. Our results indicate that propofol doses of 30, 10, and 5 mg/kg produced significant sedation, while 3 mg/kg and lower doses did not. In the LPS-induced inflammation model, propofol doses of 1 and 3 mg/kg significantly reduced levels of several inflammatory markers in plasma including TNF-a, CD30L, Eotaxin, INFg, FasL, IL-2, IL-3, IL-5, IL13, MIP-1g, TIMP-1, TNF RII and TNF RI, MCP-5, RANTES, ICAM-1, MIP-1g levels in frontal cortex. No significant reductions were observed at 0.3 mg/kg, suggesting a therapeutic index of 3-fold for propofol's anti-inflammatory effects. Given the central role of macrophages and microglia in neuroinflammation, future research will focus on developing cell-specific targeting and extended-release systems to enhance propofol's therapeutic index, potentially allowing for the exploitation of its anti-inflammatory properties without inducing sedation.

Disclosures: M. Huang: None. **Y. Su:** None. **B.S. Slusher:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.129/LBA124

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Inflammation as a potential target for mitigating neurodegeneration in the Braak’s hypothesis model for Parkinson’s Disease

Authors: *S. SENAPATI[1], I. NESTER[2], C. C. SWAIN[3], V. V. PESHATTIWAR[5], K. M. LE[6], T. SUBRAMANIAN[4], K. VENKITESWARAN[7];
[1]Neurol., Univ. of Toledo Col. of Med., Toledo, OH; [2]Univ. of Toledo Col. of Med. Neurosci. & Neurolog. Disorders, Toledo, OH; [3]Dept. of Neurosciences, Univ. of Toledo Col. of Med. and Life Sci., Toledo, OH; [4]Neurology, Neurosci. and Bioengineering, Univ. of Toledo Col. of Med. and Life Sci., Maumee, OH; [5]Neurol., The Univ. of Toledo, Toledo, OH; [6]Neurol., Univ. of Toledo, Toledo, OH; [7]7262 Violet lane, Univ. Toledo Col. of Med., Toledo, OH

Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder characterized by dopaminergic neuron loss and the presence of pathologically misfolded alpha-synuclein (αSyn) aggregates. As proposed by Braak’s staging hypothesis, PD originates in the gut, spreading to the brain via the vagus nerve. Our lab studies the Paraquat and Lectin (P+L) rat model, which mimics key aspects of PD using oral subthreshold doses of Paraquat (herbicide) and Lectin (a carbohydrate-binding protein found in the human diet). This model induces Parkinsonism, which

can be prevented by performing a bilateral vagotomy, and affected animals can be treated effectively with Levodopa. Pathological examination of the brain shows dopaminergic loss in the Substantia Nigra (SN), accompanied by accumulation of misfolded S129-Phospho-αSyn. However, little is known about inflammation within the P+L rat model and the overall role of inflammation in PD pathology. Therefore, we tested for the presence of microglial and astroglial inflammatory markers in this model. This study utilizes archived 60-micron coronal brain sections from previous experiments where rats were treated with P+L in 1% sucrose, inducing PD-like symptoms. The brain sections were immunohistologically examined for GFAP positive astrocytes, and OX-42 positive, OX6 positive, and OX18 positive microglia. Neurodegeneration in the SN is accompanied by significantly increased presence of inflammatory markers such as GFAP positive astrocytes and activated microglia when compared to control subjects. Our findings support the notion that ascending pathology in the P+L model is accompanied by an increased inflammatory response. Further studies are required to understand the inflammatory response in time to understand the pathophysiological understanding of our findings. The identification of inflammation suggests treatment modalities mitigating inflammation may be of value to treat the ascending pathology of Parkinson's disease as reported by Braak.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.013/LBA13

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

Support: Lindquist Undergraduate Research Award

Title: Microglia Expressing the Alzheimer's Disease Protective Variant PLCG2-P522R Downregulate the NLRP3 Inflammasome

Authors: *A. SRIRAM, M. P. SADGROVE, G. A. GARDEN;
Neurol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: The NLRP3 inflammasome is a critical inflammatory signaling platform in microglia, the tissue-resident macrophage of the brain. The NLRP3 inflammasome can be activated by sterile, non-pathogenic triggering stimuli such as ATP, amyloid-β (Aβ) or α-synuclein following specific receptor priming (e.g., LPS, TNFα). When NLRP3 activity is initiated, the cell assembles an inflammasome complex comprised of apoptosis-associated speck-like protein containing a CARD (ASC) and mature caspase-1. This promotes the release of mature interleukin-1β (IL-1β), IL-18, and the ASC speck. Hyperactivation of the NLRP3 inflammasome

in microglia promotes widespread neuroinflammation and Aβ aggregation in patients with Alzheimer's disease (AD). The NLRP3 inflammasome lies downstream of the phospholipase C gamma 2 (PLCG2) signaling pathway. PLCG2 is a membrane protein specifically expressed by microglia and other myeloid cell types. GWAS studies reveal that the P522R variant of the *PLCG2* gene is associated with a reduced risk for AD. *PLCG2*-P522R expresses a protein with mildly enhanced enzymatic activity, but the precise mechanism(s) by which protection from AD pathology is achieved remains unclear. This study assessed the role of *PLCG2*-P522R in modulating the NLRP3 inflammasome as a potential mechanism by which the P522R variant protects against AD. Cortical microglia were cultured from age-controlled WT and $P522R^{+/+}$ P4 neonatal mice. A canonical inflammasome activation paradigm was employed. WT and $P522R^{+/+}$ microglia were exposed to LPS (100 ng/μL) for 3 hours before being triggered with ATP (5 mM) for 1 hour. Untreated and LPS-only controls were also included. ASC Speck aggregates subsequently released into culture media were collected and stained with an AlexaFluor 647-conjugated primary antibody. Labeled specks were quantified with flow cytometry as a readout for inflammasome activation. Additionally, this study assessed whether the P522R variant influences NLRP3 inflammasome activation in response to Aβ. WT and $P522R^{+/+}$ microglia were primed with LPS and triggered with Aβ (5μM) for 6.5 hours. The same ASC speck quantification protocol was used. In response to triggering from both ATP (n=3) and Aβ (n=4), LPS-primed microglia with the P522R variant released less ASC Speck compared to LPS-primed WT microglia. There was no statistical difference in ASC Speck release in the untreated or LPS-only conditions. These findings could support the development of NLRP3-targeted therapeutics for AD that mimic the neuroprotective effects of P522R variant in *PLCG2*.

Disclosures: A. Sriram: None. **M.P. Sadgrove:** None. **G.A. Garden:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.130/LBA125

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01 NS066801
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DC-CFAR P30 AI117970

Title: Clonal hematopoiesis in monocytes may contribute to HIV-associated neuroinflammation

Authors: *C. MORENO SORIANO, S. MAGGIRWAR;
MITM, George Washington Univ., Washington, DC

Abstract: The effect of chronic immune cell activation on cognitive impairment among aging HIV+ individuals is of great clinical significance. Among the many mechanisms that might explain the interactive effects of age and HIV on the central nervous system (CNS), blood brain barrier (BBB) compromised permeability induced by viral proteins stands out. Interestingly, a phenomenon known as clonal hematopoiesis of indeterminate potential (CHIP) may also have implications in this aging population. Chronic inflammation has been implicated in the development of CHIP, causing a wide range of mutations believed to be involved in this process. As people leaving with HIV (PLWH) experience chronic inflammation, a role for CHIP in mediating HIV pathogenesis is hypothesized. We explore if PLWH (n=52) harbor an increased number of CHIP-monocytes compared to controls (n=75) and if this subset from ART-treated PLWH presents a phenotype that could contribute to HIV-associated neurocognitive disorders (HANDs). To this aim whole blood was collected from PLWH and control individuals and PBMCs isolation was performed for flow cytometric analysis of surface and intracellular marker expression. Then, FACS isolation of monocyte subsets was followed with further analysis by RT-qPCR, cytokine profiling, transcription factor promoter-binding and functional migration assays. Our studies reveal that the ART-treated PLWH harbor higher numbers of inflammatory monocytes ($CD14^{low}CD16^{hi}$) and exhibit characteristics of CHIP, such as loss of DNMT3A and TET2 and increased JAK2. We further demonstrate that this monocyte subset (1) overexpresses cell adhesion molecules such as PSGL-1, (2) presents an altered transcriptional network regulating PSGL1 expression, (3) a higher release of inflammatory cytokines and (4) infiltrates human brain organoids at a higher rate. The results obtained in these studies strongly support the notion that HIV chronic infection mediates regulation of CHIP in monocytes and might play a role in HANDs, contributing to our understanding of CNS pathogenesis and revealing that CHIP-monocytes might be capable of infiltrating the CNS at higher rates than non-CHIP-monocytes thus establishing inflammation. Our findings are expected to further reveal the pathophysiological mechanisms of HANDs.

Disclosures: C. Moreno Soriano: None. **S. Maggirwar:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.131/LBA126

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

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Title: Cocaine regulates antiretroviral therapy CNS access through pregnane-x receptor-mediated drug transporter and metabolizing enzyme modulation at the blood brain barrier

Authors: *R. COLÓN-ORTIZ[1,5], S. KNERLER[5], A. MERCADO[2], A. PRICE[3], J. ROSADO-FRANCO[5], H. WILKINS[4], D. W. WILLIAMS[6];
[1]Neurosci., [2]Mol. and Comparative Pathobiology, [3]Cell. and Mol. Med., [4]Pharmacol. and Mol. Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [5]Pharmacol. and Chem. Biol., Emory Univ. Sch. of Med., Atlanta, GA; [6]Pharmacol. and Chem. Biol., Emory Univ., Atlanta, GA

Abstract: Human Immunodeficiency Virus (HIV) infects the brain within the first weeks of exposure. Appropriate interactions between antiretroviral therapies (ART), drug transporters, and metabolizing enzymes at the blood brain barrier (BBB) are crucial to ensure adequate dosing of the brain to achieve HIV suppression. However, complete ART penetration at the BBB remains a challenge. As a result, the brain becomes a viral reservoir, which contributes to BBB disruption, chronic neuroinflammation, and adverse neurological outcomes in people with HIV. Furthermore, illicit substances, such as cocaine, are highly used among people with HIV and share drug transport and metabolic pathways with ART. We hypothesized that cocaine increases adverse drug:drug interactions and substance-mediated damage at the BBB during ART treatment. We used our in vitro model of the human BBB to assess the extravasation of three ART drugs, emtricitabine (FTC), tenofovir (TFV), and dolutegravir (DTG), in the presence or absence of cocaine. BBB integrity, permeability, drug transporters, metabolizing enzymes, and their regulating transcription factors, such as the pregnane-x receptor (PXR) and constitutive androstane receptor (CAR), were evaluated to determine the mechanisms by which cocaine impacts ART availability. We discovered that cocaine selectively increased extravasation of FTC across the BBB while decreasing that of TFV. Surprisingly, cocaine did not breach the BBB, but instead selectively decreased PXR and transporter expression and activity in endothelial cells of the BBB. Additionally, increased cytochrome P450 3A4 (CYP3A4) enzymatic activity coincided with decreased expression following cocaine exposure. Our findings suggest that cocaine use in people with HIV may limit ART efficacy in the brain by dysregulating drug-transport and metabolism at the BBB. Additionally, we introduce awareness of the clinical ramifications of comorbid substance use in HIV cure strategies, specifically for viral eradication in the brain.

Disclosures: R. Colón-Ortiz: None. **S. Knerler:** None. **A. Mercado:** None. **A. Price:** None. **J. Rosado-Franco:** None. **H. Wilkins:** None. **D.W. Williams:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

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FAPERJ grant SEI-260003/006875/2021
FAPERJ grant SEI-260003/004942/2021
FAPERJ Fellowship grant E-26/201.875/2020

Title: Comparison of cerebrospinal fluid biomarkers in patients with severe COVID-19 neurological outcomes and Alzheimer's disease

Authors: *F. BARROS-ARAGÃO[1,3], T. PINHEIRO[1], T. PEIXOTO PINTO[1], B. VANDERBORGHT[1], N. BRAGA[1], G. B. DE FREITAS[3], G. DE FREITAS[1], F. BOZZA[1], E. C. RODRIGUES[2], C. BRANDAO[5], P. E. MATTOS[2], F. SUDO[1], F. TOVAR-MOLL[1], F. DE FELICE[4,1];
[1]D'Or Inst. for Res. and Educ., Rio de Janeiro, Brazil; [2]D'Or Inst. for Res. and Educ., Rio De Janeiro, Brazil; [3]Ctr. for Neurosci. Studies, [4]Queen's Univ., Kingston, ON, Canada; [5]Neurolife, Rio de Janeiro, Brazil

Abstract: Background. COVID-19 induces acute and persistent neurological symptoms. Links between COVID-19 neurological disease and Alzheimer's disease (AD) have been hypothesized because neuroinflammation plays a significant role in both diseases. In AD, neuropathological changes develop years before symptoms, and it is unknown if COVID-19 patients with neurological disturbance present AD-related molecular alterations. A better understanding of possible molecular links between COVID-19-induced neurological disease and AD would lead to improved patient follow-up and prevention of possible late-onset disease. Here, we aim to compare early AD biomarkers in controls, COVID-19 patients with neurological symptoms, amnestic mild cognitive impairment (aMCI), and AD patients. We also aim to correlate AD-related biomarkers with systemic and neuro-inflammation markers in COVID-19 patients.
Methods. We analyzed cerebrospinal (CSF) biomarkers of neuroinflammation (interleukin-6 (IL6), amyloid-beta proteinopathy (Aβ42/40), phosphorylated Tau (pTau181), and the neurodegeneration biomarker total Tau in Brazilian controls (n=30), COVID-19 patients with neurological symptoms (n=31), aMCI (n=20), and AD patients (n=21). Comparisons were corrected by possible sex and age confounding effects. The CONEP/Brazilian Ministry of Health and the IDOR Committee for Research Ethics approved the study protocol and all amendments, #29496920.8.0000.5262; #41576620.7.0000.5249.
Results. We found that severe COVID-19 patients presented elevated CSF Tau compared to controls, comparable to AD patients. However, we did not find changes in CSF Aβ42/40, pTau-181/Aβ42, or Tau/Aβ42 ratios in COVID-19 patients compared to controls. Compared to mild diseased patients, severe COVID-19 patients presented lower CSF Aβ42 and higher Tau, Tau/Aβ42, and pTau181/Aβ42. In COVID-19 patients, increased CSF pro-inflammatory cytokine IL6 and early AD biomarkers correlated with systemic inflammatory index (SII).
Interpretation. Our findings reveal possible ongoing neurodegeneration in COVID-19 neurological disease but no specific biomarker alterations related to AD pathology. CNS AD-related biomarker levels in COVID-19 patients changed in association with disease severity and

systemic inflammation. Considering that inflammation may persist post-COVID, our findings urge assessing possible AD-related biomarker changes in COVID-19 survivors with lingering symptoms.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.133/LBA128

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: 5 F31 MH 131486-02

Title: Astrocytes exhibit counter-productive inflammatory responses in a model of CNS HIV infection

Authors: *J. GESUALDI[1], K. L. JORDAN-SCIUTTO[2];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Dept Oral Med., Univ. of Pennsylvania, Lansdale, PA

Abstract: HIV currently infects over 38 million people worldwide. Despite the high efficacy of antiretroviral therapies, HIV persists via transcriptionally silent latent infection and long-lived viral reservoirs in tissue sites such as the central nervous system (CNS). Viral persistence in the CNS leads to sustained neuroinflammation, which in turn may play a role in the development of a spectrum of deficits in memory, learning, and/or motor functions referred to as HIV-associated neurocognitive disorders (HAND), observed in 40% - 50% of people living with HIV (PLWH). Microglia, the resident macrophages of the CNS, are a key population of HIV-susceptible cells in this niche. Astrocytes are also impacted by HIV infection through abortive integration of the viral genome, PRR sensing of viral components, and through indirect activation by neighboring infected cells. Because microglia are challenging to model in vitro, the dynamics of HIV replication in microglia as well as the immune response of microglia and neighboring astrocytes to HIV infection remain poorly understood. Using human induced pluripotent stem cell-derived microglia (iMg) and astrocytes (iAst) we show that HIV readily replicates in iMg but not iAst. During HIV infection, microglia fail to activate canonical intracellular anti-viral pathways or secrete pro-inflammatory cytokines, likely due to the capacity of HIV to evade detection by innate immune sensors. Surprisingly, we have shown that coculture of iAst with iMg leads to robust increases in HIV replication, suggesting that iAst act to facilitate HIV replication in iMg. iAst exposed to infected iMg produce the pro-inflammatory cytokines TNFα and IL-6. These

cytokines are known to activate NF-κB dependent transcriptional regulation, which in turn can induce transcription of the integrated HIV genome. Indeed, pharmacological inhibition of NF-κB signaling robustly reduces HIV replication in iMg-iAst cocultures. Overall, our data suggest that astrocyte-driven neuroinflammation can promote NF-κB signaling and replication of HIV in microglia. Given the associations of IL-6 and TNFα with increased neurocognitive injury in PLWH, this signaling axis may be a viable target of adjunctive immunotherapies for individuals susceptible to HAND.

Disclosures: J. Gesualdi: None. **K.L. Jordan-Sciutto:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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Program #/Poster #: LBA003.134/LBA129

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R21DA060085
NIH R01DA050528
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NIH R21MH12223
NIH R01HL126559

Title: Altered miRNA Expression in Methamphetamine and HIV-exposed Mice: Implications for Adult Neurogenesis

Authors: K. RAVISHANKAR[1], D. LEVITIS[1], M. TOBOREK[2], ***M. PARK**[2];
[1]Univ. of Miami, Coral Gables, FL; [2]Biochem. and Mol. Biol., Univ. of Miami Sch. of Med., Miami, FL

Abstract: Methamphetamine (METH) exacerbates HIV-induced deficits in adult neurogenesis, yet the underlying mechanisms remain poorly understood. In the subventricular zone (SVZ), numerous neuroblasts migrate to the olfactory bulb (OB) along the rostral migratory stream (RMS) within a tightly regulated neurovascular microenvironment. This study investigates the mechanisms by which METH and HIV alter this microenvironment and affect neuroblast migration in the SVZ. C57BL/6j mice were exposed to chronic METH and/or infected with a chimeric HIV-NDK (EcoHIV). Neural progenitor cells (NPCs) were isolated from the SVZ, followed by mRNA and miRNA sequencing analyzed via DESeq2 for differential expression. We identified 204 functional pathways related to differentially expressed genes, with 152 pathways uniquely affected by METH and HIV treatment. Additionally, 22 genes related to cell migration and motility were differentially expressed. We also identified 13 miRNAs with significantly altered expression post-METH and HIV treatment (false discovery rates (FDR) <0.1). Among these, miR-322-5p (the human equivalent of miR-424) was significantly elevated,

and miR-21a-5p was significantly reduced in the METH and HIV co-treated group. Reducing miR-21a-5p or miR-424-5p expression in ReNcells, human progenitor cells, significantly impaired their CXCL12/SDF-1 induced transmigration, similar to observations in METH and HIV co-exposed ReNcells in vitro. However, inhibiting these miRNAs did not affect ReNcell proliferation or differentiation. These findings suggest that miR-21a-5p and miR-424-5p are crucial for NPC migration in adult neurogenesis, which is disrupted by METH exposure and HIV infection.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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Program #/Poster #: LBA003.135/LBA130

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DBT Grant BT/PR44439/MED/29/1582/2021

Title: Novel Insights into molecular pathways of SARS-CoV-2 mediated neuronal damage - implication in Long COVID cases

Authors: *P. SETH;
Natl. Brain Res. Ctr., Manesar, INDIA, India

Abstract: Novel Insights into molecular pathways of SARS-CoV-2 mediated neuronal damage -implication in Long COVID cases
Archana Mehta, Rituparna Chaudhuri, Ajay Pal, Himali Arora, Imam Faizan, Dharmender Gupta, Sudhanshu Vrati, Tanveer Ahmed and Pankaj Seth
Neurological manifestations associated with the SARS-CoV-2 virus in COVID-19 survivors are a major concern worldwide. An understanding of detailed molecular mechanism of virus-mediated neuronal damage are warranted for designing potential therapies. In current study, we screened the structural and non-structural SARS-COV2 viral proteins for cell death, and found that Orf6 protein, an accessory protein of the virus known for inhibiting nuclear export and blocking host cell's interferon response, causes maximum neuronal death of primary human neurons. Upon further investigations, we found that in Orf6 expressing neurons, necroptotic cell death pathway was activated among other coronavirus-mediated cell death pathways (apoptosis, pyroptosis and autophagy). To validate this, we infected primary cultures of human neurons with the whole virus and determined cell death mechanisms. Further we used histological staining techniques for checking the expression of necroptotic cell death markers in the post mortem brain sections of COVID-19 patients. In addition to this, our studies revealed that the overexpression of Orf6 leads to mitochondrial perturbation and dysfunction in neurons via

interaction with the host MTCH1 (Mitochondrial Carrier Homolog1) and opening of MPTP (Mitochondrial Permeability Transition Pore Complex). We further attempted to rescue the neuronal death and mitochondrial dysfunction by using specific inhibitors of necroptotic pathway markers and shRNA-mediated knockdown of host MTCH1 levels and have some interesting findings. In nutshell our findings reveal novel molecular mechanisms for neuronal death in COVID-19 patients, which may help us in better management of neurological manifestations.

Disclosures: P. Seth: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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Program #/Poster #: LBA003.136/LBA131

Topic: C.08. Ischemia

Support: CONDA 3P20GM130447-04S1
NIGMS CoBRE 1P20GM139762

Title: Developing Small Molecule TREM1 Inhibitors as Therapeutic Treatment for Global Cerebral Ischemia

Authors: *P. L. TIWARI[1], H. KIM[4], V. DUNCAN[5], R. URQUHART[2], R. NAYAKWADI[6], P. ABEL[1], G. JADHAV[1], J.-Y. HWANG[3];
[1]Pharmacol. and Neurosci., [2]Pharmacol. & Neurosci., Creighton Univ., Omaha, NE; [3]Pharmacol. and Neurosci., Creighton Univ., Elkhorn, NE; [4]Pharmacol. and Neurosci., Creighton Univ. Sch. of Med., Omaha, NE; [5]Col. of St. Mary, Omaha, NE; [6]Millard Publ. Sch., La Vista, NE

Abstract: Global cerebral ischemia is a severe form of stroke often caused by cardiac arrest leading to cognitive deficits or death. While emergency treatments of cardiac arrest focus on restoring cardiac function and blood flow, an effective treatment for neurodegeneration and cognitive deficits remains an unmet medical need. TREM1 is a membrane immune receptor expressed on the surface of myeloid-derived cells where it magnifies the innate proinflammatory immune response. Our recent studies showed that global ischemia activates TREM1 and neuroinflammation in the hippocampal CA1 in rats. Additionally, TREM1 inhibition by the known peptide LR12 demonstrated neuroprotection against ischemic insult. Therefore, we hypothesized that TREM1 inhibition could be a new therapeutic strategy. Current inhibitors, however, have limitations as potential drug candidates due to their poor cell permeation, short half-life and mutagen toxicity. To address these issues and develop small molecule TREM1 inhibitors, we first identified an N^4-(amino-substituted)-*N*-substituted-benzenesulfonamide pharmacophore (GJ079) in molecular docking of 80K molecules to the hTREM1 (PDB: 1SMO)

crystal structure. Surface plasmon resonance (SPR) analysis confirmed GJ079's affinity to TREM1 with a Kd of 14.3 μM. Next, we examined the effect of GJ079 on global ischemia-induced neuronal death in rats. Administration of GJ079 attenuated neuroinflammation and neuronal death, indicating its neuroprotective effect and therapeutic potential. Therefore, we further optimized a series of chemical reactions utilizing microwave and multistep intermediate syntheses protocol to improve GJ079's solubility and affinity. A total of 39 GJ079 analogs were synthesized in four series: Series 1 (14 molecules) required an additional aromatic-acetamido substitution on a thiazolyl group containing nitrogen of *4*-amino-*N*-(thiazol-*2*-yl)benzenesulfonamide, whereas series 2 (21 molecules) involved an aromatic-acetamido substitution on the N^4- aromatic amino group. Series 3 (3 molecules) featured *ortho, meta,* and *para fluoro* substitution on the end phenyl ring of GJ079, whereas Series 4 (1 compound) involved the replacement of the *2*-thiazolyl ring with another hetero aromatic ring in the GJ079 molecule. At least one analog, the para-fluoro alteration on the phenyl ring in GJ079 showed increased TREM1 affinity (Kd=4.8 nM) and solubility. We anticipate additional potent TREM1 inhibitor analogs with improved pharmacokinetic profiles. We will use cell based TREM1 activity assays to confirm the TREM1 inhibitory efficacy of these analogs. Lead molecules will be tested in a global ischemia *in vivo* animal model.

Disclosures: P.L. Tiwari: None. **H. Kim:** None. **V. Duncan:** None. **R. Urquhart:** None. **R. Nayakwadi:** None. **P. Abel:** None. **G. Jadhav:** None. **J. Hwang:** None.

Late-Breaking Poster

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Program #/Poster #: LBA003.137/LBA132

Topic: C.08. Ischemia

Support: National Heart Lung and Blood Institute of the National Institutes of Health, Grant R25HL147665
National Institute of Neurological Disorders and Stroke of the National Institutes of Health, Grant 1R01NS131484

Title: Ras/raf/mapk pathway signaling supports neural regeneration following experimental focal ischemia

Authors: Y. GRIEGO[1], R. MARQUEZ-ORTIZ[2], N. AICH[2], *K. RODGERS[2,1];
[1]CURIOUS Program, [2]Cell. Biol. and Anat., LSU Hlth. Shreveport, Shreveport, LA

Abstract: Introduction: Ischemic stroke is a destructive neurological disease that contributes to long-term disability in millions of stroke survivors. While stroke is typically thought of as a disease of the elderly, it can occur at any age in life. Although the young brain is thought to be

more resilient, stroke in the pediatric population can be devastating due to delays in diagnosis or misdiagnosis, resulting in death or disabilities that can stretch across a lifespan. Still, it is well-documented that the young brain has an extraordinary degree of plasticity that promotes improved post-ischemic functional recovery compared to adults. Using a pediatric model of stroke in juvenile mice, we found a remarkable neural regenerative response in juvenile mice compared to adult at 30d, which was coupled with improved post-ischemic functional recovery (motor function and EEG). Brain-derived neurotropic factor (BDNF) has the capacity to repair damaged neurons and restore functioning to the injured brain. Mature BDNF binds to and activates its specific receptor TrkB, and the phosphorylation of this receptor activates downstream neural signaling pathways, including the RAS-MAPK pathway. This pathway is known to improve neuronal proliferation, differentiation, and survival after stroke. As optimized therapies for pediatric stroke survivors have not yet been identified, understanding the mechanisms underlying juvenile neural regeneration and functional recovery has implications for improving stroke outcomes in pediatric and adult/aging populations. **Methods:** Experimental ischemic stroke (MCAO) was performed in juvenile (P21-25) and adult (8-10 weeks) mice. Then, the RAS-MAPK pathway was examined at 72hr, 7d, and 30d after ischemia using immunohistochemistry, gene expression profiling, and western blots. **Results and Conclusions:** Excitingly, RAS-MAPK signaling appears to be beneficial for post-ischemic neural regeneration in juveniles and detrimental in adults, revealing opposing age-dependent effects. In adults, our findings suggest that RAS-MAPK signaling is dysregulated and pathological, most likely due to the cell types by which this pathway is activated, as we found that BDNF was released by neurons in juveniles and by astrocytes in adult mice. Neuronal BDNF supports neural survival, axon/dendrite outgrowth, synaptogenesis, and synaptic remodeling. However, astrocytic BDNF is pathological with ample experimental evidence implicating astrocytic BDNF deficits in several neuropathologies. Following stroke, astrocytic BDNF may represent a promising target for improving adult neural regeneration and post-ischemic functional recovery.

Disclosures: Y. Griego: None. **R. Marquez-Ortiz:** None. **N. Aich:** None. **K. Rodgers:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.138/LBA133

Topic: C.08. Ischemia

Support: RO1 NS106901
P20 GM109089

Title: Metabolic Interventions Influencing Recovery from Spreading Depolarization

Authors: *A. CABADA-GOMEZ[1], R. LUDWIGSEN[2], J. L. SEIDEL[2], C. W. SHUTTLEWORTH[2];
[1]Univ. of New Mexico Dept. of Neurosciences, Albuquerque, NM; [2]Univ. of New Mexico, Albuquerque, NM

Abstract: Spreading depolarization (SD) is implicated as a key contributor to secondary injury expansion after stroke, traumatic brain injury and other disorders. Promising therapeutic interventions include ketamine and related antagonists that limit the incidence of SD in injured patients. However complimentary approaches that improve neuronal recovery after SD could be valuable in conditions where SDs persist. The extended ionic loading of SD is extremely metabolically demanding and likely underlies deleterious consequences of SD in vulnerable tissues. We are investigating effects of agents that modify metabolic capacity on recovery from SD. SD was generated by localized KCl microinjection in the CA1 hippocampal region of murine brain slices, and monitored with optical and extracellular microelectrode methods. Recordings in nominally healthy conditions were compared with metabolically restricted conditions as a model for ischemic penumbra. Pre-exposure with a combination of ribose (1mM) and adenine (50µM; RibAde) was used to support the ATP levels via the purine salvage pathway (Neurochem Res 44 (2019) 661-5). In both healthy and vulnerable conditions, RibAde reduced the duration of SD and significantly improved recovery of excitatory postsynaptic potentials (epsps) after SD. In contrast, the nitric oxide donor 2-(N, N-Diethylamino)-diazenolate 2-oxide (DEANO/NO, 1-300 µM) caused a concentration-dependent suppression of mitochondrial metabolism, as assessed from NAD(P)H/flavoprotein autofluorescence imaging. Low concentrations of DEANO also sensitized slices to effects of SD, leading to persistent epsp suppression. Propagation of SD was also modified by NO, as demonstrated by increased propagation rate with a NOS inhibitor (L-NNA, 100 µM) and decreased rates with DEANO. These results suggest that partial inhibition of mitochondrial cytochrome oxidase in neurons by nitric oxide donors could contribute to deleterious outcomes following SD. This may offset beneficial effects of nitric oxide donors on SD threshold that have previously been suggested. Conversely, results with RibAde suggest that support of the purine salvage pathway could provide a useful adjunct approach to improve neuronal recovery after SD.

Disclosures: A. Cabada-Gomez: None. **R. Ludwigsen:** None. **J.L. Seidel:** None. **C.W. Shuttleworth:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.139/LBA134

Topic: C.08. Ischemia

Title: Neuroprotective Effects of a Novel Anti-inflammatory Compound AD-16 in Neonatal Hypoxic-Ischemic Brain Injury and Adult Ischemic Stroke

Authors: *Z. LUO[1], H.-S. SUN[1], Z.-P. FENG[2];
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Dept. of Physiol., Univ. of Toronto Collaborative Program In Neurosci., Toronto, ON, Canada

Abstract: Ischemic stroke is a leading cause of death and disability worldwide. Similarly, in newborn infants, hypoxic-ischemic (HI) brain injury poses significant threats to neonatal mortality and neurological morbidity. Current treatments possess narrow therapeutic windows and limited effectiveness, especially in severe cases. Therefore, there is a pressing need to identify novel therapeutic strategies. Neuroinflammation is a prominent feature in ischemic brain injury and contributes to both disease progression and recovery. The purpose of this study is to evaluate the effects of a novel anti-inflammatory compound, AD-16, on primary astrocytes and neurons under oxygen-glucose deprivation (OGD) in vitro and in mouse models of neonatal HI brain injury and adult ischemic stroke in vivo. We demonstrated that AD-16 protected against OGD-induced cell injury. In the neonatal HI model, a single dose of AD-16 (1 mg/kg) significantly reduced brain infarction volume and improved neurobehavioral outcomes, with a therapeutic window extending up to 6 hours after injury onset. Moreover, repeated daily administration of AD-16 significantly reduced the mortality rate of the animals while preserving whole-brain morphology. Molecular analysis further revealed that AD-16 potentially attenuated brain injury by regulating neuronal survival, apoptotic, and neuroinflammatory signaling pathways. In the transient middle cerebral artery occlusion (tMCAO) model, AD-16 (1 mg/kg) significantly attenuated brain infarction, blood-brain barrier breakdown, and cerebral edema at 24 hours following ischemic-reperfusion, with improved neurobehavioral outcomes through the regulation of pro- and anti-neuroinflammatory pathways. Our results suggest that AD-16 offers promising therapeutic efficacy in attenuating the progression of ischemic brain injury, with the potential to protect against associated mortality and morbidity.

Disclosures: Z. Luo: None. **H. Sun:** None. **Z. Feng:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.014/LBA14

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

Support: BrightFocus Foundation Grant A2021036S
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NEOMED institutional funds

Title: Sex chromosomes and gonads modify microglial-mediated pathology in a mouse model of Alzheimer's disease

Authors: *E. G. REED[1], B. T. CASALI[1], L. LIN[1], O. BENEDICT[1], H. ZUPPE[2];
[1]Pharmaceut. Sci., Northeast Ohio Med. Univ., Rootstown, OH; [2]Biomed. Sci., Kent State Univ., Kent, OH

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder disproportionally affecting women with sex-specific disease manifestations and therapeutic responses. Microglial-mediated inflammation occurs in response to and perpetuates disease processes, and underlying sex differences in microglia may contribute to the sex biases. Both sex chromosomes and gonad-derived hormones shape immune responses, but their contribution to immune-mediated mechanisms underlying the sex bias in AD is unclear. Crossing the Four Core Genotype (FCG) model to separate sex chromosome and gonad-derived hormone effects to the 5xFAD model, we found the sex chromosome complement impacted microgliosis, neuroinflammation, plaque burden and neuritic dystrophy. Modification of pathology was largely correlated with microgliosis, and sex chromosomes and gonad-derived hormones influenced plaque remodeling and microglial CD11c expression. Our study demonstrates the complex interplay between sex chromosomes and hormones on microglia during AD.

Disclosures: E.G. Reed: None. **B.T. Casali:** None. **L. Lin:** None. **O. Benedict:** None. **H. Zuppe:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.140/LBA135

Topic: C.08. Ischemia

Title: Anti-inflammatory actions of functionally engineered extracellular vesicles overexpressing miR-22-3p

Authors: *D. OGBU[1], S. ROTH[2];
[1]Univ. of Illinois at Chicago, Chicago, IL; [2]Anesthesiol., Univ. of Illinois, Chicago, IL

Abstract: Background: Central retinal arterial occlusion (CRAO) amplifies cellular damage characterized by inflammation of retinal cells like microglia (MG) by upregulating pro-inflammatory mediators. Extracellular vesicles (EVs) derived from dental pulp stem cells (DPSC EVs) are reportedly neuroprotective against MG inflammation, yet the mechanisms contributing to anti-inflammatory actions are unknown. Our group showed that preconditioned EVs provide enhanced protection against cellular inflammation, possibly due to the microRNA (miR) within EVs. Following this principle, we profiled miRs within preconditioned DPSC EVs and chose to

overexpress miR-22-3p in EVs due to its increased intensity among preconditioned EVs. Additionally, miR-22-3p is well known for its anti-inflammatory actions in microglia. Here, we characterize the anti-inflammatory role of DPSC EVs overexpressing miR-22-3p, termed functionally engineered EVs (FEE-22). We hypothesize that FEE-22 will reduce inflammation in microglia superior to native DPSC EVs (N-EV).

Methods: DPSC EVs were transfected with a lentiviral system containing miR-22-3p. Following stable selection with puromycin, we confirmed the overexpression of miR-22-3p in DPSCs and EVs using RT-qPCR. DPSCs were cultured in serum-free media for 48 h to isolate EVs and then centrifuged (3,000 x g) at 4C for 30 min to clear cellular debris. EVs are isolated using ExoQuick-TC EV precipitation solution overnight and resuspended in PBS. First, EVs were categorized for size and concentration via nanoparticle tracking analysis (NTA) and characterized for EV membrane markers (CD63 and CD81) via Western. To measure anti-inflammatory capacity, SIM-A9 murine microglia were stimulated with "TII" (10 ng/uL TNF-α, 10 ng/uL IL-1β, and 5 ng/uL IFNγ) for 6 h, rinsed with PBS, then treated with EVs for 18 h. Levels of pro-inflammatory mediators, including nitrite, will be assessed via Griess reagent, and expression of iNOS will be measured via immunoblotting. Pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 will be measured via ELISA. A one-way ANOVA will be used for statistical analysis.

Results: We have successfully generated FEE-22, as confirmed by RT-qPCR. NTA illustrates that N-EV and FEE-22 have the same 1.6 x 107 particles/ mL concentration and fall within the 50-150 nm range. Western shows N-EV and FEE-22 express CD63. Uncovering the anti-inflammatory process of FEE-22 and N-EV is ongoing.

Conclusion: Following the generation FEE-22, current results show that N-EV and FEE-22 have the same size and concentration and express the same EV markers. We are working to discover the anti-inflammatory capabilities of FEE-22 in MG.

Disclosures: D. Ogbu: None. **S. Roth:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

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Topic: C.09. Stroke

Support: NIH Grant RF1NS113278
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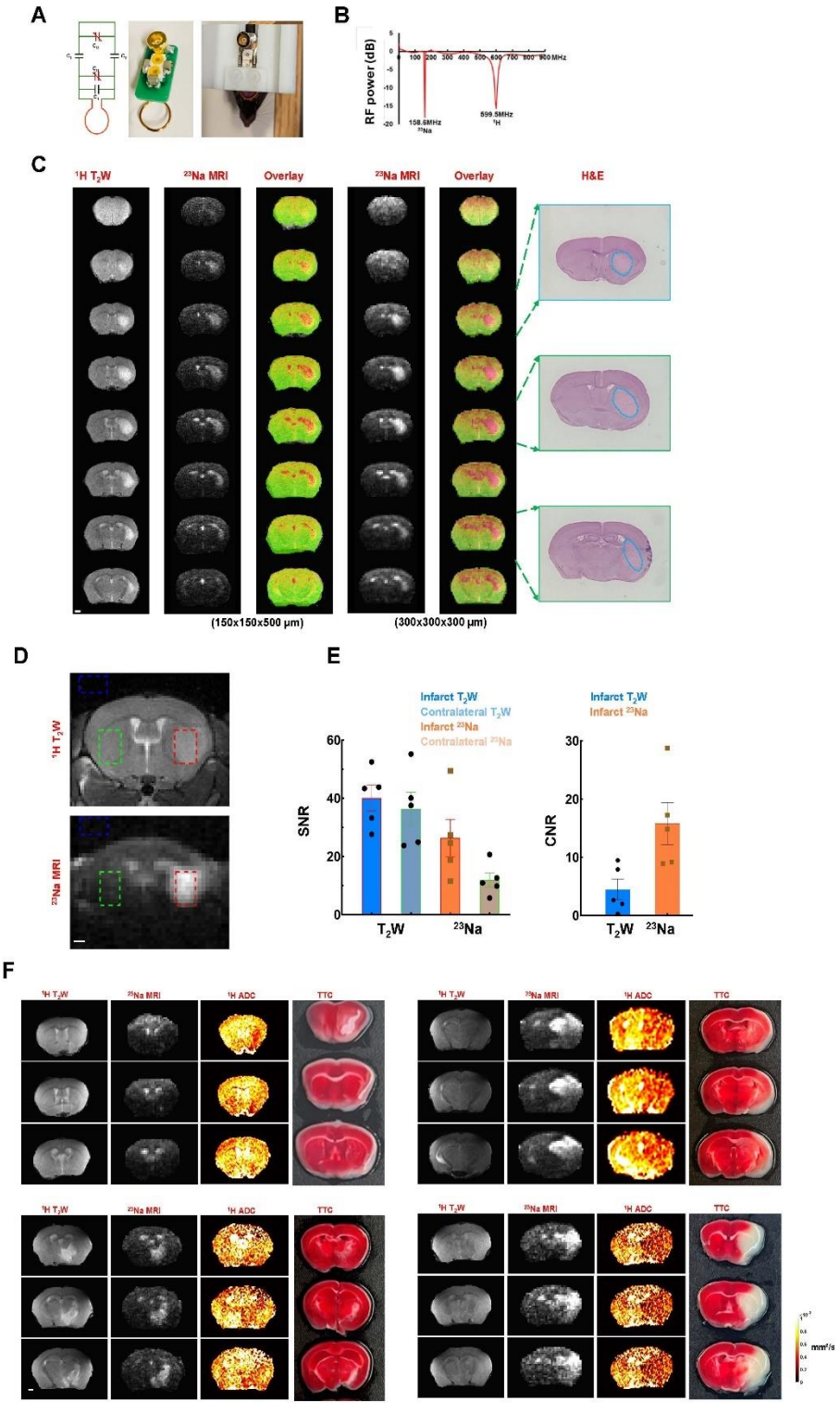
Title: High spatial resolution ^{23}Na-MRI for ischemic brain injury detection

Authors: *Y. JIANG[1], X. A. ZHOU[1], T. IMAI[1], D. Y. CHUNG[1,2], L. HAWLEY[1], C. AYATA[1,2], D. HIKE[1], **X. YU**[1];
[1]Radiology, [2]Neurol., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: We have established a high-resolution sodium (^{23}Na) MRI platform based on our high-field 14T preclinical scanner. The signal-to-noise ratio (SNR) head-implanted RF coil (<2.5g) is ~ 8 times higher with our 14T scanner than the conventional Bruker 4 array coil (**Fig 1A**). A dual-tuned was implanted for the acquisition of proton (^{1}H) based T_2-weighted (T_2W) anatomical and diffusion-weighted imaging (DWI) maps and ^{23}Na MRI from the same animal (**Fig 1B)**. The ^{23}Na-MRI was performed to map the brain lesion in mice with acute r middle cerebral artery occlusion (MCAO) induced ischemic stroke within the first 4 hours of stroke induction. This implantable double-tuned ^{1}H/^{23}Na RF coil can improve the SNR with an impressive 150×150 μm^2 or 300×300 μm^2 in-plane brain-wide ^{23}Na-based MRI readout for ischemic stroke (**Fig 1C)**, demonstrating a superior SNR and spatial resolution. The hyperintensity is detected in the lesioned brain areas with ^{23}Na-MRI, presenting a significantly enhanced MRI signal (**Fig 1D**). The SNR of the ^{23}Na-enhanced signals remained lower than the ^{1}H-based rapid imaging with refocused echoes (RARE) images, while the contrast-to-noise ratio (CNR) from hyperintense regions of interest (ROIs) is higher than the T_2-weighted images (**Fig 1E**). We were able to observe high CNR ^{23}Na (15.80 ± 3.20) and a significant ^{23}Na signal increase with the damaged cortical/subcortical lesions compared to contralateral ROIs. Infarct regions can be well-identified in the increased signals in ^{23}Na images, which could also be detected in apparent diffusion coefficient (ADC) maps, indicating water restriction in the core of brain lesions. Both ^{23}Na-MRI and ADC maps revealed more robust brain lesions in comparison with the TTC staining across different slices (**Fig 1F**). **Conclusion:** We optimized the implanted double-tuned ^{1}H/^{23}Na RF coils for high-resolution ^{23}Na-based and T_2-weighted ^{1}H MRI readout of early brain injuries after the stroke induction. We observed distinct temporal and spatial features of the ^{23}Na dynamic with high sensitivity for brain lesion detection.



Disclosures: Y. Jiang: None. **X.A. Zhou:** None. **T. Imai:** None. **D.Y. Chung:** None. **L. Hawley:** None. **C. Ayata:** None. **D. Hike:** None. **X. Yu:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.142/LBA137

Topic: C.09. Stroke

Support: This work was supported by Relmada Therapeutics, Inc., Coral Gables, Florida.

Title: Chronic non-psychedelic psilocybin therapy promotes visual rehabilitation in mice post-occipital stroke

Authors: S. NASINI[1], B. BARZON[1], M. CAMBIAGHI[2], S. DE MARTIN[1], A. MATTAREI[1], M. PAPPAGALLO[3], P. MANFREDI[4], ***S. COMAI**[1];
[1]Univ. of Padova, Padova, Italy; [2]Dep. Neurosci., Univ. of Verona, Verona, Italy; [3]Relmada Therapeutics, Inc, NYC, NY; [4]Relmada Therapeutics, Inc, Coral Gables, FL

Abstract: Stroke is a leading cause of death and a major contributor to serious disability worldwide. Occipital stroke, affecting the brain's visual processing centers, often results in significant visual deficits. These strokes are typically unilateral, impacting one hemisphere of the visual cortex and leading to pronounced impairments in visual perception and processing, drastically affecting the quality of life. There are currently no treatments promoting visual restoration, prompting exploration of novel therapies. Psychedelics like psilocybin are known for inducing neuroplastic changes and stimulating neurogenesis, potentially offering therapeutic benefits in neurological conditions. This study investigates the effects of a chronic treatment (45 days) with a low non-psychedelic dose of psilocybin (0.05 mg/Kg) on visual recovery in adult (2-3-month-old) mice subjected to photothrombotic unilateral stroke at the visual cortex. Visual abilities were evaluated after 45 days of psilocybin post-stroke treatment using the Visual Cliff test, the Looming test, and the Cued Morris Water Maze test. Additionally, lesion size and dendritic spine density in the perilesional and contralateral regions were assessed. In the Visual Cliff test, mice with unilateral visual cortex stroke treated with psilocybin exhibited a significant higher speed when travelling in the depth/unsafe zone compared to mice treated with saline, indicating potential better visual depth discrimination abilities. In the Looming test, the response latency to the looming visual stimulus was significantly longer in stroke mice treated with saline compared to control mice, but no difference was observed between control mice and psilocybin-treated stroke mice. In the Cued Morris Water Maze test, the number of goals reached on the first day was significantly higher in control and psilocybin-treated stroke mice compared to saline-treated stroke mice. These behavioral changes were accompanied by a significant reduction in lesion volume after 45 days of psilocybin treatment compared to the initial volume (24 hours post-stroke). Additionally, there was a significant increase in spine density in both perilesional and distal regions in psilocybin-treated mice compared to vehicle-treated mice. Overall, these preliminary experiments indicate that a 45-day treatment with 0.05 mg/Kg psilocybin, starting 24

hours after inducing a photothrombotic visual cortex stroke in mice, is well tolerated and may improve visual abilities to levels similar to those of non-stroke mice.

Disclosures: S. Nasini: None. **B. Barzon:** None. **M. Cambiaghi:** None. **S. De Martin:** 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.; MGGM LLC. F. Consulting Fees (e.g., advisory boards); Neuroarbor LLC. **A. Mattarei:** 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.; MGGM LLC. F. Consulting Fees (e.g., advisory boards); Neuroarbor LLC. **M. pappagallo:** A. Employment/Salary (full or part-time):; Relmada Therapeutics, Inc. **P. Manfredi:** A. Employment/Salary (full or part-time):; Relmada Therapeutics, Inc. **S. Comai:** 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.; MGGM LLC. F. Consulting Fees (e.g., advisory boards); Neuroarbor LLC.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.143/LBA138

Topic: C.09. Stroke

Support: Chinese Postdoctoral Science foundation Grant 2020M67229
Henan Research grant for young scientists No.
The national foreign expert program QN2022026001L

Title: Core circadian clock genes "Clock and Per2" can regulate intracerebral hemorrhage in the aspects of progression and recovery

Authors: *S. KHAN;
The Second Affiliated Hosp. of Zhengzhou Univ., Zhengzhou, China

Abstract: Intracerebral hemorrhage (ICH) is the most debilitating type of stroke, which is caused by bleeding within the brain. ICH survivors have been known to experience sleep disorders, time-dependent severity of symptoms, immunological dysregulation, and disturbed metabolic functions, which are known to be regulated by the circadian clock. The rhythmicity of the circadian system is 24 hours, driven by transcription-translation feedback loops of circadian clock genes. Targeting clock machinery may help accelerate the ICH recovery process. We have investigated the association of circadian rhythms (core clock genes) with the ICH onset,

progression, and recovery and tested the impact of novel MyD88 inhibitory peptide (MIP2) against ICH. Disruption of the circadian clock caused the alteration of genes associated with neurological disease in different brain regions of mice, indicating that circadian clock disruption increases the risk of neurological diseases. Genes related to the circadian clock, especially *Clock* and *Per2* were found to have connections with ICH. Sleep piezoelectric test results revealed that ICH caused a decrease in sleep bout number during daytime and increased the length of sleep bout during nighttime. The wheel run activity test results indicated that ICH significantly increased the period (longer free period), while under light conditions (LL) ICH mice showed a long period of about 27.5 h unlike control mice, which lost rhythm. knockout (KO) conditions (Clock) by inducing ICH in *Clock* KO and *Per2* KO mice in comparison with the ICH model of wild-type mice and normal saline as control. Results based on behavioral tests, MRI scans, Hematoxylin and Eosin (H&E) staining, Immunohistochemical and Immunofluorescent staining results showed that in the case of *Clock* KO condition, the severity of ICH was increased and the recovery from ICH was delayed as compared to ICH model of wild type mice. Similar results were obtained in the case of the *Per2* KO mice model. Our results have demonstrated that MIP2 holds great potential for treating ICH, by inhibiting the activation of microglia/macrophages and neutrophil infiltration. Overall, this study provides a new insight into the role of circadian clock disruption in the recovery and progression of ICH, which was further demonstrated by animal experiments on the *Clock* and *Per2* KO mice model. ICH can dysregulate circadian rhythm, while disrupted circadian clock can increases the severity and delays the recovery of ICH. MIP2 can be a potential treatment option for ICH treatment based on its anti-inflammatory effect.

Disclosures: S. Khan: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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Topic: C.09. Stroke

Support: NIH Grant 1R01AG083164
NIH Grant R21NS127177
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NIH Grant R01NS107365

Title: Ablation of the choroid plexus decreases hippocampal neurogenesis under physiological conditions and after ischemic stroke

Authors: *A. TARANOV[1], A. LUO[2];
[1]Neurosci. Grad. Program, [2]Mol. and Cell. Biosci., Univ. of Cincinnati, Cincinnati, OH

Abstract: Harnessing adult neurogenesis, the endogenous neuroreparative process of the adult brain, is an ongoing challenge for therapy of CNS injuries such as ischemic stroke. In the course of adult neurogenesis, neural stem cells (NSCs) proliferate, ultimately producing newly-born neuroblasts (NBs), which become dentate gyrus granule cells in the hippocampus. This process is known to be important for memory formation/maintenance and is involved in neurorepair after ischemic stroke. The choroid plexus (ChP) and cerebrospinal fluid (CSF) produced by it have been shown to control neurogenesis and neuroblast (NB) migration in the subventricular zone, however little is known about the role of the ChP in controlling subgranular zone (SGZ) neurogenesis. To determine the role of ChP/CSF in hippocampal neurogenesis under physiological conditions and ischemic stroke, we used a novel non-invasive ChP ablation mouse model (the ROSA26iDTR mouse line), in which administration of diphtheria toxin (Dtx) induces rapid ChP epithelium cell death and nearly complete loss of CSF volume. We first investigated adult neurogenesis in the SGZ of WT and ChP-ablated mice using immunostaining, and show that loss of ChP/CSF results in markedly reduced population of doublecortin (DCX)+ newly-born NBs, with no effect on proliferating (Ki67+) cell number, under physiological conditions at 4 months of age (3 months post-ablation). Furthermore, at 4 weeks after ischemic stroke (transient middle cerebral artery occlusion), our data show a corresponding decrease in DCX+ NBs, with no change in proliferating cells in the post-stroke SGZ, suggesting a role for the ChP in supporting post-stroke neurogenesis. To determine the possible ChP-derived/CSF-borne factors causing the deficits in SGZ neurogenesis, we collected CSF from WT and ChP-ablated mice at 6-7 mo post-Dtx and performed label-free quantitative proteomics, identifying a decrease in TTR (choroid plexus epithelium secretory marker), and pronounced upregulation of multiple lipid carriers and immune-associated proteins. Determining the role of these CSF-borne factors warrants further investigation in future studies. Our data show that the ChP may be essential in maintaining hippocampal neurogenesis under physiological conditions and after stroke. Thus, identifying the ChP-derived factors facilitating adult neurogenesis could be promising in treatment of diseases associated with reduced hippocampal neurogenesis, such as depression, PTSD, as well as neurodegenerative diseases. Furthermore, modulating the levels of these factors may be useful in therapy of epilepsies characterized by aberrant SGZ neurogenesis.

Disclosures: A. Taranov: None. **A. Luo:** None.

Late-Breaking Poster

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Program #/Poster #: LBA003.145/LBA140

Topic: C.09. Stroke

Support: JST Moonshot R&D (JPMJMS2012)

Title: Integrating electrophysiological and kinematic analyses for a comprehensive clinical assessment of post-stroke hemiplegia hand motor function

Authors: *K. ADACHI[1], T. FUJIMAKI[1], Y. KATAYAMA[2], M. MURAKAMI[4], T. KINOSHITA[1], R. HIROSE[3], S. IWAMA[3], M. HAYASHI[3], J. USHIBA[3];
[1]Grad. Sch. of Sci. and Technol., [2]Dept. of Biosci. and Informatics, [3]Fac. of Sci. and Technol., Keio Univ., Kanagawa, Japan; [4]Dept. of Neurol., Tokyo Women's Med. Univ. Hosp., Tokyo, Japan

Abstract: Effective physical therapy requires a comprehensive assessment of the patient's motor function to determine treatment plans for maximal recovery and to maintain patient motivation. However, current clinical motor function assessment scales are prone to inter-rater variability, are inherently subjective, and suffer from ceiling effects. Furthermore, these scales often lack sensitivity to changes, particularly in patients with severe paralysis. To address these limitations, this study aimed to develop and test the efficacy of a multimodal assessment tool that integrates electrophysiological and kinematic assessments to provide a more objective and reliable evaluation of hand motor function. A software tool for simultaneous recording of electroencephalogram (EEG), electromyogram (EMG), and video footage was originally developed and initially validated on healthy subjects. From this validation, event-related desynchronization (ERD), modulation index, and range of motion (ROM) were selected as the assessment parameters for each modality, respectively. To test the feasibility of clinical application, 7 subjects with post-stroke hemiplegia were recruited. Each subject underwent a 40-minute real-time ERD feedback training session for the paralyzed hand, and pre- and post-training assessments were conducted. Video recordings of the finger extension task from the assessment sessions were used for blinded evaluations using a custom subjective scale. Among the subjects, 2 showed improvement and 5 remained unchanged according to this scale. However, the multimodal assessment revealed improvement in ROM, even in a subject whose subjective score did not change ($p < 0.05$; paired t-test). Additionally, a one-way ANOVA revealed a significant main effect of session on ERD acquisition time ($F = 4.62$, $p < 0.05$), with post-hoc Tukey's HSD test showing a decrease in acquisition time in the alpha band (8-12Hz) after intervention in the same subject. The multimodal tool demonstrated greater sensitivity to changes compared to the subjective scale, suggesting its potential for enhancing the reliability of motor function assessments in rehabilitation. Future research should explore its application across diverse patient populations to further evaluate its efficacy.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.146/LBA141

Topic: C.09. Stroke

Support: Max Planck Society

Title: Quantitative Multi-Parameter MRI Reveals Structural Brain Changes Following Short-Term BCI Intervention in Chronic Stroke Patients

Authors: *K. A. GRIGORYAN[1], K. MUELLER[1], K. J. PINE[1], A. VILLRINGER[1,2,3], B. SEHM[1,4];
[1]Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany; [2]Clin. for Cognitive Neurology, Univ. Hosp. Leipzig, Leipzig, Germany; [3]Ctr. for Stroke Research, Charité Universitätsmedizin Berlin, Berlin, Germany; [4]Neurol., Martin Luther Univ. of Halle-Wittenberg, Halle, Germany

Abstract: There is evidence suggesting brain-computer interface (BCI) systems aid in overcoming the limited functional recovery potential in chronic phase of stroke. However, underlying neural mechanisms driving motor function improvements remain poorly understood. Quantitative multi-parameter mapping (MPM) may elucidate these mechanisms byproviding quantitative estimates of magnetization transfer saturation (MTsat),longitudinal and effective transverse relaxation rates R1 and R2*, and proton density(PD). Particularly, MTsat is sensitive to myelin density, reflectingsubtle changes in tissue composition by quantifying interactions between free waterprotons and macromolecules.
In this study, we employed a longitudinal crossover design with two groups of chronic stroke patients for 4 weeks to allow within-subject (n = 21) and cross-group comparisons. Group 1 (n = 11) underwent a 6-day motor imagery (MI)-based BCI intervention during week 2, while Group 2 (n = 10) received the same intervention during week 3. The BCI intervention consisted of wrist dorsiflexion motor imagery while receiving visual and tactile feedback. MPM scans (MTsat, PD, R1, R2*) were acquired before and after each week. Resulting images were preprocessed using hMRI and CAT12 toolboxes, and VBQ analysis was performed using SPM12. A flexible-factorial model was constructed and fitted to evaluate the effect of the intervention.
Quantitative analysis of MTsat images revealed significant structural changes following BCI intervention. Compared to baseline, combined post-intervention MRIs of both groups showed decreased MT saturation in the contralesional primary motor cortex, SMA, extending into parietal areas associated with sensorimotor integration ($pFWE < 0.002$; cluster size: 14,515 voxels; peak MNI coordinates: 24, -37, 70 mm, additional local maxima:17, -26, 74 mm, -1, -17, 75 mm). MT saturation returned closer to baseline levels 1-week post-intervention.
The decrease in MTsat suggests transient reduction in myelin density in motor areas following BCI intervention. It could indicate increased neuroplasticity, potentially reflecting processes such as axonal remodeling or synaptic reorganization. The return of MTsat values towards baseline may reflect dynamic remodeling, with initial demyelination followed by remyelination as the

brain adapts to the intervention. These findings highlight MTsat's sensitivity to subtle myelin changes and underscore the potential of BCI intervention in promoting neuroplasticity in chronic stroke. Further analyses of R1, R2*, and PD maps will provide a more comprehensive understanding of the mechanisms driving these changes.

Disclosures: K.A. Grigoryan: None. **K. Mueller:** None. **K.J. Pine:** None. **A. Villringer:** None. **B. Sehm:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.147/LBA142

Topic: C.09. Stroke

Support: Joseph and Marie Field Laboratory for Cerebrovascular Research
Vickie and Jack Farber Institute for Neuroscience

Title: Handling associated with repeated behavioral testing and high dose of human bone marrow mesenchymal stem cells (hBM-MSCs)-derived extracellular vesicles (EVs) improve recovery in the transient middle cerebral artery occlusion (tMCAO) model of stroke in male rats

Authors: *Y. GOMEZ GALVEZ[1], M. GUPTA[2], M. KAUR[2], S. FUSCO[3], M. V. PODDA[4], C. GRASSI[5], A. SRIVASTAVA[2], L. M. IACOVITTI[1], E. BLANCO SUAREZ[1];
[1]Neurosci., [2]Med., Thomas Jefferson Univ., Philadelphia, PA; [3]Inst. of Human Physiol., Univ. Cattolica Del Sacro Cuore, Roma, Italy; [4]Neurosci., Univ. Cattolica S. Cuore, Rome, Italy; [5]Dept. of Neurosci., Univ. Cattolica, Rome, Italy

Abstract: Ischemic stroke, caused when a clot disrupts the blood supply to the brain, often causes long-term disabilities and death across the world. The first treatment involves removing the clot to allow reperfusion, but it is effective only in selected patients during a narrow therapeutic window. To improve sensorimotor function, patients may undergo rehabilitation with physical therapy. Recently, bone marrow mesenchymal stem cells (BM-MSCs)-derived extracellular vesicles (EVs) have been shown to be promising in restoring brain damage and function in stroke models, mainly using the intravenous route. Using this administration route, however, causes many of these EVs to accumulate in peripheral organs. In comparison, the non-invasive intranasal route allows EVs to reach the brain, targeting specific ischemic regions. This study aims to understand how intensive handling (exposing animals to multiple sensorimotor behavioral tests) and/or intranasal human BM-MSCs-derived EVs restore neurological function and ischemic damage in the transient middle cerebral artery occlusion (tMCAO) model of stroke in male rats (age 8-12 weeks). Non-handled rats did not receive intensive behavioral testing, being only exposed to the modified Neurological Severity Score (mNSS) and Magnetic

Resonance Imaging (MRI) at 2, 28, and 56 days post-stroke (dps). Handled rats performed a battery of sensorimotor behavioral tests, including the mNSS, but also the beam balance, corner, grid walking, forelimb placement, and cylinder tests, together with MRI at 2, 7, 14, 21, and 28 dps. Non-handled and handled rats received either saline (control) or intranasal EV treatments as follows: low multidose (2 doses per week, for 4 weeks, each dose containing 0.8 x 10^9 EVs in 120 µl), high single dose (2.4 x 10^9 EVs in 200 µl), or high multidose (2 doses per week, for 4 weeks, each dose containing 2.4 x 10^9 EVs in 200 µl), starting at 2 dps. Animals were sacrificed at 28 or 56 dps, and brains were dissected for *postmortem* analysis. Our results showed that handling alone restores sensorimotor function after MCAO compared to non-handled rats. Additionally, a high single dose of EVs is effective at enhancing behavioral recovery, but only when used in combination with handling. Lastly, a high multidose of EVs, but not a low multidose, can improve neurological function even without handling. Altogether, this work reveals how handling (in the form of intensive behavioral testing) and dose/frequency-dependent EV treatments contribute to functional recovery after MCAO stroke.

Disclosures: Y. Gomez Galvez: None. **M. Gupta:** None. **M. Kaur:** None. **S. Fusco:** None. **M.V. Podda:** None. **C. Grassi:** None. **A. Srivastava:** None. **L.M. Iacovitti:** None. **E. Blanco Suarez:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.148/LBA143

Topic: C.09. Stroke

Support: JSPS KAKENHI 23H00485
JSPS KAKENHI 23K25244

Title: Evolution of muscle synergies during intention-based robot-assisted rehabilitation training targeting the shoulder in chronic stroke survivors

Authors: *M. N. LAFITTE[1], H. KADONE[2], M. TAKETOMI[3], Y. SHIMIZU[3], C. TAN[4], S. KUBOTA[5], Y. HADA[3], K. SUZUKI[2], M. YAMAZAKI[5];
[1]Artificial Intelligence Laboratory, Inst. of Systems and Information Engin., Univ. of Tsukuba, Tsukuba, Ibaraki, Japan; [2]Ctr. for Cybernics Res., [3]Dept. of Rehabil. Medicine, Fac. of Med., [4]Artificial Intelligence Lab., [5]Dept. of Orthopaedic Surgery, Fac. of Med., Univ. of Tsukuba, Tsukuba, Japan

Abstract: After a stroke, upper limb deficits are highly detrimental to quality of life. The acute period is critical and rehabilitation in the chronic phase is challenging. Yet, an increasing amount of evidence suggests the potential of robot-assisted active rehabilitation, allowing intense,

repetitive and consistent training and the integration of biological signals representing the user's intention, which has been suggested to promote neuroplasticity and cortical reorganization. We aimed to test active rehabilitation training using the voluntary-driven shoulder type Hybrid Assistive Limb (sHAL), an exoskeleton assisting arm raising and triggered by the user's deltoid activity. 8 stroke survivors (6 men, mean age 68.25 ± 8.14) with hemiparesis and in chronic phase (1-20 years after onset) underwent a 10-session rehabilitation training consisting of sHAL-assisted arm raising motion. Kinematics and EMG of 6 upper-body muscles (Deltoid, Trapezius, Infraspinatus, Pectoralis Major, Biceps, Triceps) were recorded during sHAL-assisted and unassisted trials in patients and 10 age-matched healthy controls. Muscle synergies were extracted using non-negative matrix factorization. Similarity to healthy controls was calculated using cosine similarity (CS) for weighting coefficients and Pearson correlation coefficients (PCC) for temporal activation profiles. Mean range of motion of patients increased from 40.9° ± 19.8 to 49.8° ± 17.9 (paired t-test, $p=0.017$) but progression varied among patients, who could be divided into responders and non-responders. The number of synergies remained constant and similar to healthy controls throughout rehabilitation, namely 2 synergies corresponding to the up and down phases of elevation. CS of both synergies and PCC of the up synergy of non-responders were significantly higher than responders (unpaired t-tests, $p<0.01$). Post-rehabilitation, weight coefficients stayed consistently high but activation profiles of the up synergy in non-responders became more similar to healthy controls, surpassing levels of responders (ANOVA, $p<0.05$) during the use of sHAL. Results indicate that intention-based robot-assisted rehabilitation training might promote functional recovery in chronic stroke patients for whom traditional therapy was limitedly efficient. The stable number of synergies and weight coefficients during rehabilitation suggests a robustness of modular organization. The evolution of temporal activation profiles in the up phase for non-responders only, surprisingly more similar to healthy controls, calls attention to the role of a reorganization of descending signals in long-term functional recovery.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.149/LBA144

Topic: C.10. Brain Injury and Trauma

Support: T32 DA060139

Title: Early kynurenine pathway activation after traumatic brain injury (TBI)

Authors: *I. NAHMOUD[1,2,3], M. WU[2,3], S. LLOYD[2,3], E. A. WOODCOCK[4,5], A. CONTI[2,3]; [1]Wayne State Univ. Sch. of Med., Detroit, MI; [2]Res. and Develop. Service, John D. Dingell VA Med. Ctr., Detroit, MI; [3]Dept. of Psychiatry and Behavioral Neurosciences, [4]Psychiatry, [5]Dept. of Pharmacol., Wayne State Univ., Detroit, MI

Abstract: TBI affects nearly 3 million Americans annually, resulting in chronic neuroinflammation, which may underlie outcomes such as chronic pain or depression. Studies have shown the kynurenic pathway (KP) mediates neuroinflammatory responses, specifically implicating KP metabolites, kynurenic acid (KynA, anti-inflammatory) and quinolinic acid (QUIN, pro-inflammatory). However, the roles of the KP and its metabolites in TBI-induced inflammation and pain remain elusive. KP inhibitors attenuate neuroinflammation, pain sensitivity and depression-like symptoms after nerve injury in rodents, highlighting the unrealized potential of KP modulation to mitigate these symptoms post-TBI.
To examine KP activation after TBI, we quantified a comprehensive panel of KP metabolites in C57Bl/6 adult male mice (n=5-8 per group) at 1, 7, or 14 days after injury. Mice were secured in a stereotaxic frame and administered isoflurane to induce anesthesia. A 5mm diameter metal tip was aligned along the midline suture of the intact mouse skull and driven to a 2 mm depth at 5 m/s velocity using an electronically-controlled impact device, producing a moderate, non-contusive TBI. Sham mice were surgically prepared, but not impacted. As a third group, naïve animals were not exposed to any intervention, including anesthesia. Serum was harvested and analyzed using ELISAs at each timepoint. One-way ANOVAs, using injury as the main factor, followed by Šídák's multiple comparisons post-hoc tests were performed. Kynurenine (KYN) was significantly increased on days 1 ($p=0.02$) and 7 ($p=0.02$) in injured mice, with no difference on day 14 ($p=0.71$), compared to respective sham controls. Similarly, QUIN was increased on days 1 ($p=0.01$) and 7 ($p=0.02$) in injured mice, with no difference on day 14 ($p=0.85$) compared to respective sham controls. KynA was increased only on day 7 ($p=0.003$) in injured mice, with no differences compared to respective sham controls on days 1 and 14 ($p=0.83$ and $p=0.10$, respectively). All KYN and KynA levels in naïve animals were comparable to sham. However QUIN was significantly elevated in 14 day sham ($p=0.02$) compared to naïve animals, warranting further investigation.These findings suggest that QUIN activation, is acutely initiated by 1 day and sustained out to 7 days after injury. In contrast, KynA levels are elevated only 7 days after injury, occurring after QUIN activation, returning to sham levels by 14 days after TBI. Due to divergent effects of QUIN and KynA on inflammation, analyses of cell-specific expression may be warranted.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.015/LBA15

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

Support: NIH R01AG068330
NIH P20GM148326
BrightFocus

Title: Metabolic reprogramming in microglia drives lactate production and modulates Aβ levels in Alzheimer's disease

Authors: R. J. PETTIT-MEE[1], A. SNIPES[2], R. IRMEN[2], N. J. CONSTANTINO[2], C. ASHLEY[3], H. WILLIAMS[2], L. JOHNSON[2], J. M. MORGANTI[4], ***S. L. MACAULEY**[3]; [1]Physiol. & Pharmacol., Wake Forest Univ., Winston-Salem, NC; [2]Physiol., [4]Neurosci., [3]Univ. of Kentucky, Lexington, KY

Abstract: Alzheimer's disease (AD) is a multifactorial disease that extends beyond the gold standard amyloid and tau. Our group and others have shown that alterations in metabolism are central to the development of AD. While regional hypometabolism associated with neurodegeneration is well established in late stage AD, recent studies suggest that changes in glial metabolism may occur much earlier in disease progression. In this study, we explore how amyloid-beta (Aβ) aggregation impacts brain metabolism and metabolic reprogramming in microglia. Using in vivo microdialysis to measure the hippocampal interstitial fluid (ISF) levels of glucose and lactate, we demonstrate, as expected, that ISF glucose levels decrease in the hippocampus with Aβ pathology in APP/PS1 mice; however, this is accompanied by a concurrent rise in the ISF lactate levels, suggesting the brain is becoming increasingly glycolytic. Using metabolomics, we confirmed that the total abundance of brain lactate increases with Aβ pathology. Next, we show that pharmacologically blocking lactate metabolism reduces ISF lactate and ISF Aβ levels by 50%. Lactate is the metabolic end product of glycolysis and is produced in excess during shifts from oxidative metabolism to glycolysis. While the role of lactate in the brain and in AD is widely debated, reactive microglia undergo a metabolic shift from oxidative metabolism to glycolysis upon activation. Therefore, we hypothesized the brain's glycolytic shift in AD may be due to reactive, proinflammatory microglia. We found that the genes responsible for lactate production (*Ldha*) and lactate consumption (*Ldhb*) are highly expressed in microglia, and *Ldha* expression increases proximal to amyloid plaques. Using single cell RNAseq in 5xFAD mice, we delineated subpopulations of homeostatic (Hm), disease associated (DAM), and interferon responsive (IRM) microglia and show that *Ldha* is upregulated in DAMs and IRMs. Finally, we show that systemic injections of the proinflammatory endotoxin, lipopolysaccharide (LPS), increases hippocampal lactate levels, CD68 expression (DAM marker), and MCT4 expression (glial lactate transporter). This suggests that microglia produce and release lactate in response to pro-inflammatory stimuli like Aβ and LPS. Moreover, it suggests the metabolic reprogramming early in AD could be driven by reactive microglia and represents an important therapeutic target for treating AD.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.150/LBA145

Topic: C.10. Brain Injury and Trauma

Support: University Of Cincinnati Research Scholar Award
University of Cincinnati Start-up funds

Title: Cell-specific mitochondria dysfunction after moderate injury in human 3D in vitro brain model

Authors: *V. LIAUDANSKAYA, S. KANSAKAR, S. STERBEN;
Biomed. Engin., Univ. of Cincinnati, Cincinnati, OH

Abstract: Extensive research demonstrated that traumatic brain injury causes mitochondria dysfunction, characterized by reduced ATP production, increased reactive oxygen species generation, calcium dysregulation, and eventual apoptosis. However, cell-specific mitochondrial alterations in response to trauma remain to be elucidated. This study aimed to determine short-term and long-term cell-specific alterations of mitochondrial function post-moderate brain injury.We tagged brain cells' mitochondria with a fluorescent probe and seeded 2 mln mtRFP-neurons, 0.5 mln mtGFP-astrocytes, and 0.1 mln mtBFP-microglia in 3D silk scaffolds embedded in collagen type 3 the following day, and cultured for 6 weeks before treatment. Controlled cortical injury (CCI) was used to inflict moderate injury (6m/s, 3mm tip, 0.6mm penetration). At 24h, 72h, 1 wk, 4 wk, and 8 wk post-injury, we measured the bioenergetic function of FACS-sorted cell-specific mitochondria. The results demonstrated an acute (24h) increase in total mitochondria amount for each cell type, followed by a significant drop in long-term (4w). Neuronal oxygen consumption (OCR) substantially dropped 24h after injury, while the extracellular acidification rate (ECAR) increased 4-fold. The neuronal bioenergetic function and TUJ1 network return to sham level within 4 weeks post-injury. While neurons quickly recovered to baseline post-injury, astrocytes demonstrated a prolonged increase in both OCR and ECAR rates, potentially producing energy to support neurons. Finally, microglial mitochondria increase their ATP production through OCR and ECAR only in an 8-week period.The acute spike in mitochondria amount correlates with increased cellular demand for ATP production after injury. In contrast, the decrease in mitochondria suggests progressive mitophagy due to increased oxidative stress and mtDNA damage. Neuronal switch to glycolytic energy production acutely after injury correlates with diffuse axonal injury and is associated with severe damage to

mitochondria networks with compromised OXPHOS. At the same time, astrocytes increased ATP production, suggesting their support of neuronal repair and activity. At last, microglial increase in the baseline energy production 8 weeks post-injury suggests their transition to a chronic activation state. Our next steps focused on the correlation of mitochondria bioenergetic and metabolic functions.We thank the University of Cincinnati Start-Up Funds, Research Scholar Award, Cincinnati Children's Hospital Bioimaging and Analysis Facility, and Research Flow Cytometry Facility.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.151/LBA146

Topic: C.10. Brain Injury and Trauma

Support: National Research Foundation, Korea (NRF-2020R1C1C1008033)
KHIDI-AZ Diabetes Research Program (SNU-800-20230665)
Seoul National University Hospital (SNUH-800-20240012)

Title: Perk pathway contributes mitochondrial fission-induced neuronal damage following hypoglycemia

Authors: *S. LEE[1], J.-Y. JOO[1], H. JUNG[2], O. KWON[3];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Biochem. and Mol. Biol., [2]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: One of the major adverse effects of insulin therapy in patients with diabetes is severe hypoglycemia (HPG), which can cause neuronal damage, potentially leading to cognitive impairment. Our recent study showed that increased neuronal mitochondrial fission in the retrosplenial cortex (RSC) after HPG leads to oxidative damage and neuronal death, resulting in cognitive impairment. As we had also defined the effect of low-dose pancreatic endoplasmic reticulum kinase inhibitor (PERKi) on modulating ER stress and related metabolic diseases, the current study aimed to examine the role of PERK, a mediator of ER stress, in our model of HPG-induced neuronal damage. For the HPG mouse model, 9-week-old male C57BL/6 mice were fasted for 24 hours, and insulin-induced hypoglycemia (blood glucose levels below 20 mg/dl) was maintained for 5 hours. Seven days after HPG, oxidative damage [4-HNE] increased and ER stress [pPERK] was activated in neurons of RSC. A significant increase in pDrp1 was detected 6 hours after HPG, while pPERK started to increase 24 hours after HPG, suggesting that mitochondrial fission may precede ER stress. Intracerebroventricular administration of glucose reduced pPERK, suggesting that pPERK elevation is dependent on neuroglycopenia. PERKi

treatment reduced pPERK and 4-HNE signals, indicating that the PERK pathway is critical to HPG-induced neuronal damage in the RSC. In contrast, there was no difference in pDrp1 signal, confirming that ER stress follows mitochondrial fission. In line with this finding, administration of mdivi-1, a mitochondrial fission inhibitor, resulted in decreased pPERK levels. For the *in vitro* study, a neuronal cell line SH-SY5Y was used. Glucose deprivation led to an increase in pDRP1 at 12 hours and an increase in mitoSOX signals at 18 hours, indicating that mitochondrial fission precedes the generation of mitochondrial-derived superoxide. Treatment with a low dose superoxide scavenger reduced pPERK and cleaved caspase 3, confirming that mitochondria-derived superoxide contributes to ER stress and subsequent neuronal damage. However, there was no change in pDRP1 levels, suggesting that mitochondrial fission is rather upstream signal for ROS generation. In summary, our findings demonstrate that severe hypoglycemia leads to increased mitochondrial fission, subsequent ROS generation, and ER stress through PERK pathway, resulting in neuronal oxidative damage and death.

Disclosures: S. Lee: None. **J. Joo:** None. **H. Jung:** None. **O. Kwon:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.152/LBA147

Topic: C.10. Brain Injury and Trauma

Support: Institutional support from the University of Illinois Chicago
R01EB027769-01
R01EB028661-01

Title: Advancements in neonatal brain imaging: functional Insights and enhanced hemorrhage detection using transfontanelle photoacoustic and thermoacoustic imaging

Authors: *D.-A. M. PILLERS[1], F. CHARBEL[2], K. AVANAKI[3];
[1]Pediatrics, Univ. of Illinois Chicago, Chicago, IL; [2]Neurosurg., Univ. of Illinois Chicago, chicago, IL; [3]Biomed. Engin., Univ. of Illinois Chicago, Chicago, IL

Abstract: Neonatal brains are vulnerable to a range of potential injuries including hypoxic ischemic encephalopathy and, for premature neonates, periventricular-intraventricular hemorrhage. Cranial transfontanelle ultrasound (ctUS) is the standard of care for assessing the neonatal brain and is routinely performed on neonates. ctUS is based on a transducer sending out acoustic waves and reading the reflected waves. ctUS lacks sensitivity for detection of small hemorrhages and also cannot provide functional information on intracranial tissue. We have developed low cost, bedside instrumentation for two acoustic-induced based imaging techniques (photoacoustic imaging (PAI) and thermoacoustic imaging (TAI)) that, like ultrasound, do not

require either ionizing radiation or sedation. Here we show that transfontanelle PAI (tPAI) and transfontanelle TAI (tTAI) can provide functional information (tissue oxygenation) and higher sensitivity for hemorrhage detection than ctUS. Relying on chromatic differences in the light absorption of oxyhemoglobin and deoxyhemoglobin, we analyzed the ability of tPAI to measure oxygen saturation (sO_2) in an *in vivo* large animal model in which we constructed an artificial fontanelle. Compared with results from a blood gas analyzer (BGA), tPAI measured sO_2 values with less than 3.5% deviation from the readings from the BGA. Next, we tested the capability of tPAI to detect small hemorrhages. tPAI was able to detect periventricular and intraventricular hemorrhages with a limit of quantification (LOQ) of 0.3mL, whereas ctUS demonstrated a LOQ of 0.5mL. Relying on the high dielectric constant of hemorrhaged blood, the sensitivity was further improved by implementing tTAI, which demonstrated 0.1mL LOQ for detection of intraventricular hemorrhages. Our findings suggest the acoustic-based technologies tPAI and tTAI hold promise for a new generation of clinical neonatal brain imaging.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.153/LBA148

Topic: C.10. Brain Injury and Trauma

Support: Human Frontier Science Program Award RGP0036/2020
Seed Grant from the Office of the Senior Vice President of Research SUNY Downstate Health Science University

Title: Rapid volume pulsations of the brain's extracellular space, a novel process that may contribute to epileptogenesis after traumatic brain injury in rats

Authors: *A. R. FRINGUELLO[1,3], J. HRABE[4,2], D. S. LING[1,5], S. HRABETOVA[1,5];
[1]Dept. of Cell Biol., [2]SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [3]SUNY Downstate Hlth. Sci. Univ., Neural and Behavioral Sci. Grad. Program, Brooklyn, NY; [4]Translational Neurosci. Labs., Nathan S. Kline Inst., Orangeburg, NY; [5]SUNY Downstate Hlth. Sci. Univ., The Robert F. Furchgott Ctr. for Neural and Behavioral Sci., Brooklyn, NY

Abstract: The extracellular space (ECS) acts as an ionic reservoir between cells and is the primary avenue of neuronal signaling. A shrinkage in ECS volume increases concentrations of the ions and neurotransmitters it contains. Recently, we reported that transient shrinkages of the ECS, Rapid Volume Pulsations (RVPs), coincide with epileptiform activity in the neocortex of rats after controlled cortical impact (CCI), an established model for Post Traumatic Epilepsy (PTE) (Fringuello et al. 2024, Epilepsy Res). RVPs may promote epileptogenesis after traumatic

brain injury (TBI) by increasing neuronal excitability and synchrony within an epileptic region and by recruitment of neighboring healthy cells into epileptic focus through increased diffusive spread of neuroactive substances. To test this, we investigated RVPs at early and chronic timepoints after TBI and performed dynamic MCell numerical modeling.We assessed RVPs at an early timepoint associated with hyperexcitability (4 weeks) and a chronic timepoint where spontaneous recurrent seizures occur (12 weeks) following CCI in rodents. Epileptiform activity and RVPs were triggered in neocortical slices with a low dose of 4-Aminopyridine (10 µM). Probe Transients Quantification (PTQ) with the extracellular probe tetramethylammonium (TMA) was used to detect RVPs. RVPs were then analyzed to calculate relative ECS shrinkage (Colbourn et al. 2021, J Physiol.). Using dynamic MCell software, RVPs were simulated in a grid of cells surrounded by ECS containing TMA. RVPs were induced by rapidly swelling a central region of cells. In PTQ experiments, RVPs always accompanied epileptiform activity. At four weeks, RVP shrinkage averaged 5.2% (SEM ± 0.34, 10 slices, five rats) and averaged 5.7% (SEM ± 0.76, 12 slices, seven rats) at 12 weeks. Between timepoints, we observed an increased range of shrinkages between slices (4 weeks, 3.9-7.5%, 12 weeks, 2.0-11.9%). MCell simulation revealed increased concentration of molecules surrounding the swollen cells, and a wave of diffusion spread TMA to neighboring cells. Together, these results show that RVPs accompany epileptiform activity in early and late timepoints after CCI, suggesting a close relationship with ictal activity following TBI. MCell simulations illustrate how RVPs enhance two components that govern seizure activity: 1) hyperexcitability through the increased concentration of neuroactive agents within the ECS, and 2) hypersynchrony through increased diffusive range of neuroactive agents to neighboring cells, possibly recruiting them into epileptic focus. These data implicate RVPs as a potential ictogenic and epileptogenic factor in the brain following TBI.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.154/LBA149

Topic: C.10. Brain Injury and Trauma

Support: DoD Grant W81XWH-22-1-0287
VA Grant 1I21RX004629-01

Title: Alterations in the Circadian Circuitry Following Experimental TBI

Authors: *J. VELAZQUEZ[1], E. MIRZAKHALILI[2], J. A. WOLF[3], A. V. ULYANOVA[4]; [1]Univ. of Pennsylvania, Philidelphia, PA; [2]Neurosurg., Univ. of Pennsylvania, Philadelphia, PA; [3]Univ. of Pennsylvania, Wayne, PA; [4]Neurosurg., Perelman Sch. of Medicine, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Research Objectives and Rationale: Disrupted sleep is a common and persistent symptom after traumatic brain injury (TBI), which can significantly complicate recovery and contribute to cognitive dysfunction. While sleep disturbances such as difficulty falling and staying asleep are often caused by abnormal circadian rhythm, the extent of circadian-related sleep disruption following TBI remains poorly understood. Circadian rhythms are generated by a highly synchronized activity of the GABAergic interneurons in the suprachiasmatic nucleus of the hypothalamus (SCN). Previously, it has been reported that interneurons in the cortex and hippocampus are selectively vulnerable following TBI. However, the effects of TBI on the circadian circuitry and its neuronal network have not been explored. Methods: Using a novel porcine model of controlled cortical impact (CCI) injury (6-month-old male Yucatan miniature pigs), we performed in vivo electrophysiological examination of the circadian network at 6hr post-CCI (n=3) versus shams (n=2). MRI-based neuronavigation (Brainsight system) was used to place 128-channel silicon probes into the SCN precisely. Chronic SCN implantations for continuous video EEG recordings were also performed in the sham (n=1) and CCI-injured (n=2) animals, with four ECoG screws placed on both hemispheres for sleep detection. Results: Under anesthesia, the firing rate of the SCN neurons significantly decreased while the spike amplitude significantly increased (p=0.0323). Light stimulation caused sham activation (p=0.0024) but not CCI-injured SCN interneurons, despite more active cells being detected electrophysiologically. In addition, continuous video recordings of both sham and CCI-injured groups were analyzed pre- and up to 4 weeks post-implantation using animal pose estimation software DeepLabCut to determine changes in sleep patterns. Home cage behavior was analyzed for velocity, moving/still, and occupancy, while synchronized video EEG data were analyzed for sleep and circadian behaviors. KiloSort4 software was used to detect single units in the SCN, with continuous over 48-hour weekly recordings up to the study's endpoint. Chronic neuronal activity of the SCN neurons (firing rate, spike amplitude, and width) was analyzed for their contribution to the circadian network post-injury. Conclusions: We demonstrated that changes in the firing properties of the SCN interneurons may indicate hyperexcitability of the circadian network post-injury. Understanding how early changes in the circadian network might contribute to TBI-disrupted sleep will provide important insights into recovery post-injury.

Disclosures: J. Velazquez: None. **E. Mirzakhalili:** None. **J.A. Wolf:** None. **A.V. Ulyanova:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.155/LBA150

Topic: C.10. Brain Injury and Trauma

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UPR Med Sci Campus Chancellor's Office
School of Medicine Deanship

Title: Dissociating the interpretation of either decreased anxiety or increased risk-taking behavior in the open field after brain injury in rats

Authors: *P. VÁQUEZ MARTÍNEZ[1], M. RIVERA-LÓPEZ[1], L. C. VICENTE-RODRÍGUEZ[2], D. SIERRA-MERCADO[1];
[1]Anat. and Neurobio., Univ. of Puerto Rico, Med. Sci. Campus, San Juan, Puerto Rico; [2]Univ. of Puerto Rico, Cayey, Puerto Rico

Abstract: Traumatic brain injuries (TBI) may influence cognition related to anxiety or risk-taking behavior. Preclinical models of TBI are useful for understanding the biological mechanisms leading to potential impairments in cognition. Rodent models of TBI include controlled cortical impact, fluid percussion, blast injury, and weight drop models, which vary in severity and mode of injury. In all four models, anxiety levels have been measured using the Open Field Test (OFT), typically by comparing the time spent in the center versus the periphery. Here, decreased time spent in the center is interpreted as an anxiety-like trait, while increased time in the center has variable interpretations. Some studies interpret increased time in the center as either decreased anxiety or increased risk-taking behaviors. In the current study, we use a weight drop model that is well-established in rodents to decode the mechanisms behind increased time in the center in the OFT. Preliminary results showed that one closed head impact results in increased time in the center in both male and female rats. Specifically, male rats (Sham: n=10; CHI: n=10) that underwent CHI showed increased time in the center 1-day post-injury compared to Sham-injured controls (Sham=8.07% ± 1.47, CHI=13.65 % ± 1.65; p=0.0244, t17=2.471). Additionally, female rats (n=12) that underwent CHI showed increased time in the center on day 8 (Sham=8.65% ± 1.45, CHI 15.01% ± 1.74 , p=0.01, t17=2.776), day 13 (Sham=11.28% ± 1.79, CHI= 18.05 % ± 2.67 , p=0.045, t17=2.125), and day 17 post-injury (Sham= 6.57 % ± 1.11 , CHI= 13.07% ± 1.34, p=0.001, t17=3.698). Next, we are now evaluating brain tissue of the same rats for biomarkers of neuronal change in brain regions implicated in anxiety (i.e. insular cortex and amygdala) and decision making (i.e. prefrontal cortex). This will set us up for our future studies which would incorporate the administration of either an anxiolytic or a psychostimulant, with the goal of dissociating the mechanisms of changes in the brain with anxiety-like and risk-taking behaviors induced by TBI.

Disclosures: P. Váquez Martínez: None. **M. Rivera-López:** None. **L.C. Vicente-Rodríguez:** None. **D. Sierra-Mercado:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.156/LBA151

Topic: C.10. Brain Injury and Trauma

Support: Merit Review Award # 1 I01 RX003123-01A1, from the United States (U.S.) Department of Veterans Affairs Rehabilitation Research and Development Service (RR&D)
SPiRE Award B4097-P/I21 RX004097, from the United States Department of Veterans Affairs Rehabilitation Research and Development Service (RR&D)

Title: Connection-wise analysis in chronic traumatic brain injury (TBI): A novel approach as a potential biomarker for TBI in a clinically relevant rat model

Authors: S. HEJAZI[1,5], J. HOU[5,1], J. MURPHREE[1,5], D. PLANT[5], M. FEBO[2], F. J. THOMPSON[5,3], *P. BOSE[5,1,4];
[1]Anesthesiol., [2]Psychiatry, [3]Neurosci., [4]Neurol., Univ. of Florida, Gainesville, FL; [5]North Florida/South Georgia Veterans Hlth. Syst., Gainesville, FL

Abstract: Traditional nodal-based functional MRI data analysis has long been employed to investigate brain connectivity. In early 2020, the application of connection-wise analysis emerged as a novel approach in the field of neurological disorders. However, it has not been applied to rodent models or Traumatic Brain Injury (TBI), despite its potential to provide additional insights beyond region-based analysis.

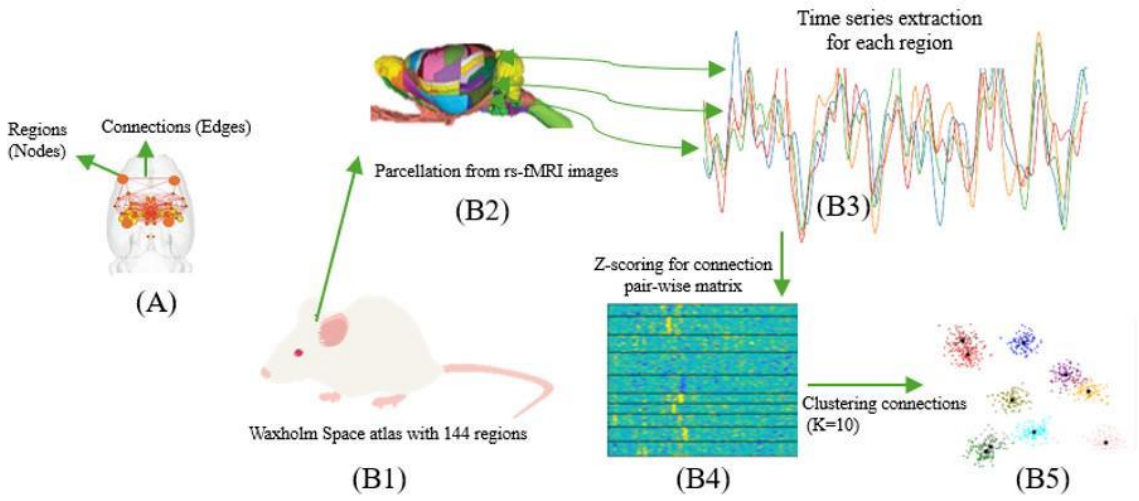

Figure 1: (A) Network analysis elements. (B) Schematic pipeline of connection-wise analysis in rat models. (B1) we acquired rs-fMRI from 48 naïve female adult Sprague-Dawley rats and 18 clinically relevant acceleration-deceleration mild/moderate closed-head chronic TBI (1.25 m weight-drop) rats. (B2) Waxholm Space atlas with 144 nodes for the brain region was then utilized for parcellation. (B3-B4) Moving beyond traditional nodal-based analysis, time-series data were z-scored to calculate edge correlations. (B5) Finally, the k-means algorithm was employed to cluster (k=10) these edges to explore the community overlapping index entropy.

Entropy, as a measure of community diversity for all connections, was calculated in each hemisphere and network for both naïve rats (n=48) and TBI-chronic injured rats (n=18). Brain-specific functional networks were developed to examine entropy changes in Emotion, Motor, Sensory, Memory, and Homeostasis & Sleep-related brain areas. Significant differences were observed in entropy measures in the TBI group compared to naive. In the Memory network, a t-test between naïve and TBI rats revealed a t-statistic of 3.3574 and a p-value of 0.0020. In the Homeostasis & Sleep function-specific areas, the t-test indicated a t-statistic of -2.4661 and a p-value of 0.0228. We also analyzed the left and right hemispheres separately. The right hemisphere showed significant differences in Sensory, Memory, and Homeostasis & Sleep areas when compared to those of naïve values. However, no significant differences were observed in the left hemisphere. These results suggest that connectivity and community overlapping indices in one hemisphere are altered more than in the other. Our study introduces a novel approach by using **connection-wise network analysis with functional network** categories instead of structural networks. In addition, our study found that **community structures within brain connections** in chronic TBI rats differ from those in naïve rats, particularly in two specific networks, indicating potential biomarkers for TBI. Finally, our results highlight that connection-wise analysis effectively identifies important brain connectivity changes in a clinically relevant TBI model providing a **valuable addition to traditional region-based analysis.**

Disclosures: S. Hejazi: None. **J. Hou:** None. **J. Murphree:** None. **D. Plant:** None. **M. Febo:** None. **F.J. Thompson:** None. **P. Bose:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

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Topic: C.10. Brain Injury and Trauma

Support: NSF NCS Award #1926818
VA BLRD Merit Award I01 BX006155
NIH P30 AG066518

Title: Reducing Interdataset Covariate Shift in Sleep EEG of Traumatic Brain Injured Humans and Mice Using Transfer Euclidean Alignment

Authors: *M. VISHWANATH[1], S. CAO[1], A. RAHMANI[2], N. DUTT[1], M. M. LIM[3], H. CAO[1]; [1]Univ. of California Irvine, Irvine, CA; [2]Nursing and Computer Sci., Univ. of California, Irvine, Irvine, CA; [3]Veterans Affairs Portland Hlth. Care Syst., Portland, OR

Abstract: Mild Traumatic Brain Injury (mTBI) is a prevalent health issue, and predicting which individuals develop persistent disability remains a challenge. Variability in patient data and the scarcity of high-quality data poses challenges in deploying machine learning (ML) models in the real world. Our research addresses this gap by introducing Transfer Euclidean Alignment (TEA), an unsupervised transfer learning (TL) technique that aims to identify EEG biomarkers for mTBI prognostication representing the first use of TL from mouse to human data. The study utilizes 2 mouse datasets. Dataset 1 includes 10 male C57BL/6J mice with TBI induced by Fluid Percussion Injury, while Dataset 2 consists of 18 male mice with TBI induced by Controlled Cortical Impact, both divided equally into TBI and sham groups. Human dataset constitutes EEG recordings from 35 participants (19 TBI patients and 16 age-matched controls) who underwent overnight polysomnography at the VA Portland Health Care System. In this study, a common analysis pipeline for mouse and human EEG data is developed. For the classical ML approach, a comprehensive set of features, including spectral, connectivity, time-domain, and non-linear features, is extracted, normalized, transformed, and selected using the recursive feature elimination method. For the DL approach, a refined EEGNet architecture tailored for mouse and human EEG data is utilized, and its performance is evaluated using independent validation. TEA aligns the mean covariance matrices of different datasets to the identity matrix, significantly reducing differences between them. Transforming EEG trials into a common Euclidean space allows for the direct application of ML algorithms to the aligned data. The study reduces covariate shifts in EEG datasets through TEA in both intraspecies case, involving mice data as source and target datasets, and interspecies case, involving mouse data as the source and human data as the target dataset. We show that the use of models pre-trained on TEA source dataset significantly improves classification accuracy on the target dataset across all models, with EEGNet-based DL showing a 40% average performance increase post-TEA. Models pre-trained with aligned mouse data achieve higher accuracy on human data, highlighting TEA's effectiveness in reducing the need for extensive human data during the training phase. The average accuracy increase of 14.42% for intraspecies and 5.46% for interspecies datasets

underscores the importance of TEA in boosting the performance of ML models trained on diverse datasets, enhancing cross-species TL.

Disclosures: M. Vishwanath: None. **S. Cao:** None. **A. Rahmani:** None. **N. Dutt:** None. **M.M. Lim:** None. **H. Cao:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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Program #/Poster #: LBA003.158/LBA153

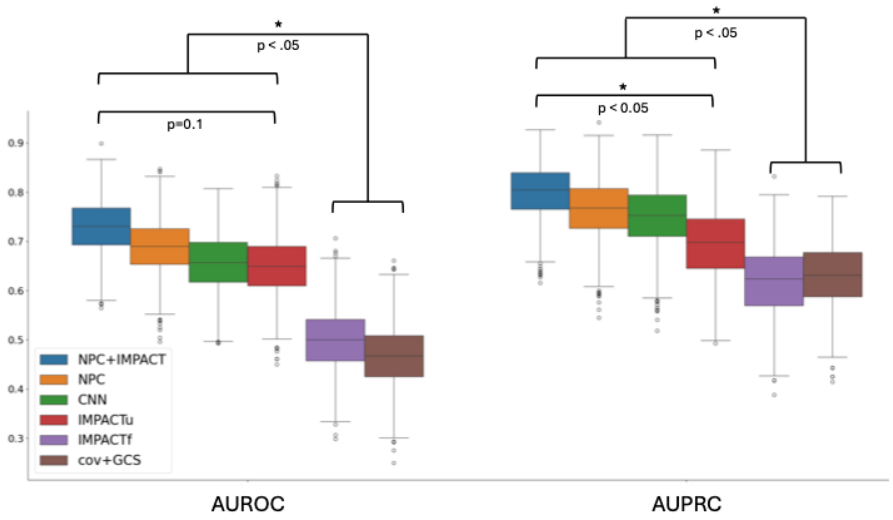
Topic: C.10. Brain Injury and Trauma

Title: Predicting recovery following traumatic brain injury using multimodal MRI

Authors: A. CHEN[1], Y. HALPERIN ORTIZ[1], P. M. VESPA[1], M. M. MONTI[1], ***J. N. CHIANG**[2];
[2]Neurosurg. and Computat. Med., [1]UCLA, Los Angeles, CA

Abstract: Current prognostic models for traumatic brain injury (TBI) consider clinical and demographic factors collected at the bedside to predict favorable or unfavorable long term outcomes, but do not incorporate imaging-derived features which may be associated with recovery trajectories in disorders of consciousness. The goal of this study is to assess the added utility of multimodal MR imaging features in predicting 6 month outcomes following TBI. Aggregate multimodal MR scores were computed from 84 patients with moderate to severe TBI using non-parametric combination (NPC) joint inference over T1-weighted, T2-weighted, susceptibility weighted imaging (SWI), and apparent diffusion coefficient (ADC) modalities using FSL PALM. Logistic regression models were developed using combinations of clinical (age, sex, Glasgow Coma Scale) and NPC features to predict 6 month functional impairment based on Glasgow Outcome Scale-Extended (GOSe) score and assessed using cross-validation. A data driven clinical score (IMPACT) and neural network model (CNN) were also assessed. Statistical significance was assessed using two sample nonparametric bootstrap tests. Performance was quantified in terms of area under the receiver operating characteristic (AUROC) and precision-recall curve (AUPRC). The clinical IMPACT score and all models including multimodal MR features significantly outperformed logistic regression models using clinical and demographic covariates alone. No significant differences were observed between IMPACT, NPC, and CNN predictions of 6 month outcome. Combining the NPC and IMPACT features (NPC+IMPACT: 0.80, 95% CI [.69, .89]) resulted in significantly improved AUPRC relative to the clinical IMPACT model alone (IMPACT: 0.70 [0.54, 0.83], p=0.04), with a trending improvement in AUROC (NPC+IMPACT: 0.73 [.62, .83], IMPACT: 0.65 [0.53, 0.77], p=0.1). Overall, machine learning models can predict 6 month GOSe outcomes following severe

traumatic brain injury. Features derived from multimodal MR improve prognostic performance relative to the clinical standard.



Disclosures: A. Chen: None. **Y. Halperin Ortiz:** None. **P.M. Vespa:** None. **M.M. Monti:** None. **J.N. Chiang:** None.
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Topic: C.10. Brain Injury and Trauma

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NIH 5T32GM007356-47
NSF BCS-1 349 042
P30 EY001319

Title: Right hemisphere functional connectivity patterns predict left hemisphere glioma infiltration of the parietal and insular cortex

Authors: *E. STRAWDERMAN[1,3], F. GARCEA[1,3], M. E. TIVARUS[1,2], W. BURNS[3], B. MAHON[3,4];
[1]Neurosci., Univ. of Rochester, Webster, NY; [2]Imaging Sci., Univ. of Rochester, Rochester, NY; [3]Neurosurg., Univ. of Rochester Med. Ctr., Rochester, NY; [4]Psychology, Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Gliomas can infiltrate functional brain networks, resulting in widespread changes in functional connectivity. These dynamic network alterations can extend into the contralesional hemisphere. This study investigated whether the presence of a glioma in a given brain region is linked to specific patterns of contralesional functional connectivity. We hypothesized that resting state functional connectivity patterns in the right hemisphere could predict glioma lesion location in the left hemisphere.

High resolution T1 imaging and resting state fMRI data were acquired in 48 left unilateral glioma patients in the pre-operative phase of their neurosurgical care. We used the Yan 2021 homotopic atlas to quantify the percent lesion damage in each left hemisphere region-of-interest (ROI). We identified 49 ROIs that were lesioned in at least 10 patients. We then calculated ROI-to-ROI connectivity (RRC) matrices across the 100 right hemisphere ROIs. For each left hemisphere ROI, support vector regression with leave-one-out cross-validation was used to train a model to learn the relation between the percent lesion damage in that ROI and the RRC matrix within the right hemisphere. Given a left out patient's right RRC matrix, the model predicted that patient's percent of lesion damage in the left hemisphere ROI. This was repeated across all patients and all 49 left hemisphere ROIs. Spearman correlations between actual and predicted percent lesion damage scores were calculated and assessed for significance with permutation tests (with Benjamini-Hochberg correction for multiple comparisons across the 49 left hemisphere models).

We found that right hemisphere functional connectivity patterns predicted glioma lesion damage in 10 left hemisphere ROIs ($p < 0.10$). The areas identified were concentrated around the left inferior parietal lobule and the left posterior insular lobe, suggesting tumors in these areas may be associated with greater recruitment of contralesional functional connectivity. We propose that this regional focus in the inferior parietal and insular cortex of the core finding is driven by the reorganization of functional connectivity to both homologous and non-homologous regions in the non-lesioned hemisphere, potentially representing a strategy to preserve cognitive function. In sum, right hemisphere functional connectivity patterns predict left hemisphere glioma infiltration in posterior insular and inferior parietal regions. These findings demonstrate the widespread impact that gliomas have on functional networks well beyond the radiological boundaries of the lesion.

Disclosures: E. Strawderman: None. **F. Garcea:** None. **M.E. Tivarus:** None. **W. Burns:** None. **B. Mahon:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.016/LBA16

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

Support: Series A venture funding from the Alzheimer's Drug Discovery Foundation, Cleveland Clinic, Brain Trust Accelerator Fund II and Dolby Family Ventures
Grant funding from the Alzheimer's Association
Series B venture funding from the Cleveland Clinic Foundation, Brain Trust Accelerator Fund II, Dolby Family Ventures and Alzheimer's Drug Discovery Foundation, Foundation for a Better World and CRUINT

Title: A phase 1b double-blind multiple ascending dose study and a randomized placebo-controlled phase 2a study of NTRX-07 in participants with Alzheimer's disease

Authors: *M. KIRALY, J. FOSS, T. GIORDANO;
NeuroTherapia, Inc., Cleveland, OH

Abstract: NTRX-07, an orally bioavailable, small molecule, has been shown in several animal models of Alzheimer's Disease (AD) to bind to the CB2 receptor on reactive microglia, causing them to revert to their surveillance state. Importantly, this led to reduced neuroinflammation, the clearance of Aβ, improved long-term potentiation, and improved learning and memory. NeuroTherapia has recently completed a 7-day Phase 1b study in healthy volunteers and a cohort of AD subjects that demonstrated the safety and tolerability of the molecule at blood levels consistent with the bioactivity observed in animal models of AD. In addition, in the AD cohort, a trend was observed in reducing errors in the ADAS-cog test and in partially reversing the AD deficits in quantitative EEG. To determine whether these trends will continue to be observed with more subjects and for a longer duration of treatment, a 28-day, single-dose study will be carried out in AD subjects. Quantitative EEG recordings (10 minutes eyes shut followed by 10 minutes eyes open) and CSF biomarkers for neuronal function will be collected pre- and post-treatment in all 48 subjects. In addition, free-water MRI and CSF biomarkers of inflammation will be collected to determine whether treatment is acting directly to reduce neuroinflammation. We aim to determine whether plasma biomarkers can be identified that correlate to the CSF findings, providing a potential screening tool in future trials to identify subjects who might best respond to treatment with NTRX-07 or other neuroinflammatory inhibitors. We will recruit AD subjects with an ApoE4 allele since these patients are most likely to have a high amyloid burden and neuroinflammation. The primary endpoint of the study will be to assess safety and tolerability following 28 days of treatment in AD subjects. Although 24 subjects per group may not be enough to demonstrate statistically significant improvement, coupling this with changes in biomarkers from the CSF associated with neuronal function will provide compelling support that NTRX-07 can improve neuronal function. In addition, the free-water MRI and neuroinflammatory CSF biomarkers will potentially link the changes in neuroinflammation to improved neuronal activity, translating the results observed in the preclinical animal studies. Furthermore, a change in a plasma biomarker following NTRX-07 treatment could be used to inform the subsequent trial as an inclusion criterion.

Disclosures: M. Kiraly: None. **J. Foss:** None. **T. Giordano:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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Topic: C.10. Brain Injury and Trauma

Support: German Research Foundation (grant number: 544183227; CH)
NIH/NIMHD Loan Repayment Program L32 MD016519 (HA)
Burroughs Wellcome Fund Postdoctoral Diversity Enrichment Program (HA)

Title: Implications of Maternal Traumatic Brain Injury During Pregnancy

Authors: *A. MIRMAJLESI[1], C. HELLER[2], M. KRAFT[2], M. MARTINEZ[1], H. ARCINIEGA[1];
[1]Dept. of Rehabil. Med., New York Univ. Grossman Sch. of Med., New York, NY; [2]Dept. of Clin. Psychology, Jena Univ. Hosp., Jena, Germany

Abstract: Traumatic brain injuries (TBIs) are a global health concern, causing a spectrum of effects from mild symptoms to severe neurological impairments that impact cognitive, physical, and emotional well-being. Pregnant women with acquired TBI face heightened rates of morbidity and mortality, necessitating complex management during this critical period. In this study, we conducted a systematic review to investigate the effects of TBI during pregnancy on maternal and fetal outcomes and identify appropriate management strategies for this population. The systematic literature search was conducted in the electronic databases PubMed, Web of Science, and PsycInfo to identify eligible studies published in English, German, or Spanish between 1990 and 2023, that included at least one pregnant individual with TBI. Two independent reviewers screened abstracts and potentially relevant full-text articles to extract study characteristics, pregnancy outcomes, management methods, and authors' conclusions and suggestions. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline was followed. 16 eligible studies were included involving 4,112 individuals who experienced TBI during pregnancy. The included studies comprised 10 case reports, 2 case series, and 4 cohort studies. Motor vehicle accidents (MVA) were the most common cause of injury, reported in 12 studies. The average Glasgow Coma Scale (GCS) score was 9.11, including 1 case of mild, 3 cases of moderate, and 6 cases of severe TBI. Conservative management was reported in 7 studies, and surgery was performed in 6 cases. Maternal outcomes ranged from improved functional recovery to severe cognitive impairment, while fetal outcomes varied from stable to severe adverse outcomes such as stillbirth and death. Risk of bias assessment indicated moderate to good methodological validity overall, yet most studies demonstrated poor quality of evidence. This systematic review confirms that pregnant

individuals who experience TBI face heightened risks of adverse pregnancy outcomes, including placental abruption and cesarean delivery, as well as adverse maternal and fetal outcomes, requiring specialized and multidisciplinary care. Early intervention and collaborative management involving neurosurgeons, obstetricians, neonatologists, and anesthesiologists are essential to optimize outcomes for both mother and fetus.

Disclosures: A. Mirmajlesi: None. **C. Heller:** None. **M. Kraft:** None. **M. Martinez:** None. **H. Arciniega:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.161/LBA156

Topic: C.10. Brain Injury and Trauma

Support: Programa de Concurrencias Financieras para la Investigación y Atención de la Vinculación 2023

Title: Cerebrolysin induces motor recovery along with plastic changes in motoneurons in the ventral spinal cord following a kainic acid excitotoxic lesion in the rat motor cortex

Authors: *N. I. MARTINEZ TORRES;
Neurosci., Ctr. de Investigación Biomédica de Occidente/Universidad de Guadalajara, Guadalajara, Mexico

Abstract: Lesions in the motor cortex induced by contusions or pathological insults can exert the degeneration of afferent neurons lying distal to these lesions. Axon degeneration and demyelination are hallmarks of several diseases sharing pathophysiological and clinical characteristics, mainly affecting motor function. These conditions are very disabling due to the disruption of motor abilities, with lesions that affect motor areas proving to be a therapeutic challenge, which has driven increasing efforts to search for treatments. Cerebrolysin contains a mix of pig brain-derived peptides with activity similar to neurotrophic factors. Here, the effect of cerebrolysin administration on the motor impairment produced by kainic acid (KA) lesion of the motor cortex was evaluated in Sprague-Dawley female rats (n=27), defining its effect on motoneurons dendritic tree and spine density from the thoracolumbar regions of the spinal cord. Ten days after the KA lesion of the motor cortex, rats were administered cerebrolysin, and their motor performance was evaluated using the “Basso, Beattie, and Bresnahan” (BBB) and Bederson scores. Cerebrolysin administration improved motor activity according to the BBB and Bederson scales, in conjunction with an increase in dendritic intersections and spine density on motoneurons.Hence, this study suggests that cerebrolysin could promote motor recovery

following motor cortex lesions by driving dendritic tree intersections and spine density increase in motoneurons.

Disclosures: N.I. Martinez Torres: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.162/LBA157

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life - Spinal Cord Research Foundation

Title: Role of RNA stress granules in axonal repair after spinal cord injury

Authors: *M. HERNAIZ[1], Y. JIN[2], B. ZHENG[3];
[1]Neurosciences, UCSD, San Diego, CA; [2]Neurobio., UCSD, LA Jolla, CA; [3]Dept. of Neurosciences, Univ. of California San Diego, La Jolla, CA

Abstract: Role of RNA stress granules in axonal repair after spinal cord injury.
M Hernaiz-Llorens[1], Y Jin[1, 2, 3] and B Zheng[1, 4][1]Department of Neurosciences, School of Medicine, University of California San Diego, La Jolla, California 92093[2]Department of Neurobiology, School of Biological Sciences, University of California San Diego, La Jolla, California 92093[3]Department of Cellular and Molecular Medicine, School of Medicine, University of California San Diego, La Jolla, California 92093[4]VA San Diego Healthcare System Research Service, San Diego, California 92161
Neuron-intrinsic mechanisms that regulate axon regeneration remain incompletely understood. As a response to cellular stress, cytoplasmic mRNA is sequestered into insoluble ribonucleoprotein granules, known as stress granules. These are membraneless mRNA-protein assemblies that prevent trapped mRNA species from being actively transcribed. Stress granules are assembled upon non-translating mRNAs which serve as scaffolds for RNA-binding proteins such as G3bp1 and Tia1. These core components of the stress granules are required to nucleate granule formation through protein-protein interactions. Recent findings have demonstrated that such core components of RNA stress granules regulate axon regeneration in C. elegans and the mammalian peripheral nervous system (PNS).In this study we show that G3bp1+ and Tia1+ stress granules form upon different stressors. Intriguingly, Bortezomib treatment *in vitro*, a chemotherapeutic agent, results in axon degeneration and triggers stress granule aggregation, making it a useful tool to study stress granule aggregation in the context of axonal damage. Moreover, we have found that AAV-mediated overexpression of G3bp1 and Tia1 limits axon elongation in cortical neurons *in vitro*. *In vivo*, overexpression of these proteins limits the ability of intact axons to sprout after unilateral pyramidotomy model in Pten deleted mice. Our ongoing

work includes assessing the genetic loss of function for G3bp1 and Tia1 in axonal sprouting and regeneration post-spinal cord injury. Overall, our findings suggest a detrimental role of stress granule aggregation in response to axonal injury, providing insights into potential therapeutic targets for enhancing axon regeneration after nervous system trauma.

Disclosures: M. Hernaiz: None. **Y. Jin:** None. **B. Zheng:** None.

Late-Breaking Poster

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Program #/Poster #: LBA003.163/LBA158

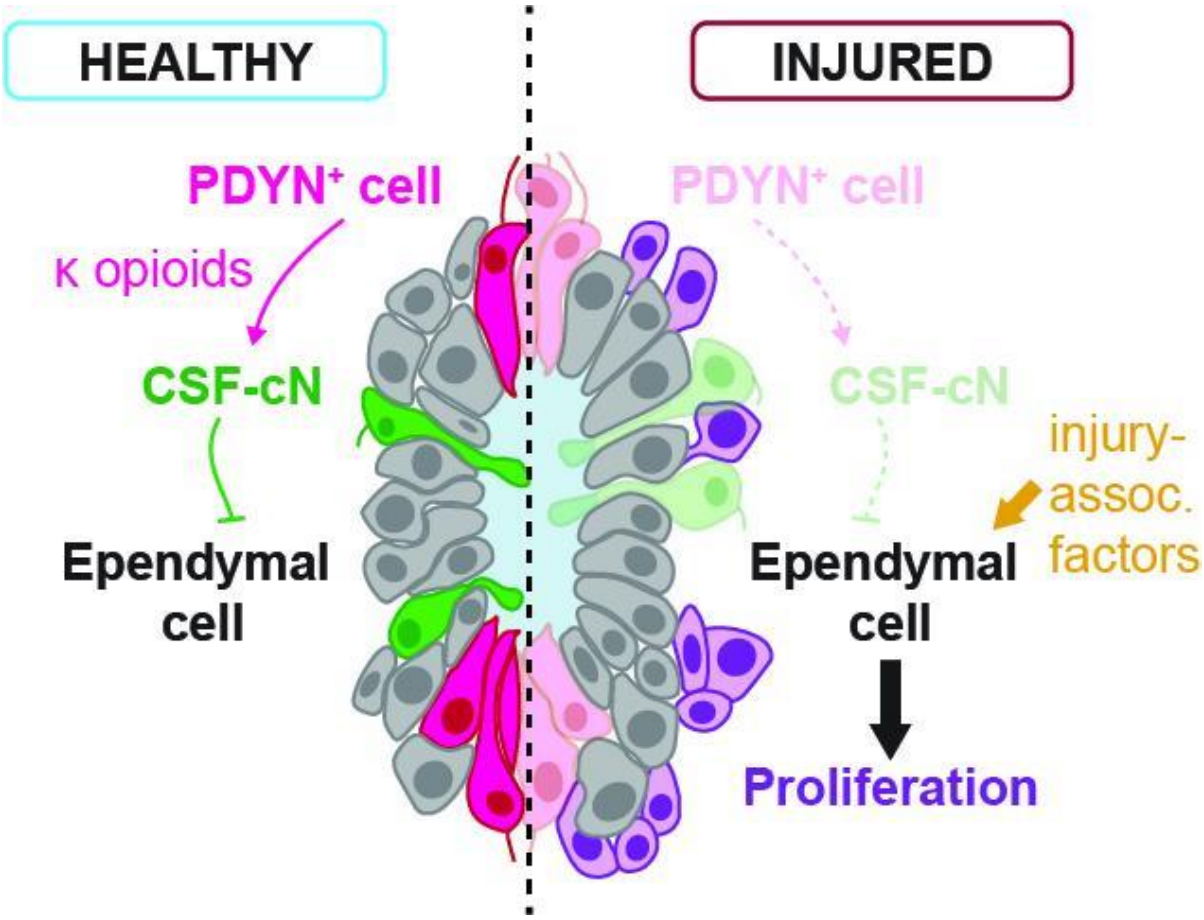
Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant NS105038
NIH Grant EY030138
HHMI Hanna Gray Fellowship
Croucher Fellowship for Postdoctoral Research
UCSF Program for Breakthrough Biomedical Research
Damon Runyon Cancer Research Foundation Fellowship DRG-[2387-30]

Title: Endogenous opioid signaling regulates scar formation in spinal cord injury

Authors: *W. YUE[1], K. K. TOUHARA[3], K.-I. TOMA[2], X. DUAN[4], D. JULIUS[5];
[2]Ophthalmology, [1]Univ. of California San Francisco, San Francisco, CA; [3]Physiol., [4]Ophthalmology, [5]Dept. of Physiol., Univ. of California, San Francisco, San Francisco, CA

Abstract: After injury, mammalian spinal cords form scars to limit tissue damage, but excessive scarring can hinder neural regeneration and functional recovery. While previous research has focused on astrocytes, recent evidence highlights the role of ependymal cells. These cells, usually lining the central canal, proliferate and differentiate into astroglia post-injury, becoming core components of the scar. We identified an endogenous kappa (κ) opioid signaling pathway that regulates ependymal proliferation. The κ opioid receptor, OPRK1, is expressed in cerebrospinal fluid-contacting neurons (CSF-cNs), with nearby cells expressing the ligand prodynorphin (PDYN). Contrary to the typical inhibitory role of κ signaling, κ opioids excite CSF-cNs to inhibit ependymal proliferation. Systemic administration of a κ antagonist enhances proliferation in uninjured condition. Most recently, we also found that a κ agonist significantly reduces proliferation post-injury, impacting scar formation and motor function. These findings reveal a paracrine signaling mechanism where PDYN+ cells release κ opioids to modulate ependymal proliferation, providing potential therapeutic targets for controlling scarring and improving recovery after spinal cord injury.



Disclosures: W. Yue: None. **K.K. Touhara:** None. **K. Toma:** None. **X. Duan:** None. **D. Julius:** None.
Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.164/LBA159

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ)
Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)
Instituto Nacional de Neurociencia Translacional (INNT)
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)

Title: Development of a functional silicon chamber for in vitro spinal cord tissue regeneration with support for cell migration and neurite outgrowth.

Authors: *J. SANTOS[1], G. SARDELLA DA SILVA[3], V. RIBEIRO-RESENDE[2];
[1]Federal Univ. of Rio de Janeiro, Niteroi, Brazil; [2]Inst. de Biofísica Carlos Chagas Filho, Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [3]Carlos Chagas Filho Biophysics Inst., Univ. Federal Do Rio De Janeiro, Rio de Janeiro, Brazil

Abstract: Unlike the peripheral nervous system, the mammalian central nervous system does not have the ability to regenerate after injury. This is due to the presence of inhibitory molecules, such as those derived from myelin degradation, which create a toxic environment for neurons and prevent their survival and regeneration. Strategies to overcome this limitation have received increasing attention over the years, mainly in the development and application of biomaterials. The aim of this work was to evaluate the growth of motor neuron axons from the spinal cord of embryonic rats (CEUA protocol #092/20) from a tissue culture model using modified chambers and surfaces. Polycaprolactone (PCL) filaments coated with laminin were used as an extracellular matrix mimetic support, and three-dimensional silicone chambers (Sylgard 184) provided a hermetic environment for culture. Both were prepared in three steps: surface hydrophilization by O2+ plasma discharge, washing, and sterilization by ultraviolet radiation. To prepare the culture environment, the chambers were placed in Petri dishes and the filaments were cut to uniform thickness and length before being placed in the chambers. Pregnant Wistar rats at 17-18 days of gestation were euthanized, and the embryos were collected, decapitated individually, and the bodies placed in ventral decubitus in Petri dishes containing DMEM medium. Samples were obtained from the lumbar portion of the spinal cord, and the ventral region of the H-medulla was accessed via a transverse cut, resulting in small fragments that were placed on the filaments. One set of chambers was filled with 100 µL of neurobasal medium and another set with 100 µL of motor neuron selective medium (Cold Spring Harbor protocol). After six days of incubation, fixation, immunostaining (Tuj-1, GFAP) and histological staining (DAPI), the filaments were visualized by fluorescence optical microscopy (Colibri Zeiss). Consistent adherence of explants to the filaments and intense cell migration along the filaments were observed. Tuj-1 immunostaining showed that these neurons survived and projected neurites along the filaments, while GFAP indicated astrocytic proliferation on the filaments in both culture medium. Despite a visual difference in cellular migration from the explants between Neurobasal and CSH conditions, quantitative analyses did not show a significant difference.

Disclosures: J. Santos: None. **G. Sardella Da Silva:** None. **V. Ribeiro-Resende:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.165/LBA160

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NYS DoH C34463GG
NIH 1DP2NS106663
PVA22_R_00037
NIH NIGMS 1S10OD028547

Title: Conditioning electrical stimulation enhances functional rewiring in a mouse model of nerve transfer to treat chronic spinal cord injury

Authors: *M. SOLIMAN[1], J. JARA[2,3], A. BERNSTEIN[1], P. DI GRAZIA[1], A. R. FERGUSON[4], J. BROWN[5,6], A. TORRES ESPÍN[7,8,9], E. R. HOLLIS[1,10];
[2]BNI, [1]Burke Neurolog. Inst., White Plains, NY; [3]Scripps Res. Inst., La Jolla, CA; [4]Neurolog. Surgery, UCSF, San Francisco, CA; [5]Massachusetts Gen. Paralysis Ctr., Massachusetts Gen. Hosp., Boston, MA; [6]Harvard Med. Sch., Boston, MA; [7]Neurolog. Surgery, Univ. of California San Francisco, San Francisco, CA; [8]Univ. of Waterloo, Waterloo, ON, Canada; [9]Univ. of Alberta, Edmonton, AB, Canada; [10]Feil Family Brain and Mind Res. Inst., Weill Cornell Med., New York, NY

Abstract: Nerve transfer surgery is a state-of-the-art surgical approach to restore hand and arm function in individuals living with tetraplegia, significantly impacting daily life. While nearly a third of all individuals with chronic SCI may benefit from this intervention, variability in outcomes can limit the functional impact. A bedside to bench approach was taken to address the variable response of tetraplegic individuals to nerve transfer surgery. We used a hierarchical multiple factor analysis to evaluate the effects of conditioning electrical stimulation (CES) on outcomes in a mouse model of nerve transfer to treat chronic cervical spinal cord injury. We found that CES of donor nerves one week prior to nerve transfer surgery enhanced anatomical and functional measures of innervation of targeted muscles. Furthermore, CES increased the rate of recovery of naturalistic behavior. While the model has some limitations due to the small size of the rodent, our results support the use of CES as an effective approach to improve outcomes in clinical nerve repair settings.

Disclosures: M. Soliman: None. **J. Jara:** None. **A. Bernstein:** None. **P. Di grazia:** None. **A.R. Ferguson:** None. **J. Brown:** None. **A. Torres Espín:** None. **E.R. Hollis:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.166/LBA161

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NINDS R01NS122961
Wings for Life Spinal Cord Research Foundation

Title: Adam17 regulates neutrophil activity after spinal cord injury

Authors: *S. K. REID[1], A. V. TRAN[2], D. A. MCCREEDY[2];
[1]Biol., Texas A&M Univ., Bryan, TX; [2]Biol., Texas A&M Univ., College Station, TX

Abstract: After traumatic spinal cord injury (SCI), inflammation and other reactive processes can exacerbate tissue damage and worsen long-term functional recovery. Circulating neutrophils invade the spinal cord in large numbers after injury and peak within the first day after SCI; however, the molecular mediators of pathogenic neutrophil activities in SCI remain unclear. One potential master regulator of cytotoxic neutrophil function(s) is ADAM17, a metalloprotease responsible for cleavage of over 90 substrates including TNF-α and L-selectin. Prior work has shown that conditional knockout of ADAM17 in myeloid cells improves motor recovery after hemisection SCI, however, the role of neutrophils in ADAM17-mediated pathogenesis has yet to be investigated. Our preliminary studies have indicated a possible role for neutrophil ADAM17 in impairment of long-term functional recovery. To explore the role of ADAM17 in neutrophil function following SCI, we utilized a neutrophil specific knockout of ADAM17 (Adam17cKO). Using immunofluorescence, we quantified neutrophil numbers (Ly6G+) across the SCI lesion and found fewer neutrophils in Adam17cKO mice relative to WT controls at 1 day post-injury, indicating that ADAM17 may support neutrophil accumulation in the spinal cord after injury. To characterize further the neutrophils that accumulate in the injured spinal cord, we performed flow cytometry after SCI in Adam17cKO and wild-type controls. At 1 day post-injury, we found that surface L-selectin (CD62L) on neutrophils isolated from the injured spinal cord was elevated in Adam17cKO animals compared to WT controls. Additionally, Adam17cKO neutrophils exhibited increased activation (CD11b MFI of neutrophils) and increased neutrophil extracellular trap formation (CitH3+ neutrophils) compared to WT controls. Together, these data indicate a potential novel role of ADAM17 in regulation of neutrophil accumulation, activation, and effector functions (NETosis) in the injured spinal cord and expand the understanding of neutrophil pathogenesis in SCI.

Disclosures: S.K. Reid: None. **A.V. Tran:** None. **D.A. McCreedy:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.167/LBA162

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation Grant 993497
NIH Grant CA208765
NIH Grant DC016328

Title: Targeting retinoid acid metabolic pathway to improve neurobehavioral function after spinal cord injury

Authors: G.-Y. XU, ***K. SATO**, Z. WU, Q. YANG;
The Univ. of Texas Med. Br., Galveston, TX

Abstract: Targeting retinoid acid metabolic pathway to improve neurobehavioral function after spinal cord injury Guoying Xu, Kasumi Sato, Zizhen Wu, Qing YangDepartment of Neurobiology, University of Texas Medical Branch, Galveston, TX 77555
Neuroinflammation and neurodegeneration are key events contributing to poor patient outcomes following spinal cord injury (SCI). The strategies to reduce neuroinflammation hold potential to prevent neurobehavioral function and improve patient outcomes after SCI. Considering the role of retinoic acid (RA) in neuroinflammation under pathological conditions, strategies to inhibit RA clearance could be beneficial for SCI. We hypothesize that targeting CYP26s, the enzymes that predominantly mediate clearance of a major isomer of endogenous RA, will improve neurobehavioral function following SCI by reducing neuroinflammation. We used DX308, a patented specifical inhibitor of CYP26A1 and CYP26B1 from Dr. Philippe Diaz, to test this hypothesis in a preclinical T10 contusion model. Multidisciplinary approaches including behavioral tests of sensory (*Von Frey*, Thermal Hargreaves, and CPP tests) and locomotor (BBB, and Horizonal Ladder tests) function, and immunohistochemistry are utilized in the study. We found that 1) DX308 prevent development of SCI-chronic pain at three different dosages (i.p. for 10 days, 3,10, and 20 mg/kg; 3 hrs after contusion), without significant differences in efficacy among the dosages; 2) DX308 improved locomotor dysfunction of SCI at three different dosages; 3) There is no gender difference of improvement in locomotor and sensory dysfunction after DX308; 4) DX308 increased spared spinal tissue at the lesion site; 5) DX308 decreased the expression of GFAP and Iba-1 of spin cord. Our result indicated that application of DX308 during the acute/subacute stage improves morphological and functional outcomes after SCI. This study provides promising evidence that inhibiting CYP26 enzymes by DX308 to maintain higher levels of endogenous retinoic acid can mitigate the detrimental effects of SCI and enhance neurobehavioral recovery.
Acknowledgement: The research was funded by grants from the Craig H. Neilsen Foundation (993497 to Q.Y.), National Institutes of Health (NIH) grants (CA208765 to Q.Y., DC016328 to Z.W.).

Disclosures: G. Xu: None. **K. Sato:** None. **Z. Wu:** None. **Q. Yang:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.168/LBA163

Topic: C.11. Spinal Cord Injury and Plasticity

Support: the National Research Foundation of Korea (NRF) grant funded by the Korea government (MIST) (RS-2024-00347913)
the National Research Foundation of Korea(NRF) grant funded by the Ministry of Science and ICT (RS-2024-00348012)
the Pioneer Research Center Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning (2022M3C1A3090851)

Title: Characteristics of pathological changes in sensory-motor function and spinal neuronal activities following contusive spinal cord injury in rats.

Authors: *H. OK[1], M. KWON[2,3], E. PARK[4], J. KIM[2,3,5];
[1]Col. of Hlth. Science, Korea Univ., Seoul, Korea, Republic of; [2]Rehabil. Sci. Program, Dept. of Hlth. Sci., [3]Transdisciplinary Major in Learning Hlth. Systems, Dept. of Healthcare Sci., Grad. School, Korea Univ., Seoul, Korea, Republic of; [4]Dept. of Physiol., Col. of Med. and Neurosci. Res. Institute, Korea Univ., Seoul, Korea, Republic of; [5]Dept. of Hlth. and Envrn. Sci., Undergraduate School, Col. of Hlth. Science, Korea Univ., Seoul, Korea, Republic of

Abstract: Traumatic spinal cord injury (SCI) is a devastating event that disrupts spinal cord neuronal homeostasis, inducing chronic pain and spasticity in patients. Although these pathological symptoms and related mechanisms following SCI have been widely studied, the association between sensory-motor dysfunction and spinal neuronal hyperexcitability remains unclear. The present study aimed to investigate the association between behavioral changes related sensory-motor function and neuronal firings in the spinal cord following SCI in rats. The spinal cord was contused at T11 spinal segment using Infinite Horizons (IH) impactor (150 kydn) in adult male Sprague-Dawley rats. The Basso, Beattie, and Bresnahan (BBB) locomotor scale and combined behavioral score (CBS) were performed to evaluate motor functions and Modified Ashworth Score (MAS) for spasticity, a sensory-motor disorder, was measured. Paw withdrawal threshold (PWT) for mechanical sensitivity and acetone drop test for cold allodynia were tested before and after SCI. At 28 days post-SCI, *in vivo* electrophysiological studies were performed to observe evoked (maximal firings/sec; 0.16-26 g von Frey filaments to hind paw) and spontaneous (regular, irregular, and burst pattern) neuronal activities at the L4-6 spinal segment. Immediately after SCI, paralysis in bilateral hindlimbs was observed with a BBB score of zero. SCI rats showed a joint movement from 3 days post-SCI and then gradual motor recovery was continued until day 28. Following SCI, MAS was progressively increased and PWT decreased until 21d after SCI. Sensory and motor behaviors showed an almost plateau at around 28 days post-SCI. In the case of evoked neuronal responses, the response threshold to mechanical stimuli significantly decreased in the SCI group and neuronal firing rates of the SCI group were higher than in both normal and sham groups. In spontaneous neuronal responses, SCI groups also showed a significant increase in neuronal firing in both regular and burst patterns, but not in an irregular pattern, compared to normal and sham groups. The present data demonstrated that behavioral changes representing impaired locomotor function, spasticity, and pain-related behavior are strongly associated with changes in neural excitability after SCI. In future studies, it is necessary to validate changes in neural excitability and sensory-motor behavior in a time-dependent manner after SCI.

Disclosures: H. Ok: None. **M. Kwon:** None. **E. Park:** None. **J. Kim:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.169/LBA164

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 2022/06609-6
2024/01736-5
2021/05180-3
2018/05006-0

Title: Memantine enhances motoneuron survival and reduces gliosis after spinal root crush in mice

Authors: G. G. BÍSCARO[1], A. V. M. LEÃO[1], A. L. OLIVEIRA[2], ***L. CARTAROZZI**[1]; [2]Structural and Functional Biol., [1]Univ. of Campinas - Lab. of Nerve Regeneration, Campinas, Brazil

Abstract: Injuries within the spinal canal often involve the spinal roots, leading to longitudinal spinal cord injuries, which cause significant changes in the spinal cord microenvironment. These include motoneuron death, chronic gliosis, and synaptic pruning stand out. Glutamate excitotoxicity, mediated by excessive NMDA receptor (NMDAr) stimulation, is detrimental in this pathological scenario. Therefore, NMDAr antagonists, such as memantine, are considered putative treatments for central and peripheral nerve injury. The present study investigated the neuroprotective effects of memantine following ventral spinal root crush (VRC) in mice. Adult C57BL/6J mice underwent unilateral L4, L5, and L6 motor root crush and were divided into four groups: Vehicle, and Memantine at 30 mg/kg, 45 mg/kg, and 60 mg/kg. Memantine or Vehicle was administered daily for 14 days post-injury. Twenty-eight days post-lesion, mice were perfused, and lumbar intumescences were processed for immunohistochemistry. The animal use and handling protocol was approved by the local ethics committee (CEUA/IB/UNICAMP, protocol number 5740-1). Motoneuron survival was quantified via toluidine blue staining, and gliosis was assessed using GFAP and Iba-1 immunolabeling. Synaptophysin and VGLUT-1 (glutamatergic inputs) staining assessed the density of pre-synaptic terminals at the motor nucleus (Rexed lamina IX). All memantine doses significantly increased motoneuron survival, with the highest effect at 45 mg/kg ($p<0.001$). Memantine reduced microgliosis at 45 mg/kg and 60 mg/kg ($p<0.01$ and $p<0.05$, respectively) and astrogliosis at all doses ($p<0.01$). Additionally, memantine enhanced motoneuron input coverage ($p<0.001$), although VGLUT-1 expression showed no significant differences among groups ($p=0.08$). In conclusion, memantine

significantly improved motoneuron survival, reduced gliosis, and inhibited synaptic pruning, suggesting its potential clinical application.

Disclosures: G.G. Bíscaro: None. **A.V.M. Leão:** None. **A.L. Oliveira:** None. **L. Cartarozzi:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.017/LBA17

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

Support: NIA/NIH RF1AG081203
Cure Alzheimer's Fund.

Title: Impact of ABCA7 deficiency on mitochondrial function in iPSC-derived oligodendrocytes

Authors: *T. NAMBARA, T. KANEKIYO;
Neurosci., Mayo Clin., Jacksonville, FL

Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disorder with multiple genetic and environmental factors contributing to its pathogenesis. Genetic studies have identified several risk factors for AD, among which the *ABCA7* gene encoding ATP-binding cassette (ABC) subfamily A member 7 has emerged as significant risk factors for late-onset AD. Particularly, *ABCA7* loss of function variants have been demonstrated to increase AD risk. The ABC transporter family is known to be involved in lipid homeostasis and the regulation of various proteins, ions, and peptides that are crucial for neuronal health and function. While ABCA7 expresses in various bran cell types, our previous study demonstrated that ABCA7 deficiency influences mitochondrial lipid metabolism in neurons. In this study, we focused on oligodendrocytes, a critical glial cell type that support neuronal function and stability. To investigate the specific effects of ABCA7 deficiency on glial cell types, we conducted experiments using oligodendrocytes differentiated from ABCA7 knockout (KO) and isogenic control iPSCs. We assessed mitochondrial respiratory function in the iPSC-derived oligodendrocytes using the Seahorse XF Analyzer. This high-throughput assay assessed parameters such as oxygen consumption rate (OCR) and extracellular acidification rate (ECAR), providing insights into cellular metabolic states. The Cell Mito Stress Test showed that ABCA7-KO iPSC-derived oligodendrocytes exhibited a significant reduction in mitochondrial respiratory capacity compared to controls. This was evidenced by reductions in basal respiration, ATP production, and maximal respiration rates. Furthermore, the Glycolysis Stress Test showed that ABCA7deficiency reduced glycolytic activity in the iPSC-derived oligodendrocytes. The lower glycolysis rate was indicated by a significant decrease in ECAR, which measures glycolytic flux.

Our study demonstrated that ABCA7 deficiency leads to significant impairments in mitochondrial respiration and glycolysis in iPSC-derived oligodendrocytes. These metabolic disruptions may contribute to the neurodegenerative processes observed in AD. Understanding cell-type specific metabolic changes could inform the development of targeted therapeutic strategies for AD.

Disclosures: T. Nambara: None. **T. Kanekiyo:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.170/LBA165

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Cervical Spine Research Society Post-Doctoral Grant

Title: Assessing "LDX" Induced Restoration of Inhibitory Signaling after Traumatic Spinal Cord Injury

Authors: *O. I. HASSAN[1], S. TAKAMIYA[2], A. ASGARIHAFSHEJANI[3], M. ZAVVARIAN[4], A. D. MODI[4], T. MIMURA[2], J. HONG[6], M. G. FEHLINGS[5];
[1]Inst. of Med. Sci. Univ. of Toronto, Toronto, ON, Canada; [2]Krembil Brain Inst., Toronto, ON, Canada; [3]Dept. of Cell and Systems Biol., [5]Div. Neurosurg., [4]Univ. of Toronto, Toronto, ON, Canada; [6]Genet. and Develop., Krembil Res. Inst., North York, ON, Canada

Abstract: Traumatic spinal cord injury (SCI) is a life-threatening condition which threatens the physical, social, and vocational well-being of patients. The initial injury in SCI involves the mechanical disruption of neural tissue and is followed by secondary injury which impedes recovery in the spinal cord around the lesion site. Furthermore, functional losses extend beyond the lesioned area, disrupting synapses in anatomically preserved tissue, worsening SCI symptoms and recovery. The aim of this study was to evaluate the optimal dosage and efficacy of 'Loop Diuretic X' (LDX), a pharmacological inhibitor of NKCC1 in enhancing neurobehavioral outcomes in a cervical SCI model of injury. Female Wistar rats (4 weeks) received a clip compression-contusion injury at the C6/C7 level of the spinal cord as the model for patients with SCI. The SCI model is highly clinically relevant with 60% of all traumatic SCI cases occurring at the cervical level. An initial drug dosage curve was generated through LDX IP administration bidaily in non-injured rats with n=5 in 0mg/kg (vehicle), 4mg/kg, 8mg/kg, and 12mg/kg. This found no significant adverse effects on neurobehavioral outcomes 8 mg/kg and below, with 12 mg/kg reducing grip strength. Subsequently, finding the optimal LDX concentration for recovery in rats with SCI, n=7,8,8,7 rats with corresponding dosages of 0, 2, 4, & 6 mg/kg of LDX were administered the drug over 8 weeks. Significant improvements in grip

strength ($p<0.05$) and trunk balance ($p<0.05$) were observed. Electrophysiological assessments found a decreased latency between motor evoked potentials in the forelimbs of the 6 mg/kg group ($p<0.05$). The novelty and significance of the study is in the model, drug, and patient applicability. Other studies of different NKCC1 inhibitor drugs have been limited in effect after BSCB repair due to poor permeability. LDX's neutral pH, low affinity for hydrogen bonding, and no carboxyl group presents it as a hopeful candidate over its predecessors for better BSCB penetrance. Hence, in comparison to other proposed SCI treatments, this therapy closely addresses patient requirements for long-term neuromodulation therapy after SCI — beyond the acute phase of injury.

Disclosures: O.I. Hassan: None. **S. Takamiya:** None. **A. Asgarihafshejani:** None. **M. Zavvarian:** None. **A.D. Modi:** None. **T. Mimura:** None. **J. Hong:** None. **M.G. Fehlings:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.171/LBA166

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant NS117103

Title: Nanoparticle and epothilone D intervention improves motor performance and regeneration in chronic cervical spinal cord injury

Authors: *S. HOCEVAR[1], B. ROSS[2], S. SCHWARTZ[2], B. M. SMILEY[3], L. SHEA[2]; [1]Neurosci. Grad. Program, [2]Biomed. Engin., Univ. of Michigan, Ann Arbor, MI; [3]Biomed. Engin., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Spinal cord injury (SCI) causes permanent loss of sensory and motor function below the level of injury due to neuron and oligodendrocyte death. A variety of factors exacerbate the injury and limit the regenerative capability of the spinal cord. First, the infiltration of myeloid cells and the cytokines that they secrete exacerbate cell death and create a pervasive inflammatory environment. Second, fibroblasts and astrocytes migrate to the injury site and form scar tissue. Third, low expression of regeneration associated genes in the CNS and the presence of myelin debris and scar tissue inhibit axonal regeneration by neurons. To combat these issues, we proposed a combinatorial approach in a chronic model of a cervical hemisection injury. First, to combat the inflammation following injury, we administered cargo-less poly(lactide-co-glycolide) (PLG) nanoparticles (NPs). NPs are injected intravenously following injury and are phagocytosed by circulating monocytes and neutrophils, decreasing their migration to the SCI and reprogramming them towards an anti-inflammatory phenotype. Mice that received NP

treatment made fewer mistakes on a ladder beam test of motor performance. Second, 4 weeks after injury, we resected scar tissue and inserted a microporous, multichannel PLG bridge. This removes inhibitory astroglial scar tissue and provides a scaffold to guide regenerating axons across the injury site. We tested whether NP administration after the resection surgery can have a further beneficial effect. Mice that received NPs after both the initial injury and resection performed better on the ladder beam test than mice that received vehicle or NPs after only one surgery. Lastly, we administered epothilone D (epoD), a microtubule stabilizer that can penetrate the blood-brain barrier, to limit axon retraction and boost elongation. Mice received two doses of epoD, the first after the resection surgery, and the second two weeks post-resection. Mice that received epoD performed better on the ladder beam task than mice that did not, and mice that received both epoD and NPs after both surgeries performed the best out of all groups. Underlying this performance, all mice that received NPs or epoD exhibited robust axon growth into the injury and both oligodendrocyte and Schwann cell myelination of regenerating axons. Together, these results suggest that a combinatorial treatment plan that targets both inflammation and growth-inhibitory factors can improve motor performance following SCI.

Disclosures: S. Hocevar: None. **B. Ross:** None. **S. Schwartz:** None. **B.M. Smiley:** None. **L. Shea:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.172/LBA167

Topic: C.11. Spinal Cord Injury and Plasticity

Support: San Raffaele Hospital Starting Donation
Bertarelli Foundation Donation

Title: Combined High and Low-Frequency Epidural Electrical Stimulation Improves Spastic Co-contraction and Facilitates Walking Recovery in Spinal Cord Injury Patients

Authors: *S. ROMENI[1], E. LOSANNO[2], D. EMEDOLI[5], L. ALBANO[5], F. AGNESI[5], L. TONI[3], V. FOSSATI[3], C. CIUCCI[4], S. IANNACCONE[6], P. MORTINI[7], S. MICERA[8]; [1]MINE Lab, UniSR and TNE Lab, EPFL, Milano, Italy; [2]Scuola Superiore Sant'Anna, Pisa, Italy; [4]The Biorobotics Inst., [3]Scuola Superiore Sant'Anna, Milano, Italy; [5]MINE Lab, UniSR, Milano, Italy; [6]San Raffaele Scientific Inst., Milano, Italy; [7]San Raffaele Hosp., Milano, Italy; [8]Swiss Federal Inst. of Technol., Lausanne, Switzerland

Abstract: Spinal cord injury (SCI) causes severe motor and sensory deficits, and there is currently no approved treatment for recovery. Recently, the integration of epidural electrical stimulation (EES) with rehabilitation has demonstrated significant potential in enhancing the

restoration of motor functions. However, individuals with abnormal muscular co-contraction and spasticity may not benefit fully from these interventions. Here, we demonstrate the efficacy of high-frequency EES (HF-EES) in alleviating undesired muscular co-contraction and spasticity in two patients with incomplete SCI. Moreover, we exploited a combination of HF-EES and low-frequency EES (LF-EES) to enhance various functional movements, with notable improvements in lower limb kinematics, muscle performance and functional assessments. This study suggests that HF-EES could be an important supplementary tool in SCI treatment, emphasizing the importance of personalized rehabilitation approaches and advanced tools to optimize EES treatments, offering hope for individuals with SCI-related deficits.

Disclosures: S. Romeni: None. **E. Losanno:** None. **D. Emedoli:** None. **L. Albano:** None. **F. Agnesi:** None. **L. Toni:** None. **V. Fossati:** None. **C. Ciucci:** None. **S. Iannaccone:** None. **P. Mortini:** None. **S. Micera:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.173/LBA168

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH-NINDS NS112535
NSF 2015317 NeuroNex C3NS

Title: Evaluating decoders of locomotion intent after spinal cord injury to drive restoration of movement using FES

Authors: *S. NARAYANAN[1], M. C. TRESCH[2];
[2]Biomed. Eng, Physical Med. and Rehab, Physiol., [1]Northwestern Univ., Chicago, IL

Abstract: After spinal cord injury (SCI), voluntary control of the muscles below the level of injury is severely impaired. Functional electrical stimulation (FES) has been used to help patients withSCI regain control of their paralyzed limbs. It has further been suggested that delivering FES inaccordance with movement intent decoded by a brain machine interface (BMI) can aid inrehabilitation and recovery in patients with SCI by strengthening descending supraspinalprojections. In a BMI-FES system, neural signals are recorded and decoded into motor intent,which is then used as the control signal to stimulate muscles to evoke the intended movement.Our group has been working on developing a BMI-FES system to restore hindlimb movementduring locomotion in a rat model. We examine here the ability of two different decoders toestimate intended locomotor phase from cortical activity that can be used within a BMI-FESsystem after SCI. Following previous work in our group, we recorded hindlimb cortical activityin rats following SCI and created decoders to estimate intended movements. Since

hindlimbmovements were impaired after SCI, we trained decoders to predict ongoing forelimbmovements, relying on the close coupling between forelimb and hindlimb movements duringquadrupedal locomotion in rats. We evaluated predicted locomotor phase using either a Wiener filter or a Kalman filter. We found that the Wiener filter had marginally better accuracy than theKalman filter, as evaluated by the root mean squared error. Predictions using the Kalman filter,however, significantly outperformed the Wiener filter in producing a useful signal for drivingmuscle stimulation as part of a BMI-FES system, as evaluated by measures assessing phasevariability and similarity of predicted step durations to those typically observed in rats. We conclude that the Kalman filter is a better decoder for predicting simple locomotion intent in ratswith SCI when used within a system for BMI-FES.

Disclosures: S. Narayanan: None. **M.C. Tresch:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.174/LBA169

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The Advancing a Healthier Wisconsin (AHW) Endowment
The Hammes Family Endowment

Title: Cortical activity and connectivity changes after virtual reality-based hand dexterity training for degenerative cervical myelopathy

Authors: R. DE LEON[1], V. RAJU[2], A. VEDANTAM[3], M. GHASSEMI[4], D. G. KAMPER[5], *B. SCHMIT[6];
[1]Joint Dept. of Biomed. Engineering, Med. Col. of Wisconsin - Marquette University, Milwaukee, WI, Milwaukee, WI; [2]Neurosurg., Med. Col. of Wisconsin, Milwaukee, AL; [3]Neurosurg., Med. Col. of Wisconsin, Milwaukee, WI; [4]Biomed. Engin., Joint Biomiedical Engin. Dept. at Univ. of North Carolina at Chapel Hill and North Carolina State Univ., Raleigh, NC; [5]Biomed. Engin., North Carolina State Univ., Cary, NC; [6]Joint Dept. of Biomed. Engin., Marquette Univ. and MEdical Col. of Wisconsin, Milwaukee, WI

Abstract: In this study, we used electroencephalography (EEG) to determine the effect of 4 weeks of hand dexterity training on post-surgical cortical plasticity in degenerative cervical myelopathy (DCM). DCM is the most common cause of adult spinal cord dysfunction, often resulting in impaired hand dexterity. Over 30% of DCM patients do not achieve meaningful recovery of hand dexterity after surgery. Currently, there are no targeted interventions available to augment recovery for DCM and no available evidence of how hand motor rehabilitation alters cortical motor processing. Post-surgical DCM participants (n=13, mean age = 68±11 years, 10

males, 4.71±2.59 months post-surgery) participated in the study for 11 weeks. EEG signals were recorded before the start of training, after 4 weeks of training, and 4 weeks after training ended. For all visits, we investigated changes in the EEG temporal patterns in the β-band (13-30Hz) during and after simple individuated finger movements. We quantified the change in β-band power relative to baseline, as cortical activation or event-related desynchronization and synchronization (β-ERD & β -ERS) and change in β-band task-based coherence relative to baseline (β-tbCoh) as connectivity. Contralateral cortical activity and connectivity between motor and frontal regions after movement showed statistically significant differences between pre- and post-training. At post-training, the contralateral β-ERS area was significantly higher (median = 11.34%, W = 6, z = 2.76, p = 0.006) than pre-training (median = 3.54%). There was also a significant increase in β-tbCoh post-task between the contralateral motor and frontal region post-training (mean = -0.001, SD = 0.0235) compared to pre-training (mean = 0.0157, SD = 0.0223); t(12)=3.602, p = 0.004. A similar trend was observed in β-tbCoh post-task between contralateral sensory region and frontal region post-training (mean = -0.0038, SD = 0.0257) versus pre-training (mean = 0.0164, SD = 0.0256); t(12) = 3.546, p = 0.004. These results suggest training-induced cortical changes potentially indicating improved sensorimotor function and better synchronization of neural activity, consistent with significant improvements in Jebsen Taylor Hand Function scores at post-training (t(13) = 4.075, p = 0.002).

Disclosures: R. De Leon: None. **V. Raju:** None. **A. Vedantam:** None. **M. Ghassemi:** None. **D.G. Kamper:** None. **B. Schmit:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.175/LBA170

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NS104194
Craig Nielson Foundation
Philadelphia Foundation Brody Fund

Title: Differential alterations in Hoffman reflex modulation in rats that do and do not become hyperreflexive following combined SCI treatments

Authors: *A. BORISYUK[1], M. SHARMA[2], K. J. DOUGHERTY[1], S. F. GISZTER[1]; [1]Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Augusta Univ., Augusta, GA

Abstract: Previously, sustained expression of brain-derived neurotrophic factor (BDNF) during SCI therapy spontaneously induced stepping in rats. However, the increasing prevalence of developing hyperreflexia after 3-4 weeks caused functionally deleterious ‘collapse’ in

locomotion. Collapse is a process that can be phenotypically characterized as the increase in frequency of one or more symptoms of hyperreflexia in the trunk and/or hindlimbs, including rapidly progressing clonic movements, twitching, and prolonged flexion of the hindlimbs at the knee or hip. Although the precise mechanism of collapse is unknown, the dysregulation of spinal interneurons modulating spinal reflexes may result in dysregulated spinal circuit excitability that contributes to the hyperreflexia phenotype of collapse. To investigate this outcome and further improve BDNF-based rehabilitation, we explored combined rehabilitations using gene therapy (AAV-BDNF), different epidural stimulation types (ES), and robotic training for SCI in rats. To understand chronic spinal circuit-level changes mediating locomotor reflexes in gastrocnemius, we implanted a stimulating cuff around the tibial nerve, and monitored hindlimb muscle responses over the course of robot rehabilitation. Monosynaptic reflex testing and reflex rate depression (frequency dependent depression, FDD) was used to test spinal excitability. We tested if different types of ES therapy can better recover and maintain locomotion by preventing BDNF-associated hyperreflexia in the combined therapy. We hypothesized that the spinal reflex controls are altered in rats with hyperreflexia collapse. Our data show that suprathreshold ES extends the therapeutic window of BDNF-induced plasticity to significantly improve assisted locomotion before any BDNF-driven ‘collapse’. Analysis of tibial nerve H-reflex tests revealed a loss of part of the range of FDD modulation in the collapsed rats, whereas rehabilitated rats without collapse had reflex modulation similar to uninjured rats. Independent component analysis (ICA) of hindlimb electromyography in these rats revealed high post-SCI correlation values of the weighting matrices and synergy matching in all groups, supporting a conserved modular control of locomotion after SCI, even in collapse patterns. Altogether, the data suggest that the development of hyperreflexive collapse after the combined SCI treatments is associated with the progressive dysregulation of spinal interneurons modulating the spinal reflexes, at higher frequencies of activation, which can be delayed by appropriate ES.

Disclosures: A. Borisyuk: None. **M. Sharma:** None. **K.J. Dougherty:** None. **S.F. Giszter:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.018/LBA18

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

Support: NIA R01AG065836

Title: A multi-omics approach reveals novel astrocyte dysfunction in a murine model of Alzheimer disease

Authors: *J. LI[1], X. WEI[1], H. SONTHEIMER[2], M. L. OLSEN[1];
[1]Virginia Tech. Neurosci. PhD Program, Blacksburg, VA; [2]Neurosci., Univ. of Virginia, Charlottesville, VA

Abstract: Alzheimer's disease (AD) is the most common age-related neurodegenerative disease, with 58 million individuals affected worldwide. Pathological sequelae include abnormal aggregation of β-amyloid (Aβ) peptides and neurofibrillary tangles (NFTs), neuronal loss and astrocyte and microglial activation. Astrocytes play an important role in brain health and express high levels of the three AD causative genes *APP, PSEN1 and PSEN2* and are the primary cell type expressing the strongest risk factor gene in late onset Alzheimer disease, *APOE.* Research obtained evaluating astrocyte gene expression in bulk, single cell, single nuclei and spatial transcriptomic RNA sequencing in human AD tissue, IPSC derived astrocytes and in AD animal models reveal alterations in genes driving inflammation, cell senescence, morphology and territory size. It is not clear how these transcriptomic changes relate to protein expression and astrocyte cell function. Here, we applied a multi-omics unbiased, transcriptome and proteome approach in hAPPJ20 mice (a commonly used AD animal model, with vascular Aβ accumulation) to evaluate the astrocyte transcriptome and proteome across healthy aging and AD disease progression (3, 6, 12 and 18 months) in female J20 and WT mice. Our data indicate robust astrocyte gene and protein expression differences increase with age, and disease progression. Gene Ontology (GO) enrichment analysis indicates global inflammation, disrupted astrocyte metabolism and vascular dysfunction after the 6-month time point. Intriguingly, we identified cell apoptotic pathways in female J20 mice relative to WT littermates. Immunohistochemistry reveals astrocyte numbers are significantly decreased in J20 mice at 12 months. Ongoing work includes identifying if loss of astrocytes is plaque-associated and integrating data from our studies with publicly available data in other AD murine models and human AD tissue.

Disclosures: J. Li: None. **X. Wei:** None. **H. Sontheimer:** None. **M.L. Olsen:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.019/LBA19

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

Title: Cd33-targeting sirna conjugates for treatment of alzheimer's disease

Authors: *J. C. PARK[1], A. G. SORETS[2], E. S. LIPPMANN[3];
[1]Medicine, Health, and Society, [2]Biomed. Engin., [3]Chem. and Biomolecular Engin., Vanderbilt Univ., Nashville, TN

Abstract: Advances in biotechnology have generated a deeper understanding of Alzheimer's Disease (AD) pathophysiology, yet many therapeutic targets remain undruggable either due to their protein structure or location within the brain. Notably, CD33 is implicated as an AD risk gene because its activation in microglia inhibits clearance of Aβ. Genetic knockout of CD33 reduces amyloid burden and improves cognition in mouse models, yet current therapeutic approaches to inhibit CD33 are ineffective. Traditional small molecule therapies are challenging because CD33 does not contain specific binding pockets, and gene therapy approaches to lower CD33 expression are ineffective because microglia are notoriously difficult to transfect. We previously identified a non-viral conjugate (termed L2-siRNA) that mediates gene silencing in microglia after delivery into the CSF (**Fig 1A**). Here, our aim is to identify a potent siRNA against CD33 by screening sequences *in vitro* and *in vivo*. We evaluated two lead candidates (1152, 2288) in RAW 264.7 macrophages and observed that both sequences exhibited dose-dependent carrier-free gene silencing (**Fig 1B**). Next, we injected C57Bl/6J mice intracerebroventricular (ICV) with the L2-siRNA sequences and assessed knockdown compared to a non-targeting control (L2-siRNA^{NTC}) (**Fig 1C**). CD11b positive cells were isolated to evaluate knockdown in myeloid cells selectively, and both sequences exhibited robust CD33 knockdown (**Fig 1D**). Under the premise that CD33 is exclusively expressed by microglia and macrophages, we also examined regional tissue gene silencing in the CNS. The most potent gene silencing was observed within the thoracic and lumbar regions of the spinal cord, hippocampus, and cerebellum (**Fig 1E,F**). Overall, we demonstrated that L2-siRNA achieves potent knockdown of CD33 with two different sequences. Subsequent studies will investigate therapeutic efficacy in the 5xFAD disease mouse model by assessing Aβ plaque density, neuroinflammation, and cognitive function.

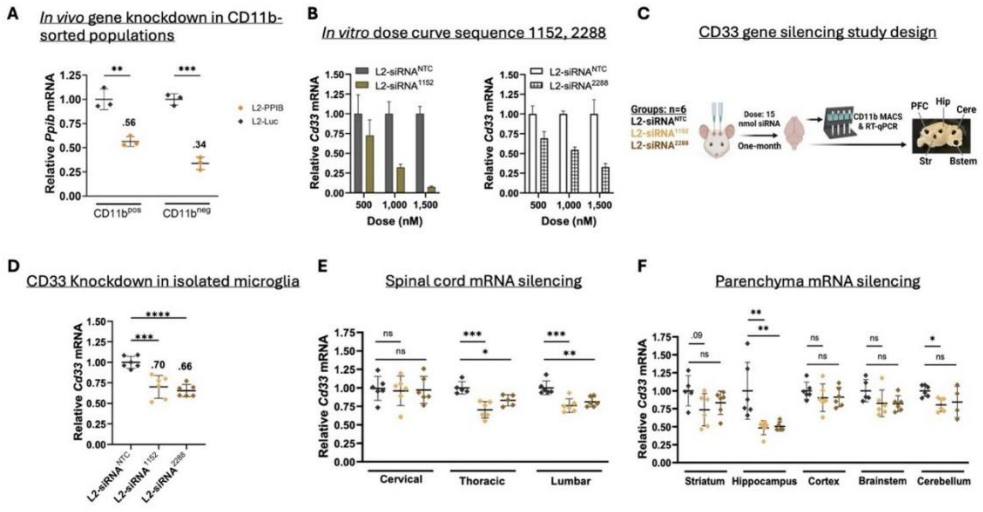


Figure 1. L2-siRNA gene silencing against PPIB and CD33 therapeutic target. A: PPIB knockdown in CD11b positive subpopulation isolated via Magnetic-Activated Cell Sorting (MACS) after 1 month. N=3 mice, normalized to a L2-siRNA^{NTC}. Unpaired t-test; **p < 0.005, ***p < 0.0005. **B:** Carrier-free gene silencing assessed in RAW 264.7 after 48 hours. Data shown is a representative experiment containing N=3 technical replicates and normalized to a non-targeting L2-siRNA^{NTC} control. **C:** Experimental design to assess CD33 silencing. C57Bl/6J mice are injected ICV with 15 nmol of siRNA and the brain is harvested after 1 month, where some tissue is collected via biopsy punch to examine regional knockdown and the remaining tissue is used to isolate microglia (CD11b^{pos}). **D:** Both CD33-targeting L2-siRNA sequences exhibit robust gene silencing in CD11b isolated cells, as measured by RT-qPCR. **E:** The spinal cord was isolated and segmented for mRNA analysis by RT-qPCR. **F:** CD33 gene silencing in five regions of the parenchyma. All statistical tests in D-F are One-way ANOVA with Bonferroni's correction; N=6 mice; data presented as mean ± SD; * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001, ns – not significant.

Disclosures: J.C. Park: None. **A.G. Sorets:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A.G. Sorets & E.S. Lippmann are inventors on a patent application covering lipophilic siRNA conjugates for the treatment of CNS diseases. **E.S. Lippmann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A.G. Sorets & E.S. Lippmann are inventors on a patent application covering lipophilic siRNA conjugates for the treatment of CNS diseases..
Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.020/LBA20

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

Support: NIH RO1 AG081774
NIH RO1 AG074999
VA I21RX004081

Title: Neurovascular coupling dysfunction in the mouse cortex and hippocampus of CVN Alzheimer's disease model

Authors: *Q. LI[1], F. GALEFFI[2], C. A. COLTON[3], D. A. TURNER[4];
[1]Duke Univesity Med. Ctr. and Durham VA Med. Ctr., Durham, NC; [2]Res. services, Duke Univ., Durham, NC; [3]Div. Neurol/ box 2900, Med. Ctr., Durham, NC; [4]Neurosurg., Duke Univ. Med. Ctr., Durham, NC

Abstract: Our recent findings indicate a significant deficiency in the hemodynamic substrate supply in cerebral cortex in transgenic Alzheimer's (CVN-AD) mice, which exhibit both AD-like behavior and pathology. However, the neurovascular mechanisms underlying these hemodynamic changes are poorly understood. We performed time-lapse IR-DIC imaging of the microvasculature in an acute slice preparation to investigate the dynamics of pericytes and capillaries in both cortical and hippocampal region. These microvessels are susceptible to the toxicity of Aβ amyloid plaques deposited near or in the walls of both arterioles and capillaries. We analyzed capillary diameter of both male and female CVN-AD mice. We compared cortical and hippocampal microvessel reactivity to a vasodilator, glutamate, in WT and age-matched CVN-AD mice. We further examined NVC reactivity in the hippocampus with NMDA and adenosine stimulation, two potent vasodilators. We found that, in mice younger than 20 weeks, glutamate (500μM) fully dilated pre-constricted capillaries, previously induced by norepinephrine (2μM), in both cortex and hippocampus of WT and CVN-AD mice. Hence, there is evidence for normal neurovascular coupling (NVC) function in younger mouse. However, the glutamate-induced vasodilatory effect was significantly attenuated in both 31-40 and 50-week-old CVN-AD mice but not in the age-matched WT mice, respectively, revealing impaired NVC

function in these aging CVN-AD mice. Activation of NMDA receptors with NMDA (100μM) also caused a full vasodilation of the pre-constricted hippocampal capillaries in WT but not in the age-matched (31 to 40 weeks old) CVN-AD mice. NMDA-induced vasodilation was, however, abolished by inhibiting NMDA receptors with APV, a specific NMDA receptor blocker, suggesting the involvement of the glutamatergic NMDA receptors in the NVC dysfunction. Tested in the same age group, adenosine (1mM), also fully restored the pre-constricted capillaries to control level in WT but this vasodilatory effect was significantly reduced in CVN-AD mice, implying that purinergic signaling is also involved in the NVC dysfunction in CVN-AD mice. Taken together, our novel results provide strong evidence for a progressive, age-related impairment of NVC reactivity with the reduced vasodilation in the neocortex and hippocampus in aged CVN-AD mice. More importantly, our results indicate that the reduced neurovascular responsivity in these brain regions could result in a focal blood flow decrease and, thus contribute to local neuronal and synaptic dysfunction and cell loss leading to cognitive decline in AD.

Disclosures: Q. Li: None. **F. Galeffi:** None. **C.A. Colton:** None. **D.A. Turner:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.021/LBA21

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

Title: Spatially resolved transcriptomics identifies increased inflammatory response in the presence of amyloid deposition in humans

Authors: *J. E. MALDONADO WENG, H. N. NORISTANI, P. N. LACOR;
Eli Lilly, Philadelphia, PA

Abstract: Cerebral amyloid angiopathy (CAA) is a major co-pathology present in over 80% of Alzheimer’s disease (AD) patients. This neuropathological hallmark is defined by an accumulation of amyloid deposits in cerebral cortical and leptomeningeal vessels. Although pathogenesis is poorly understood, CAA leads to perivascular leakage, microaneurysms and an increased risk of cerebral hemorrhages. Vascular amyloid deposition is also associated with an elevated neuroinflammatory response. To identify CAA-specific inflammatory pathways, we evaluated multiple markers using the GeoMx® digital spatial profiler (DSP) in pathology-enriched microenvironments such as amyloid deposition (plaques, parenchymal and leptomeningeal CAA) in postmortem human brain regions from AD patients with and without CAA. Using the comprehensive whole transcriptome atlas (WTA) panel that targets 18,000 transcripts, we analyzed gene expression of pathologically relevant pathways in select regions of interest. We found reduced expression of neuronal-signature genes and greater abundance of

pericytes and astrocytic signature genes in AD+CAA compared to AD and control, per cellular deconvolution estimates. A significant enrichment of genes was associated with the epithelial cell apoptosis regulation, cytokine binding and blood microparticles, which include apoE, interleukins, and members of the complement system, in AD compared to control tissues within amyloid enriched microenvironments. Pathways such as adaptive immune response, response to LPS, vasculature reorganization, and extracellular remodeling were exacerbated in AD+CAA, compared to AD. GeoMx proteomic assessment (76+ protein panel) confirmed upregulation of activated state for microglia and astrocytes within amyloid enriched microenvironments with additional differentiation in parenchymal CAA (GFAP and C4B). Based on our findings, astrocytic markers are a potential effective indicator of CAA in AD.

Disclosures: J.E. Maldonado Weng: A. Employment/Salary (full or part-time):; Eli-Lilly/Full-time. **H.N. Noristani:** A. Employment/Salary (full or part-time):; Eli-Lilly/Full-time. **P.N. Lacor:** A. Employment/Salary (full or part-time):; Eli-Lilly/Full-time.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.022/LBA22

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

Support: NIH Grant AG061800
NIH Grant AG054719
NIH Grant AG063755
NIH Grant AG068024
NIH Grant AG083305

Title: Synaptic tau seeding correlates with memory impairment and neurofibrillary tangle accumulation in older adults

Authors: *A. WEBER[1], B. NG[2], K. M. GREATHOUSE[1], D. A. BENNETT[2], N. T. SEYFRIED[3], C. GAITERI[4], J. H. HERSKOWITZ[1];
[1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]Rush Univ. Med. Ctr., Chicago, IL; [3]Human Genet., Emory Univ., Atlanta, GA; [4]SUNY Upstate Med. Univ., Syracuse, NY

Abstract: The severity of cognitive decline in Alzheimer’s disease (AD) correlates with the extent of tau pathology accumulation across the brain. In AD, pathologic tau likely spreads from the entorhinal cortex (EC) to other brain regions via synaptic connections. It has been proposed that pathologic tau can act as a “prion-like” seed which can drive misfolding and aggregation of physiological tau. Therefore, tau seeds residing in synaptic compartments may be crucial to the spread or propagation of tau in AD. In this study, we tested whether relationships exist between the bioactivity of synaptic tau seeds and cognitive or neuropathological data among individuals

within the Religious Order and Rush Memory and Aging Project (ROSMAP). Inferior temporal gyrus (ITG) synaptosome fractions were prepared from 128 ROSMAP postmortem tissue samples. We detected synaptic tau seed bioactivity from cases at high Braak stages, but little to no bioactivity from early Braak stage cases. Synaptic tau bioactivity was not correlated with age but was inversely correlated with episodic, semantic, and working memory scores. Neurofibrillary tangles and amyloid-β pathology scores were positively correlated with synaptic tau seed bioactivity. Synaptic tau seed bioactivity was integrated with multiplex tandem mass tag mass spectrometry (TMT-MS) ITG proteomics. Proteomic association analysis uncovered protein signals that could indicate key pathways involved in synaptic tau seed bioactivity in the ITG. Collectively, this data provides further evidence that the aggregative propensity of tau within synapses strongly links to AD pathology and cognitive decline.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.023/LBA23

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

Title: Investigating the dual role of Aβ peptides in Alzheimer's disease pathogenesis

Authors: *A. SIDDU;
Stanford Univ., Stanford, CA

Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disorder and the leading cause of dementia globally, marked by the accumulation of β-amyloid (Aβ) plaques in the brain. The precise roles of Aβ peptides and their precursor protein (APP) in AD pathogenesis are not fully understood. Aβ plaque formation sequesters free Aβ peptides, reducing their levels in cerebrospinal fluid and blood. Pharmacological efforts to reduce soluble Aβ have generally failed to demonstrate therapeutic benefits and, in some cases, have even worsened cognitive decline, indicating a critical physiological role for Aβ. To address these knowledge gaps, we first investigated the individual activities of Aβ42 and Aβ40, the most abundant Aβ peptides. Despite differing by only two amino acid residues, these peptides exhibit markedly different properties. Aβ42 has two additional hydrophobic amino acids (Ile-41 and Ala-42) at its C-terminus compared to Aβ40, making it more prone to aggregation, even at much lower concentrations. Using induced human neurons (hiNs), we found that Aβ42 administration significantly increases the number of synapses and overall network activity in cultured neurons before exerting its toxic effects. Surprisingly, Aβ40 also maintains this synaptogenic activity, albeit at higher concentrations. Additionally, unlike Aβ40, Aβ42 influences the formation and distribution of

pre-synaptic vesicles. Super-resolution microscopy revealed that the synaptogenic effect of Aβ42 is accompanied by an increased area occupied by pre-synaptic vesicles compared to controls. However, during its toxic phase, Aβ42 reduces the area occupied by pre-synaptic vesicles, thereby impacting synaptic architecture. Given the dual ability of the Aβ42 to induce synaptogenesis and synaptotoxicity, we explored a mutated form of Aβ42 found in AD patients caring the Arctic mutation in the APP gene. This Aβ42-am form is more prone to aggregation, leading to earlier disease onset. Our findings showed that Aβ42-am lacks synaptogenic activity and is more toxic, even at low concentrations, than non-mutated Aβ42. All investigations were blinded to reduce bias and utilized four different batches of hiNs cultures per experiment for statistical reliability. Results were compared to controls treated with vehicle alone, and data were rigorously analyzed for significance. These results collectively shed light on the still unknown physiological roles of Aβ peptides, supporting the hypothesis that they could be involved in synapse formation. Moreover, mutations of these peptide structures might ultimately result in the loss of their physiological functions and exacerbate their toxicity.

Disclosures: A. Siddu: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.024/LBA24

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

Support: University of South Carolina Office of National Fellowships and Scholar Programs to MJP
University of South Carolina Office of Undergraduate Research to AES
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University of South Carolina Office of the Vice President for Research DJH
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NIH Grant K01AG061263 to JAM
NIH Grant P20GM109091 to JAM

Title: A Comparative Analysis of Serine Synthesis and Transporter mRNA Expression in the Hippocampus: Normal Aging vs. Alzheimer’s Disease

Authors: *M. J. PITRE[1], A. E. SIKORA[1], D. J. HOROVITZ[1], C. M. HERNANDEZ, III[2], J. A. MCQUAIL[1];
[1]Univ. of South Carolina, Columbia, SC; [2]Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Age-related dysregulation of D-serine metabolism may contribute to cognitive decline and Alzheimer’s Disease (AD). D-serine acts as an essential co-agonist of NMDA receptors at

synaptic sites, pivotal for promoting neuroplasticity. Notably, D-serine levels and NMDAR activity decline with age. Research indicates age-related reduction of serine racemase (SRR), the enzyme that converts L-serine to D-serine, whereas D-serine supplementation has shown potential to reverse memory loss in aging. Of critical note, while studies on normally aging brains suggest that the loss of D-serine may contribute to memory decline, findings from AD brains propose that increased D-serine is indicative of disease progression. However, comprehensive analysis across the complete serine metabolic pathway encompassing aging, AD diagnosis, and memory performance remains scarce. Leveraging publicly available gene expression datasets, our study examined the impact of age, AD pathology, and memory performance with a focus on 11 mRNAs encoding proteins associated with serine metabolism and transport. We compared hippocampal mRNA profiles from normally aging rats and AD-affected humans. Findings reveal upregulation of PHGDH and PSAT1, involved in L-serine synthesis, in both aging and AD samples. Conversely, PSPH, another L-serine synthesis enzyme, was downregulated, along with SRR and genes related to D-serine vesicle packaging (ATP6AP1/2). In aged rats, SLC7A10, encoding a D-serine transporter, exhibited an inverse correlation with spatial learning, suggesting potential D-serine transport dysregulation in age-related cognitive decline. Additionally, D-amino acid oxidase (DAO), which degrades D-serine and is minimally expressed in the rat hippocampus regardless of age, was upregulated in the human hippocampus in AD. These findings underscore significant parallels in mRNA expression profiles between the hippocampi of aged rats and AD-affected humans, despite some differences. Ongoing investigations will analyze additional gene profiling datasets to further elucidate how aging and AD interact to influence D-serine metabolism and transport. Future studies will leverage the TgF344-AD transgenic rat model to investigate how D-serine signaling mechanisms impact learning and memory decline in both normal aging and AD.

Disclosures: M.J. Pitre: None. **A.E. Sikora:** None. **D.J. Horovitz:** None. **C.M. Hernandez:** None. **J.A. McQuail:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.025/LBA25

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

Support: NIH/NIA Grant P20AG068077

Title: Effects of acute antalarmin treatment on Alzheimer's Disease TgF344-AD rats: examining hippocampal-dependent neuronal firing and spatial navigation

Authors: *N. C. REYNA[1], D. A. HAMILTON[2];
[1]The Univ. of New Mexico, Albuquerque, NM; [2]Psychology, Univ. New Mexico, Albuquerque, NM

Abstract: Alzheimer's disease is characterized by neurobiological deterioration and cognitive impairment that is irreversible. Alzheimer's disease patients exhibit increased stress system abnormalities including upregulation of the corticotropin releasing factor type 1 receptor (CRF_1) and elevated levels of cortisol. Further, those who experience increased psychological distress in life are more likely to be diagnosed with Alzheimer's disease later in life and experience faster rates of neurocognitive decline following a diagnosis. Therefore, the current project examined the underlying systems involved in Alzheimer's disease neuropathology and stress. Previous studies have shown that administration of the CRF_1 antagonist, Antalarmin, reduced AD pathogenesis and anxiety-like behavior in mouse models of Alzheimer's disease. A newer rat model of Alzheimer's disease (TgF344-AD) has become widely used in recent years due to its ability to represent different stage of Alzheimer's disease (e.g., preclinical and MCI) as well as expression of robust neuropathology (e.g., tau, amyloid-beta, neuroinflammation and neuronal loss). Thus, the current project used the TgF344-AD model to elucidate the mechanistic functions of CRF_1 on the progression of AD neuropathology. We report on the effects of CRF_1 antagonism on anxiety-like behavior, spatial navigation and memory, olfactory memory, and alterations of long-term potentiation in the hippocampus. Our results currently indicate that Antalarmin decreased anxiety-like behavior in the EPM ($p<0.05$). Further, TgF344-AD rats who received acute Analarmin injections took more direct paths to the platform in the MWT and had shorter swim latencies compared to saline treated TgF344-AD rats ($p<0.05$). Hippocampal firing was significantly reduced in all TgF344-AD animals, regardless of drug treatment ($p<0.05$). Interestingly, TgF344-AD rats demonstrated similar olfaction memory in the socially tranmissible food preference compared to WT ($p>0.05$). This project provides a more comprehensive understanding of Alzheimer's disease and expand treatment options available while prioritizing early-interventions and promoting mental well-being.

Disclosures: N.C. Reyna: None. **D.A. Hamilton:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.026/LBA26

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

Support: Cure Alzheimer's Fund GR0032142
Brightfocus Foundation Standard Award Program 29225

Title: Circuit-specific selective vulnerability in the DMN persists in the face of widespread amyloid burden

Authors: *J. MCGREGOR[1], S. J. BRUNWASSER[2], K. BHASKARAN-NAIR[2], H. ELMORE[2], E. L. DYER[3], J. D. WHITESELL[4], J. A. HARRIS[5], K. B. HENGEN[2];
[2]Biol., [1]Washington Univ. in St. Louis, St. Louis, MO; [3]Georgia Inst. of Technol., Atlanta, GA; [4]Translational Models and Biomarkers, Cajal Neurosci., Seattle, WA; [5]Res. Mgmt., Cure Alzheimer's Fund, Seattle, WA

Abstract: The relationship between brain-wide functional decline and accumulation of pathological protein aggregates in Alzheimer's disease (AD) is complex and not well understood. A set of highly interconnected cortical regions known as the default mode network (DMN) exhibits selective vulnerability to both functional decline and amyloid beta (Aβ) plaques in early AD. One possibility is that early Aβ accumulation in the DMN drives vulnerability. It is unknown whether there is something intrinsic to neuronal projections within the DMN that biases these circuits towards dysfunction. Here we directly test this hypothesis using long-term recordings of the spiking activity of ensembles of single units in freely behaving APP/PS1 mice, a model characterized by global cortical and hippocampal Aβ burden, at ages before and after widespread amyloid plaque deposition. We track the interactions between a population of neurons within a DMN region and two additional populations that comprise monosynaptic targets, one within and one outside the DMN. In addition, we record single neurons in hippocampus and examine interactions between the in-DMN and out-DMN cortical circuits triggered on hippocampal sharp-wave ripples, stereotyped hippocampal events that contribute to memory consolidation in the cortex. We examine the statistics of local activity and inter-regional communication in a region, genotype, and brain-state dependent manner. Our data reveal a progressive dysfunction restricted to the in-DMN projecting circuit only in APP/PS1 mice following plaque accumulation. In contrast, communication along neuronal projections that originate in the DMN but target an out-DMN population is equivalent in APP/PS1 and WT mice. Circuit dysfunction is most evident throughout sleep, and particularly disrupted within sharp-wave ripples. Summarily, our results indicate that, even in the face of transgene overexpression and widespread Aβ, there is distinct intrinsic and selective vulnerability. This vulnerability to amyloidosis is circuit-specific and conditioned on target, and neither source nor amyloid burden. These data raise the possibility that neuronal function in the DMN is not universally vulnerable; DMN subnetworks whose interactions involve targets outside the DMN may be resilient to Aβ.

Disclosures: J. McGregor: None. **S.J. Brunwasser:** None. **K. Bhaskaran-Nair:** None. **H. Elmore:** None. **E.L. Dyer:** None. **J.D. Whitesell:** None. **J.A. Harris:** None. **K.B. Hengen:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.027/LBA27

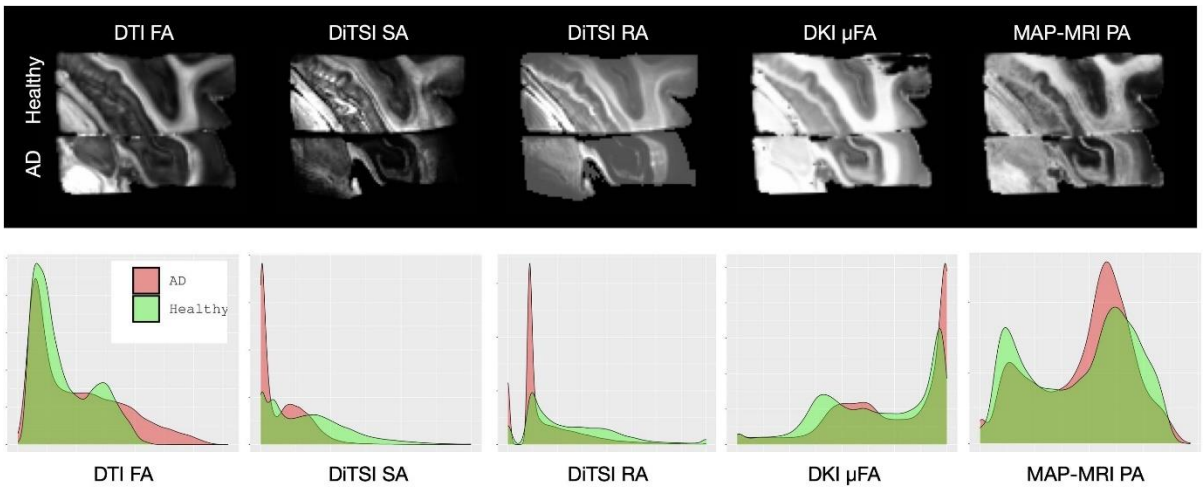
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG079280
NIH Grant S10 OD025016
NIH Grant R03AG071903
NIH Grant U24 NS072026

Title: Double diffusion encoded (DDE) MRI is more sensitive to Alzheimer's Disease pathology than conventional diffusion MRI

Authors: C. J. COMRIE[1], T. G. BEACH[3], G. E. SERRANO[4], V. GALINSKY[5], L. R. FRANK[6], ***E. HUTCHINSON**[2];
[2]Biomed. Engin., [1]Univ. of Arizona, Tucson, AZ; [4]Brain and Body Donation Program, [3]Banner Sun Hlth. Res. Inst., Sun City, AZ; [5]Univ. of California, San Diego, CA; [6]Univ. of California San Diego, San Diego, CA

Abstract: Currently, the role of MRI for Alzheimer's disease diagnosis is limited to identification late-stage atrophy[1]. Microstructural MRI methods, especially diffusion MRI (dMRI), can potentially capture cellular changes that precede neurodegeneration. Recently, we have reported that microscale anisotropy (μA) changes can be detected at earlier stages of AD than other MRI alterations[2]. These initial studies used conventional dMRI acquisition - single diffusion encoding (SDE) - but we hypothesize that specificity to altered μA in AD can be greatly improved by employing the more sophisticated double diffusion encoding (DDE) strategy. Bench experiments have shown that DDE provides length-scale and μA specificity that is not possible using SDE protocols and there have been several technical demonstrations of new DDE mapping strategies in the in vivo human brain, among the most promising is diffusion tensor subspace imaging (DiTSI)[3], which provides new μA metrics of radial and spherical anisotropy (RA and SA). However, these new tools require comprehensive comparison to existing dMRI frameworks and radiologic-pathologic validation if they are to become successful in providing early AD markers. In the current study, we have collected a comprehensive set of high resolution and high quality SDE and DDE MRI data in postmortem human temporal lobe specimens with and without AD pathology. Using this data, we have implemented DiTSI and compared RA and SA maps in AD and non-AD tissue to maps from SDE frameworks including fractional anisotropy (FA, DTI)[4], Kurtosis anisotropy (DKI-μA, DKI)[5] and propagator anisotropy (PA, MAP-MRI)[6]. The accompanying figure shows these metric maps for a longitudinal slice through both healthy and AD specimens along with histogram profiles for the specimens. FA did not show prominent differences, PA and DKI-μFA showed hippocampal reductions only and SA and RA were strongly decreased in the hippocampus and white matter of the AD specimen. Based on these results, DDE appears to have greater sensitivity to microscale features associated with AD pathology.



Disclosures: C.J. Comrie: None. **T.G. Beach:** None. **G.E. Serrano:** None. **V. Galinsky:** None. **L.R. Frank:** None. **E. Hutchinson:** None.
Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.028/LBA28

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

Support: FKZ 01ED2102B

Title: Model-derived SN volume is sensitive to cognitive and structural decline in Alzheimer's Disease and Parkinson's

Authors: *F. KROHN[1], R. YAKUPOV[2], A. SCHNEIDER[3], M. WAGNER[4], S. J. TEIPEL[5], A. SPOTTKE[6], F. JESSEN[7], E. DUZEL[8], M. BETTS[9], G. ZIEGLER[10];
[1]Inst. für kognitive Neurologie und Demenzforschung, Otto-von-Guericke Univ. Magdeburg, Magdeburg, Germany; [2]Deutsches Zentrum für neurodgenerative Erkrankungen, Magdeburg, Germany; [3]Deutsches Zentrum für neurodgenerative Erkrankung, Bonn, Germany; [4]Univ. of Bonn, Bonn, Germany; [5]Deutsches Zentrum für neurodegenerative Erkrankungen, Rostock, Germany; [6]Deutsches Zentrum für neurodegenerative Erkrankungen, Bonn, Germany; [7]Univ. Bonn, Bonn 53105, Germany; [8]Inst. Cognitive Neurol. and Dementia Res., Magdeburg, Germany; [9]German Ctr. For Neurodegenerative Dis. (DZNE), Magdeburg, Germany; [10]Inst. für kognitive Neurologie und Demenzforschung, Magdeburg, Germany

Abstract: Previous work has shown that the overall MRI-derived volume of the dopaminergic Substantia Nigra (SN) is associated with recognition memory and is decreased in clinical Alzheimer's Disease dementia (ADD) (Krohn et al., 2022) and Parkinson's Disease (PD). This

work assesses the sensitivity of a previously published probabilistic SN-specific tissue prior model (Krohn et al., 2023) to cognitive and functional decline in ADD and PD cohorts.
We estimated SN volume from T1-weighted FLASH images of 89 healthy controls (HC), 70 participants with subjective cognitive decline (SCD), 25 with mild cognitive impairment (MCI), and 13 individuals with ADD from the multi-site DZNE Longitudinal Cognitive Impairment and Dementia (DELCODE) study aging and dementia study and site-harmonized the volumina. Participants performed a recognition memory task, the preclinical PACC5, and the clinical Alzheimer's Disease Assessment Scale (ADAS-cog) task batteries. They also performed cognitive task batteries, from which a global cognitive score was calculated. We assessed FLASH images and symptom severity scores (UPDRSIII) of 22 individuals with PD. Linear regression models were generated to assess associations between SN volume and recognition memory, PACC5 and global cognition, ADAS-cog, and UDPRSIII. We used site, gender, age, and years of education as covariates.
In line with previous results, SN volume was reduced in MCI ($p<0.001$) and ADD ($p=0.02$) compared to HC and reduced in PD compared to age- and sex-matched HC ($p<0.001$). It was associated with recognition memory ($p=0.04$, $r^2=0.01$) in line with previous results, PACC5 ($p=0.003$, $r^2=0.04$), the ADAS-cog 13 score ($p=0.006$, $r^2=0.04$) and global cognition ($p=0.003$, $r^2=0.04$). In PD, SN volume was associated with symptom severity ($p=0.04$ $r^2=0.2$).
We confirm previous results showing decreased model-based SN volume in ADD and PD and an association between SN volume and both recognition memory and preclinical and clinical dementia scores. We further show an association between general cognitive function and SN volume. Therefore, our tissue prior model is suitable for SN segmentation in (longitudinal) datasets and other neurodegenerative and aging cohorts.

Disclosures: F. Krohn: None. **R. Yakupov:** None. **A. Schneider:** None. **M. Wagner:** None. **S.J. Teipel:** None. **A. Spottke:** None. **F. Jessen:** None. **E. Duzel:** None. **M. Betts:** None. **G. Ziegler:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.029/LBA29

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

Support: FPA young researcher luc arnal

Title: Alzheimer's Disease at risk young adults differences in sound processing

Authors: *E. M. M. DUCOS[1], L. ARNAL[2];
[1]Univ. Paris Cité, Inst. Pasteur, AP-HP, Inserm, Fondation Pour l'Audition, Inst. de l'Aud, paris,

France; [2]Univ. Paris Cité, Inst. Pasteur, AP-HP, Inserm, Fondation Pour l'Audition, Inst. de l’Audition, IHU reConnect, F-75012 Paris, France, paris, France

Abstract: Recent studies have suggested that prodromal stages of AD are accompanied with central auditory system dysfunction (Swords et al., 2018), which may be used as early indicators of disease onset and progression. In AD patients of 60 years old and more, atypical patterns of oscillatory entrainment to repetitive sound transients have been reported and suggested as potential neuromarker of Alzheimer's disease (van Deursen et al., 2011). Whether such alterations of auditory functions relate to genetic risk factor of AD (APOE4) at an early age (<30) is unknown. Here we used EEG recordings to measure auditory responses to repetitive sounds (1 second click trains presented at various frequencies between 10 and 250 Hz) in 34 young normal hearing participants with no known neurological impairments. To test whether auditory responsivity is affected by AD risk factor, we compared auditory brain responses from 17 APOE3 (age mean=21.6, sd=1.8) and 17 APOE4 carriers (age mean=23.6, sd=4.9). Comparing the magnitude of auditory event related potentials (ERPs) we observe that APOE4 carriers exhibit slightly lower P2 and P3 ERP responses compared to APOE3 carriers, with a consistent delay starting from the N1 component. Focusing on ASSR power across frequencies (10–90 Hz), we observed that APOE3 carriers exhibit reliably stronger neural entrainment than APOE4 carriers (Cohens’ d = 0.8, ‘large’ effect size). This difference was sustained across stimulus time course and seems mostly frontal and at low stimulus frequencies. Overall, these results suggest that central auditory differences can be detected very early in at-risk populations. Studying these signals could help identify early AD pathology and provide an entry point for therapeutic interventions against neurodegeneration.
Swords, G. M., Nguyen, L. T., Mudar, R. A., & Llano, D. A. (2018). Auditory system dysfunction in Alzheimer disease and its prodromal states: A review. In Ageing Research Reviews. https://doi.org/10.1016/j.arr.2018.04.001
van Deursen, J. A., Vuurman, E. F. P. M., van Kranen-Mastenbroek, V. H. J. M., Verhey, F. R. J., & Riedel, W. J. (2011). 40-Hz steady state response in Alzheimer’s disease and mild cognitive impairment. Neurobiology of Aging, 32(1), 24-30. https://doi.org/10.1016/j.neurobiolaging.2009.01.002

Disclosures: E.M.M. ducos: A. Employment/Salary (full or part-time):; Institut Pasteur. **L. arnal:** A. Employment/Salary (full or part-time):; inserm.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.030/LBA30

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

Support: NIH RF1AG063153

Title: A generative imputation method for multimodal Alzheimer's disease diagnosis

Authors: R. HASSANZADEH[1], *V. CALHOUN[2];
[1]Georgia Inst. of Technol., Atlanta, GA; [2]Georgia Inst. of Technol., Decatur, GA

Abstract: Multimodal data analysis can lead to more accurate diagnoses of brain disorders due to the complementary information that each modality adds. However, a major challenge of using multimodal datasets in the neuroimaging field is incomplete data, where some modalities are missing for certain subjects. Hence, effective strategies are needed for completing the data. In this study, we proposed a generative method designed to reconstruct missing modalities from existing ones while preserving disease patterns. Specifically, we employed a cycle-generative adversarial network (Cycle-GAN), as illustrated in Fig. 1, to transform functional network connectivity (FNC) maps into T1-weighted structural magnetic resonance imaging (sMRI) images and vice versa in the context of Alzheimer's disease (AD). We used 2910 T1 images and 414 FNC maps from the Alzheimer's Disease Neuroimaging Initiative (ADNI). To evaluate the quality of the generated samples, we adopted the structural similarity index measure (SSIM) between the real T1 images and their corresponding generated T1 images, and the Pearson correlation between the real FNC features and the generated ones. Our results showed an SSIM of 0.89±0.003 and a Pearson correlation of 0.71±0.004. Using the real T1 and FNC data along with the generated data, we trained a multi-modal classification model of AD vs. cognitively normal (CN) and measured the performance of the model with accuracy, precision, recall, and F1 score. Furthermore, we compared the performance of the model with the following baselines: 1) subsampling, where the input data includes only the data for which both modalities are available, and 2) zero-imputation, where the missing modality is replaced with zeros. According to our results, our generative-imputation approach achieved an accuracy of 86.87%±2.9, outperforming the subsampling and zero-imputation approaches by 8.6% and 9.4%, respectively. Additionally, our proposed approach achieved an F1 score of 0.88, a recall of 0.86, and a precision of 0.91, all of which were superior to the baselines.

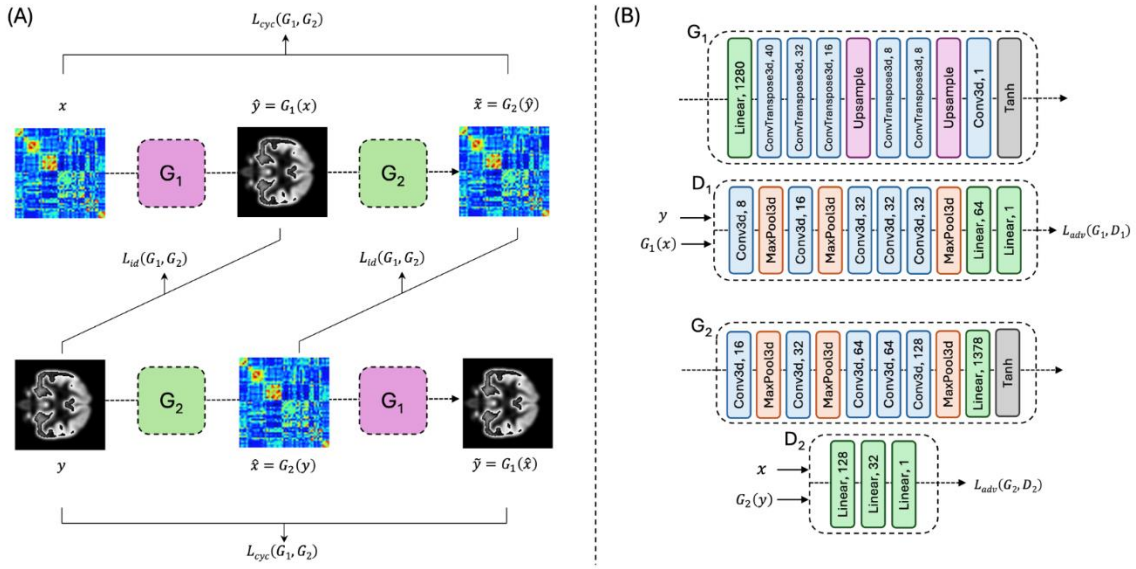


Fig. 1. Generative model architecture. The model includes two generators, G_1 and G_2, which transform FNC maps to T1 images and vice versa, and two discriminators, D_1 and D_2, which distinguish real samples from generated ones. Part (A) shows the data flow and loss functions, while part (B) details the architecture of each network component.

Disclosures: R. Hassanzadeh: None. **V. Calhoun:** None.
Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.031/LBA31

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

Title: Cross-sectional study of changes in whole brain functional connectivity with the presence of global amyloid and local tau

Authors: *D. ZIADLOU[1], R. WALES[2], H.-C. LEUNG[3];
[1]SUNY Stony Brook Integrative Neurosci. in Psychology, Stony Brook, NY; [2]Psychology, Stony Brook Univ., Stony Brook, NY; [3]Integrative Neurosci. Program, State Univ. of New York, Stony Brook, Stony Brook, NY

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive impairment, memory loss, and changes in behavior. The pathological hallmarks of Alzheimer's disease include the presence of amyloid-beta plaques and neurofibrillary tangles of hyperphosphorylated tau proteins. In the present study, we leveraged functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. We characterized the effects of amyloid and tau levels in older adults without dementia on resting-state functional connectivity, cross-

sectionally. Given that the study focused on preclinical individuals, participants included in this study were diagnosed as either cognitively normal (CN, N=209) or as having mild cognitive impairment (MCI, N=88). A small AD sample (N=29) was included for comparative purposes. In particular, we examined associations between pathological protein levels with seed-based connectivity and functional network connectivity during resting state scans. Seed-based functional connectivity analyses showed a significant negative effect of entorhinal tau level on connectivity within the temporal lobe in this group of older adults without dementia. No previous studies have shown this pattern in individuals without dementia, who have a much lower level of tau presence. Functional network connectivity analysis revealed a reduction in within-network connectivity in subjects with greater tau levels in ventral and temporal networks, more specifically in limbic, temporal parietal, and DMN based on the Schaefer 17-network whole brain parcellation atlas. Such findings agree with previous studies showing that the entorhinal cortex lobe seems to harbor tau preclinically and the elevated tau impacts functional network connectivity. Amyloid, however, was related to higher within-network connectivity in the following networks: dorsal attention, limbic, salience/ventral attention, and somatomotor. Amyloid was also related to higher overall between-network connectivity. Therefore, in this ADNI sample, older adults without dementia seem to have the same pattern as in previous reports of amyloid-related connectivity alterations in AD samples. In conclusion, the analysis showed that tau is related to decreased network connectivity, while amyloid is related to increased network connectivity in subjects without dementia. Characterizing the effects of dementia-related pathological proteins on brain network connectivity may clarify the course of cognitive decline in both normal and pathological aging.

Disclosures: D. Ziadlou: None. **R. Wales:** None. **H. Leung:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.032/LBA32

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

Support: HI22C1453
IITP-2024-RS-2023-00258971
IITP-2024-RS-2024-00437102

Title: The effect of education in enhancing brain network communicability and neural reserve

Authors: *D. KIM[1], M. KAISER[3], H.-G. JEONG[4], C. E. HAN[1,2];
[1]Electronics and Information Engin., [2]Interdisciplinary Grad. Program for Artificial Intelligence Smart Convergence Technol., Korea Univ., Sejong, Korea, Republic of; [3]Sch. of Med., Univ. of

Nottingham, Nottingham, United Kingdom; [4]Psychiatry, Korea Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Neural reserve (NR) refers to the brain's ability to stay functional despite aging or disease; individuals with high NR may have more efficient, capacious, and/or flexible brain networks than those with low NR. While previous studies have focused on network efficiency analyzing the shortest path length, they have often overlooked other important aspects of NR such as capacity and flexibility. This may be due to the lack of standardized measures for assessing them. In this study, we propose using the number of alternative paths and communicability as their surrogates. Specifically, we hypothesized that higher education may correlate with more alternative brain paths and higher communicability, since education is one of factors that increase NR. We first identified brain pathways whose communicability was associated with the education duration using DTI-derived structural brain networks. We recruited 21 healthy subjects (age: 68.86±4.59 years, 12 female and 9 male, education duration: 13.33±4.23 years) from Korea University Guro Hospital. Communicability is the length-penalized summation of the number of alternative paths, and calculated between all pairs of brain nodes (regions). We identified 8 positively and 6 negatively correlated node pairs between education and their communicability. The node pairs with positive correlations resided in the left hemisphere, while those with negative correlations were in the right hemisphere. We calculated the average number of alternative paths for all the node pairs. The node pairs with positive correlations had more alternative paths than the others. However, for the short path lengths (<=4), the numbers of alternative paths did not significantly differ. This suggested that the larger number of relatively longer paths contributes to increased communicability; the efficiency measures solely based on the shortest path may overlook such changes. We noted the role of the identified node pairs in information transmission architecture. The node pairs with positive correlations utilized inter-hemispheric connections, showing potential relationship with functional integration. In contrast, the node pairs with negative correlations relied on paths within the right hemisphere, which might increase the efficiency of intra-hemispheric communication by reducing interference. In summary, our findings suggest that individuals with higher education have more alternative paths and higher communicability for certain pathways, that show greater capacity for information transfer, and may have higher resilience to network damage by flexible reconfiguration of information pathways; this implies increased NR.

Disclosures: D. Kim: None. **M. Kaiser:** None. **H. Jeong:** None. **C.E. Han:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.033/LBA33

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

Title: A multi-modal graph-theoretic analysis of functional brain interactions and tau spread in preclinical Alzheimer's Disease

Authors: *R. VIN[1], C. FREDERICKS[2];
[1]Neurol. and Psychiatry, [2]Yale Univ., New Haven, CT

Abstract: Alzheimer's Disease (AD) is characterized by the presence of β-amyloid plaques and neurofibrillary tau tangles, with tau strongly linked to neurodegeneration and cognitive impairment. Braak and Braak (1991) found that tau tangles first appear in the entorhinal cortex, then spread to limbic regions, and finally disperse throughout cortex. Recent research demonstrates that tau can propagate across brain regions through structurally and functionally connected neurons in a prion-like fashion. In a large preclinical dataset (n=317 amyloid-positive individuals from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study), we sought to identify brain regions that (1) have the greatest potential to spread tau and (2) are most susceptible to tau spread before symptom onset. Structural and functional MRI and tau PET data were parcellated using the Human Brainnetome Atlas. We computed two multimodal graph-theoretic metrics, including a novel weighted metric of node strength, for all brain regions across participants. Tau-weighted node strength was defined as the product of regional tau uptake and its summed functional connectivity with the rest of the brain. Nodal hazard was calculated as the sum of tau uptake in all other brain regions, weighted by their connectivity to the given region. Brain regions with the highest tau-weighted node strength and nodal hazard (top 15 percent) across all subjects were identified. We found the highest tau-weighted node strength in limbic and subcortical regions, including the medial dorsal thalamus, medial amygdala, posterior hippocampus, nucleus accumbens, ventral caudate and ventromedial putamen. As expected, these regions demonstrated significantly greater tau levels than other regions ($t = 28.44$, $p = 3.97e\text{-}89$). Conversely, the group with the highest nodal hazard primarily featured multimodal association cortex, particularly the inferior frontal gyrus, inferior parietal lobule, superior temporal gyrus, middle frontal gyrus, and orbital gyrus.Our results show that regions with the highest tau-weighted node strength generally represent earlier Braak stage regions and may facilitate early tau spread. These regions are also heavily involved in emotion regulation and memory, and could contribute to the development of neuropsychiatric symptoms in AD. Regions with high nodal hazard, on the other hand, may play a critical role in the dispersion of tau pathology in later stages. Future analyses will predict the longitudinal spread of tau in preclinical individuals and its association with neuropsychiatric symptoms, potentially paving the way for new treatments and early therapeutic intervention.

Disclosures: R. Vin: None. **C. Fredericks:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.034/LBA34

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

Support: NIH Grant AG067049

Title: aβ Increases the interaction between abhd17a and psd-95 in dendritic spines

Authors: *N. JAMALIAN[1,3], A. E. SNYDER[2], K. B. DORE[4];
[1]Neurosci., [2]Neurosciences, Univ. of California San Diego, La Jolla, CA; [3]California State Univ. San Marcos, San Marcos, CA; [4]Neurosciences, UCSD Dept. of Neurosciences, La Jolla, CA

Abstract: Alzheimer's disease (AD) affects 6.9 million people in the United States. AD is characterized by loss of cognitive functioning and build up of beta-amyloid (Aβ) which can aggregate to form plaques. These plaques have been shown to contribute to memory deficits and correlate with disease progression. Overexpression of PSD-95, a synaptic protein, has been shown to block the negative effects of Aβ on synapses. PSD-95 binds to the NMDAR C-terminal domain and must be palmitoylated to remain at the synapse. ABHD17a has been shown to be the most aggressive depalmitoylating enzyme for PSD-95 which could lead to a reduction in trafficking and detachment from the membrane. We aim to further investigate the relationship between ABHD17a and PSD-95 in the presence of Aβ. Primary hippocampal neurons were cultured from P0 rodents, and cultures were transfected with ABHD17a-GFP and PSD95-mApple, then infected with fragments of the amyloid precursor protein (APP) that would either produce beta-amyloid (CT100), or the non-amyloidogenic APP fragment (CT84).To investigate the interaction between PSD-95 and ABHD17a, we used fluorescence lifetime imaging (FLIM) to measure the GFP lifetime and interaction between ABHD17a-GFP and PSD-95-mApple in dendritic spines. We found a decreased GFP lifetime in dendritic spines infected with CT100, suggesting that Aβ increases the interaction between ABHD17a and PSD-95. Future directions would be to decrease endogenous ABHD17a to investigate the therapeutic advantage of increasing PSD-95.

Disclosures: N. Jamalian: None. **A.E. Snyder:** None. **K.B. Dore:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.035/LBA35

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

Support: NIH P30 AG047266
NIH Rf1AG074569
NIH NIAR25AG076396

Title: Temporal and spatial sequence of protein accumulation in dystrophic neurites sheds light on pathophysiology of neuritic plaque formation

Authors: *L. HETRICK[1,2,3,4], W. TSERING[2,3,4], S. PROKOP[2,3,5,6];
[1]Dept. of Neurosci., High Point Univ., High Point, NC; [2]Ctr. for Translational Res. in Neurodegenerative Dis., [3]Evelyn F. William L. McKnight Brain Inst., [4]Dept. of Neurosci., [5]Dept. of Pathology, [6]Fixel Inst. for Neurolog. Dis., Univ. of Florida, Gainesville, FL

Abstract: In 2024, an estimated 6.9 million people in the United States are living with Alzheimer's disease (AD). Neuropathologically, AD is characterized by the accumulation of amyloid-beta plaques and aggregates of tau in the brain, yet how amyloid-beta drives tauopathy is still under debate. Neuritic plaques, a subcategory of amyloid-beta plaques that contain tau-positive dystrophic neurites are a potential window into how these two protein pathologies converge. In post-mortem brain tissue, neuritic plaques have a strong correlation with cognitive decline associated with AD. Our group has previously shown that neuritic plaques increase in numbers as AD pathological changes progress and that in cortical regions this increase precedes the appearance of tau-positive neurofibrillary tangles in neurons. Dystrophic neurites in neuritic plaques contain many axonally transported proteins, including ubiquitin 1 (Ubi-1), lysosome-associated membrane protein 1 (LAMP1), and reticulon 3 (RTN3), and previous studies in animal models suggest that these proteins are found in a distinct temporal sequence as neuritic plaque pathology evolves. To test if this theory holds true in human postmortem brains, we quantified the number on Ubi-1, LAMP1, RTN3 and tau-positive amyloid-beta plaques in a cohort of AD patient brains at different stages of AD progression. We identified disease stage and brain region specific differences in the temporal appearance of these proteins. Most notably, in the cortical region, the percentage of RTN3-positive plaques increased from low to intermediate AD cases and then decreased from intermediate to high AD cases. However, in the hippocampus region, the percentage of RTN3-positive plaques decreased from low to intermediate AD cases and then increased from intermediate to high AD cases. Understanding the sequence of molecular processes leading to neuritic plaque formation will enhance our knowledge of disease progression in AD and aid in identifying potential new therapeutic targets to stop the pathological cascade leading to dementia.

Disclosures: L. Hetrick: None. **W. Tsering:** None. **S. Prokop:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.036/LBA36

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

Support: I would like to thank Dr. A.S. Greene and TExpL Labs for their guidance and support.

Title: The effect of artificial sweeteners on amyloid-β plaque aggregation

Authors: *P. A. S. HINKLE;
Albright Col., Reading, PA

Abstract: Amyloid-β (Aβ) is a protein that can misfold into pathological fibril aggregations and lead to the formation of plaques in the brain—a hallmark of Alzheimer's disease (AD). While the causes of AD are not well understood, there is strong evidence of a correlation between type 2 diabetes and AD that implicates diabetes as a potential modifiable risk factor for AD prevention. The mechanisms underlying this association are not understood, but one possible explanation is that diabetics often consume artificial sweeteners as an alternative to natural sugars. The ten-year Framingham longitudinal study found a significant link between artificial sweetener consumption and AD (Pase et al., 2017); daily consumption of artificial sweeteners nearly tripled the risk of AD. This current study sought to determine whether artificial sweeteners promoted Aβ plaque aggregation in vitro to investigate a mechanism underlying Pase's findings. **Methods:** We used Thioflavin T (ThT) to assay $A\beta_{42}$ aggregation in the presence of natural sugar (glucose) and artificial sweeteners at physiological temperature (37° C). ThT is a natural fluorescence dye that binds with amyloid-fibrils. It is a widely used and sensitive reporter of fibril aggregation, with the level of fluorescence depending on the amount of Aβ aggregation. $A\beta_{42}$ has two more residues than $A\beta_{40}$ and is more prevalent in plaques. Using a 384 well plate and a GloMax microplate reader, ThT fluorescence was excited at 405 nm and measured at 505-550 nm. Background fluorescence levels of ThT with each sugar alone were measured and subtracted from the experimental results. Iglewicz and Hoaglin's robust test for outliers (z=3.0) was used as an outlier criterion. Pairwise two-tailed t-tests compared the glucose control (n=12) with each of the four artificial sweeteners: Equal Saccharin (p<0.000, n=12), Equal Original (p<0.000, n=10), Splenda Stevia (p<0.006, n=14), and Sweet'N Low (p<0.000, n=15) (Bonferroni correction α=0.05/4, α<0.0125.) **Results:** Wells contained $A\beta_{42}$ and ThT, either alone, with glucose, or with an artificial sweetener. Fibril formation, measured by ThT fluorescence, was significantly greater with the four artificial sweeteners than either of the two controls: glucose or $A\beta_{42}$ and ThT alone. Fibril formation with glucose was not different from the baseline level of $A\beta_{42}$ and ThT alone. **Conclusion:** These results indicate that artificial sweeteners can promote fibril formation in vitro when compared to glucose or no sugar. This study offers an important insight into the link between artificial sweeteners and AD, especially for those with diabetes, and suggests a mechanism explaining the Framingham study's finding.

Disclosures: P.A.S. Hinkle: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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

Support: R01AG072727
P20GM113123
DaCCoTA CTR NIH grant U54GM128729
UND SMHS funds

Title: Ad-associated app, aβ and innervation changes in the salivary glands of app$^{nl\text{-}g\text{-}f}$ mice

Authors: *S. CHANDRASEKARAN[1], *S. CHANDRASEKARAN[2], A. M. FLODEN[1], T. ISHIDA-TAKAKU[1], E. P. HUGH[1], J. P. STENSGARD[1], C. K. COMBS[1];
[2]Biomed. Sciences,, [1]Univ. of North Dakota Sch. of Med. and Hlth. Sci., Grand Forks, ND

Abstract: Alzheimer's disease (AD) is characterized by the aggregation of amyloid beta (Aβ) peptides generated from the proteolytic cleavage of amyloid precursor protein (APP). APP is a transmembrane protein widely expressed in the central nervous system but also secreted by the various cell types of peripheral tissues. AD patients experience decreased salivation over the course of disease and display higher levels of salivary Aβ42. We have previously demonstrated salivary gland epithelial cell APP immunoreactivity and saliva Aβ levels while examining APP/PS1 and *App*$^{NL\text{-}G\text{-}F}$ mouse models of AD. However, minimal immunoreactivity for salivary gland Aβ was observed. Based on these findings, we hypothesized that epithelial APP processing results in ductal secretion of Aβ into the saliva. To begin testing this idea, submandibular glands were collected from 6-7 months old male and female wild type (WT) and *App*$^{NL\text{-}G\text{-}F}$ mice. Immunostaining demonstrated, once again, robust epithelial APP immunoreactivity in both sexes and genotypes with no evidence of plaque-like Aβ deposition in either male or female *App*$^{NL\text{-}G\text{-}F}$ mice. Immunohistochemistry for tyrosine hydroxylase (TH) and choline acetyltransferase (ChAT) to visualize noradrenergic and cholinergic innervation, respectively, demonstrated a surprising increase in TH staining in female *App*$^{NL\text{-}G\text{-}F}$ mice suggesting dysfunctional regulation of secretion. To directly assess regulation of Aβ secretion, submandibular glands from *App*$^{NL\text{-}G\text{-}F}$ mice were cultured to quantify secretion of Aβ *in vitro* through ELISA and the levels of both Aβ40 and Aβ42 were detectable in the culture media. These data suggest that salivary gland dysfunction and saliva composition changes may occur in AD. Further work is required to fully validate the cellular source, regulation, and consequence of salivary Aβ. These data also support the idea that salivary gland dysfunction is a peripheral characteristic of AD.

Disclosures: S. Chandrasekaran: None. **S. Chandrasekaran:** None. **A.M. Floden:** None. **T. Ishida-Takaku:** None. **E.P. Hugh:** None. **J.P. Stensgard:** None. **C.K. Combs:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

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Program #/Poster #: LBA003.038/Web Only

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

Support: Ola HAWAII Administrative Supplement (U54 MD007601-38S1), NIH
IBR-COBRE (P20GM103457), NIH
Hawaii Community Foundation (19ADVC-95450)

Title: The exocyst is an insulin-mediated regulator of amyloid-beta production in neurons

Authors: *C. BALAAN[1], H. KUMASAKA[1], R. SACHS[2], G. PATWARDHAN[3], S. SADAGOPAN[1], S. AOU[1], A. MARTIN[1], M. ORTEGA[4], R. A. NICHOLS[4], B. FOGELGREN[1]; [1]John A. Burns Sch. of Med., Honolulu, HI; [2]CU Anschutz, Aurora, CO; [3]NIH, Bethesda, MD; [4]Cell and Mol. Biol., John A. Burns Sch. of Medicine, Univ. of Hawaii, Honolulu, HI

Abstract: Alzheimer's disease (AD) is a neurodegenerative disease and the most common form of dementia, affecting more than 6 million Americans. A pathological hallmark of AD is the accumulation of amyloid-beta (Aβ) peptides formed by the proteolytic cleavage of the amyloid precursor protein (APP) by β and γ secretases. It is known that type 2 diabetes mellitus (T2DM) is a strong independent risk factor for developing AD, and although the relationship between T2DM and AD is certainly multifactorial, some studies have indicated a connection between insulin signaling in neurons and APP amyloidogenic processing. We have recently discovered that the exocyst, an insulin-responsive eight-protein trafficking complex, regulates APP intracellular trafficking and processing in neurons, which would represent an exciting new molecular mechanism directly linking insulin signaling and AD. Our current working hypothesis is that the exocyst is required for the delivery of APP from the trans-Golgi network to the plasma membrane, and for the transcytosis of APP through the endocytic pathway into axons, and that insulin redirects the exocyst away from transport vesicles carrying APP. We are utilizing mouse primary hippocampal neurons and SH-SY5Y cells to further investigate the relationship between APP, the exocyst, and insulin-signaling pathways. Using high resolution microscopy, we show that the exocyst and APP colocalize in insulin-starved cells, but with insulin treatment, this colocalization significantly decreases specifically in dendrites and axons. We have further analyze this relationship using live-cell TIRF microscopy of fluorescently labeled APP and exocyst proteins in SH-SY5Y neurons. In our fluorescent lines, we observed highly coordinated movement of APP and exocyst subunits in soma and along neurites. Moreover, recent proteomic analysis of biotinylated cell-surface proteins showed significant reductions of plasma membrane APP, but not its paralogs APLP1 and APLP2, after treatment with the exocyst inhibitor, endosidin-2. These data suggests that the exocyst specifically targets APP-containing vesicles via the secretory pathway. Interestingly, endosidin-2 treatment also led to decreased levels of RAB5B (endocytic trafficking), EEA1 (early endosome), and APPL1 (early endosome) co-purifying with biotinylated proteins, indicating a role of the exocyst in the endocytic pathway of neurons. Elucidating the relationship of insulin, exocyst, and APP in neurons may identify novel mechanistic pathways connecting insulin dysfunction and AD pathophysiology and ultimately may identify potential targets for new therapeutic approaches.

Disclosures: C. Balaan: None. **H. Kumasaka:** None. **R. Sachs:** None. **G. Patwardhan:** None. **S. Sadagopan:** None. **S. Aou:** None. **A. Martin:** None. **M. Ortega:** None. **R.A. Nichols:** None. **B. Fogelgren:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.039/Web Only

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

Support: NIH R01AG048993
NIH RF1AG069378
NIH P20GM113123
NIH U54GM128729

Title: Differential Expression of Neural and APP-Related Markers in Colon Cancer and Alzheimer's Disease

Authors: *T. ISHIDA-TAKAKU, M. SOHRABI, S. CHANDRASEKARAN, C. K. COMBS; Univ. of North Dakota Sch. of Med. & Hlth. Sci., Grand Forks, ND

Abstract: Cancer and Alzheimer’s disease (AD) are common age-associated diseases with intriguing inverse epidemiological correlations. Amyloid precursor protein (APP) is primarily recognized for its role in Alzheimer's disease, where its enzymatic cleavage results in the accumulation of amyloid-beta peptides. Additionally, elevated expression of APP and its N-terminal fragment, sAPP, has been observed in various types of cancer, hinting at a potential mechanistic link between APP biology and tumor progression. However, the underlying mechanisms of this association remain unclear. In exploring the relationship between AD and colon cancer, we utilized the amyloidosis AD mouse model, $App^{NL\text{-}G\text{-}F}$, which features three AD-related mutations in the human Aβ sequence that are knocked into the mouse App gene. Male and female $App^{NL\text{-}G\text{-}F}$ mice were subjected to a colitis-associated colorectal cancer protocol induced by azoxymethane (AOM) and dextran sodium sulfate (DSS). These mice exhibited sex-dependent tumor outcomes: males showed increased tumor number and size, while females displayed a protective phenotype against tumorigenesis compared to wild-type C57BL/6 mice. APP immunoreactivity was observed in both normal and cancerous epithelium, as well as in enteric neurons, underscoring mutant APP’s potential contribution to sex-specific tumorigenesis effects. Additionally, immunostainings for BACE1, TACE, and Presenilin 1 were observed in both normal and cancerous epithelium. The widespread presence of BACE1, TACE, and Presenilin 1 in these tissues underscores ongoing APP processing in these environments, which could be contributing to the pathology observed in both AD and cancer. To investigate nerve invasion in tumor tissue, we performed immunostainings for PGP 9.5, choline acetyltransferase

(ChAT), and tyrosine hydroxylase (TH). PGP 9.5 and ChAT were observed in both normal and cancerous epithelium, but TH was only present in normal epithelium. The exclusive presence of TH in normal epithelium could indicate a disruption of catecholamine synthesis pathways in cancerous tissues, potentially affecting tumor behavior and local immune responses. These findings not only provide insights into the biochemical landscape of the tumor microenvironment influenced by neural components but also underscore the importance of APP and its metabolites in the pathology of colon cancer.

Disclosures: T. Ishida-Takaku: None. **M. Sohrabi:** None. **S. Chandrasekaran:** None. **C.K. Combs:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.040/LBA38

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

Support: Hoffman La-Roche
BrightFocus Foundation

Title: In vitro reconstitution of lysosomal membrane damage by tau and repair by ESCRT proteins.

Authors: *S. SHUKLA, K. ROSE, C. O'BRIEN, W. LEE, J. H. HURLEY;
UC Berkeley, Berkeley, CA

Abstract: The prion-like propagation of protein aggregates in the brain has emerged as a key hypothesis for the cell-to-cell spread of pathology in Alzheimer's disease (AD) and related disorders. In this model, pathological tau aggregates, or "tau seeds," are internalized by target cells via endocytosis, traverse the endolysosomal pathway, escape from lysosomes, and subsequently induce the aggregation of endogenous soluble tau in the cytoplasm. Lysosomal escape is a critical step in the amplification of tau seeds, which is crucial for AD progression. However, significant questions remain about the exact mechanism by which tau seeds breach lysosomal membranes and the role of cellular membrane repair machinery in specifically preventing this escape. To address these questions, we employed a combination of *in vitro* reconstitution and cell-based assays. Our results demonstrate that internalized tau seeds cause nanoscale permeabilization of the lysosomal membrane in neurons. Using super-resolution microscopy, we observed that soluble tau monomers undergo templated aggregation on the surface of damaged lysosomes. Recently, the endosomal sorting complex required for transport (ESCRT) machinery has been implicated in the repair of damage to both plasma and lysosome membranes. We found that components of the ESCRT repair machinery are recruited to

lysosomes compromised by internalized tau seeds. To identify upstream protein components that facilitate the recruitment of ESCRT machinery to damaged sites, we utilized an *in vitro* reconstitution system with a simplified membrane model. Our findings reveal that the Ca^{2+}-binding regulatory protein, Apoptosis Linked Gene-2 (ALG-2), binds directly to negatively charged membranes in a Ca^{2+}-dependent manner and orchestrates the downstream assembly of ESCRT-III machinery through two parallel pathways. Furthermore, using structure-inspired mutants of ALG-2 validated through molecular dynamics simulations, we show that ALG-2's binding to acidic membranes in the presence of Ca^{2+} is mediated by a combination of electrostatic and hydrophobic interactions. In conclusion, our study demonstrates that tau seeds induce lysosome membrane permeabilization, outlines the minimal set of components required to assemble the complete membrane repair machinery, and elucidates the essential role of Ca^{2+}-dependent membrane binding by ALG-2 in counteracting lysosomal tau seed escape.

Disclosures: S. Shukla: A. Employment/Salary (full or part-time):; BrightFocus Foundation, Hoffman La-Roche. **K. Rose:** None. **C. O'Brien:** None. **W. Lee:** None. **J.H. Hurley:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.041/LBA39

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

Support: BrightFocus Foundation A2023016S

Title: Monoaminergic neurotransmitters are phenol-type modulators of protein aggregation

Authors: *P. SEIDLER;
USC, Los Angeles, CA

Abstract: Neurotransmitters (NTs) are crucial signaling molecules in animals and imbalances in NT concentrations is associated with aging and brain disorders. Here, we uncover a role for intracellular NTs in mediating neurodegeneration by direct interaction with cytosolic proteins. Because polyphenols are inhibitors with disaggregating effects on fibril-type protein aggregates, we investigated a library of 931 chemicals to identify structural features of polyphenols that inhibit seeding. Seeding is a disease-relevant mechanism involving catalysis by fibrils, which leads to aggregation of proteins in Alzheimer's disease (AD) and other neurodegenerative diseases. Chemotyping identified monoaminergic NTs such as dopamine, norepinephrine, epinephrine, and serotonin as phenol- and polyphenol-type effectors of tau aggregation. Dose titrations using catecholaminergic NTs revealed bimodal effects, with aggregation catalysis occurring at low ratios of NTs to tau fibrils and inhibited seeding ensuing with increasing NT concentrations. Bimodal effects on seeding are indicative of disaggregant-type inhibitors, which

catalyze seeding by increasing seeding-competent fibril nucli at low concentrations, and inhibit at high concentrations by eliminating fibril templates. By establishing that monoaminergic NT levels contribute bimodally to the aggregation environment, these results pave the way for pharmacotherapy approaches to manage AD and other neurodegenerative diseases by modifying intracellular levels of NTs.

Disclosures: P. Seidler: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.042/LBA40

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

Title: A novel humanized TAU mouse model for preclinical development of oligonucleotide drugs for Alzheimer's Disease

Authors: *D. HAN[1], S. WANG[2], D. HUANG[2], Q. XU[2], F. GU[2], X. ZHOU[2];
[1]Biocytogen Boston Corp., Waltham, MA; [2]Biocytogen Pharmaceuticals (Beijing) Co., Ltd., Beijing, China

Abstract: **Introduction:** TAU protein, a microtubule-associated protein primarily expressed in neurons, plays a crucial role in the progression of Alzheimer's disease. The accumulation of hyperphosphorylated tau proteins within cells forms neurofibrillary tangles that disrupt normal neuronal cell function and ultimately lead to Alzheimer's disease (AD). **Objectives:** Given the pivotal role TAU protein plays in the pathophysiology of AD and the symptoms of AD can be alleviated by reducing TAU protein levels, there has been considerable interests in the development of TAU-targeting oligonucleotide drugs for treating AD. Therefore, it is essential to have scientifically appropriate mouse models for such research needs. **Results:** We successfully developed a mouse models, B-hTAU, which expresses humanized TAU, in which the exons 2~10 of mouse *Tau* gene that encode the full-length protein were replaced by human *TAU* exons 2~15. The 3'UTR region of the mouse gene is replaced by its human counterpart. The chimeric *TAU* expression is driven by endogenous mouse *Tau* promoter, while mouse *Tau* gene transcription and translation will be disrupted. Human *TAU* mRNA was detectable only in homozygous B-hTAU mice but not in wild-type littermates. In the B-hTAU mice, we detect all six isoforms (including both 3R and 4R forms) of human *TAU* gene present in human brain and confirmed by Sanger Sequencing. Human and mouse TAU protein expression was detectable in the brains of wild-type mice and homozygous B-hTAU mice due to cross-recognition of antibodies. Additionally, through collaboration we evaluate the inhibitory efficiency of nucleic acid drugs against human TAU in the B-hTAU mice. The human TAU-targeting nucleic acid drug or PBS were administered intracerebroventricularly to mice. And the mice were sacrificed

after 7 days, the brains were collected for the detection of human TAU expression. Compared with control group, there is a significant decrease in both mRNA and protein levels of human TAU in the treatment group. **Conclusions:** In summary, B-hTAU mice is a powerful preclinical model for *in vivo* evaluation of human TAU-targeting nucleic acid drugs.

Disclosures: D. Han: None. **S. Wang:** None. **D. Huang:** None. **Q. Xu:** None. **F. Gu:** None. **X. Zhou:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.043/LBA41

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

Support: OIST innovation/Proof of Concept (POC)/R12_70

Title: The efficacy of the synthetic peptide PHDP5 in rescuing cognitive deficits in Alzheimer's disease model mice

Authors: *A. CHANG[1], T. HORI[2], Z. TAOUFIQ[2], T. TAKAHASHI[3], K. DOYA[1];
[1]Neural Computation Unit, [2]Synapse Biol. Unit, [3]Okinawa Inst. of Sci. and Technol., Okinawa, Japan

Abstract: Dynamin is a microtubule (MT) binding protein that supports synaptic transmission by playing a key role in synaptic vesicle endocytosis and recycling in the presynaptic terminal. In the calyx of Held of mouse brainstem slices, tau loaded in presynaptic terminals induces MT over-assembly, which strongly binds to dynamin, impairing vesicle endocytosis via depletion of cytosolic dynamin. This result suggests that accumulation of tau in presynaptic terminals impairs vesicle endocytosis and synaptic transmission, leading to cognitive impairment in Alzheimer's disease (AD). The synthetic dodecapeptide PHDP5, corresponding to amino acids 560-571 of the dynamin 1 pleckstrin-homology (PH) domain, inhibits the MT-dynamin interaction and rescues endocytic impairments and EPSC rundown (Hori et al., 2022). Furthermore, intranasal administration of PHDP5 rescues learning and memory deficits of male AD model mice in a maze task, suggesting its potential as a candidate for AD therapy (Chang et al., 2024). However, almost 65% of AD patients are females, with greater frequency of tau pathology than males, and the sex difference can be critical in response to drug treatment. Therefore, potential sex-specific differences in the response to PHDP5 need investigation. We set out to compare the efficacy of PHDP5 in rescuing cognitive deficits in both female and male AD model mice. Modified PHDP5, linked to a cell-penetrating peptide (CPP) and a FITC fluorescent marker, was delivered intranasally to 6-month-old female and male 3xTg-AD mice for 4 weeks. Their spatial memory abilities were then assessed using the Morris water maze. FITC signals were found in the

hippocampal CA1 region after administration, indicating the peptide crossed the blood-brain barrier (BBB). Compared to non-treated controls, PHDP5-treated mice exhibited significant cognitive improvements in both genders, including shorter latencies and increased occupancy in the target quadrant of the water maze. These results indicated that 4 weeks of PHDP5 treatment could rescue spatial learning and memory deficits in both male and female 3xTg-AD mice, demonstrating its potential as a therapeutic candidate for human AD therapy.

Disclosures: A. Chang: None. **T. Hori:** None. **Z. Taoufiq:** None. **T. Takahashi:** None. **K. Doya:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.044/LBA42

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

Title: Detection of microglia-derived phosphorylated tau in senile plaques by the high affinity immunostaining method.

Authors: *Y. HIGASHI[1], N. KAKUDA[1], T. MIYASAKA[2], S. FUNAMOTO[1];
[1]Neuropathology Laboratory, Fac. of Life and Med. Sci., Doshisha university, Kyotanabe, Kyoto, Japan; [2]Lab. of Physiol. and Anat., Nihon university, Chiba, Japan

Abstract: Alzheimer's disease (AD) is characterized by two protein aggregates called senile plaques consisting of amyloid-β (Aβ) and neurofibrillary tangles (NFTs) consisting of phosphorylated tau protein (tau). In the AD brain, senile plaques have been found in cerebral parenchyma, following NFTs have been found in neuron. After decades of these by neuronal cell death. This process was called amyloid cascade hypothesis, and inhibiting the aggregation of these proteins is considered a therapeutic strategy for AD.
Aβ is generated from amyloid precursor protein (APP) and it aggregates extracellular region. In contrast, tau has aggregated in neuron cell bodies. Previous studies have suggested that cognitive dysfunction in AD, it has been caused by tau, not Aβ. The $APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ KI (NLGF) mouse is one of the widely used AD models carrying familial AD mutation in APP. There are no mutations in those of mouse tau. However, their cognitive function has been declined. This suggests that tau pathology might be undergoing in NLGF mouse.
Recently, we have just developed a High Affinity Staining in Histochemical Immunology (HIGASHI) method for phosphorylated proteins. In HIGASHI method, frozen sections are treated with viper 4%PFA for fixation and 2%SDS for antigen retrieval. Using this method, we detected the phosphorylated tau histologically in the 12months old NLGF mouse brain. Interestingly, the phosphorylated tau was accumulated as a core of senile plaque in the cortex and hippocampus with anti-P-tau antibody, AT8. Staining with other anti-tau antibodies also

showed tau accumulation. In addition, microglial staining merged the phosphorylated tau. We are the first that microglia-derived phosphorylated tau associate with senile plaques. Accumulation of phosphorylated tau in microglia is a potential factor in senile plaque bearing. The relationship between Aβ and tau has not been discussed histologically in conventional methods. The HIGASHI method was a good tool for detection of amyloid-dependent tau without mutations of mouse tau. In conclusion, our findings provide a new method for amyloid dependent tau and a new target for research of AD.

Disclosures: Y. Higashi: None. **N. Kakuda:** None. **T. Miyasaka:** None. **S. Funamoto:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

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Program #/Poster #: LBA003.045/LBA43

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

Support: P01AG026572
R37AG053589
Center for Innovation in Brain Science

Title: Mitochondrial fragmentation in fibroblasts from Alzheimer's Disease patients associated with age, biological sex, and APOE genotype

Authors: *M. BANTUGAN[1,2], R. D. BRINTON[3];
[2]Grad. Interdisciplinary Program in Neurosci., [3]Ctr. for Innov in Brain Sci., [1]Univ. of Arizona, Tucson, AZ

Abstract: Mitochondria are crucial in meeting cellular metabolic demands, and their dysfunction has been detected as an early driver of neurodegenerative diseases, including Alzheimer's disease (AD). Previous studies identified bioenergetic deficits linked with mitochondrial morphology between AD and age-matched control (AMC) neurons and fibroblasts, including smaller mitochondrial size and volume, in addition to their increased abundance. However, research on mitochondrial morphology in fibroblasts that considers critical AD risk factors such as age, female sex, and *APOE ε4* genotype is limited. Developing our understanding of fibroblast mitochondrial morphology has the potential to advance precision medicine for AD.
We explored phenotypic differences in fibroblast mitochondria between clinically diagnosed AD (N=15, 62.8 ± 12.9 years old, 8 female, 6 male, and one patient lacking sex information, 11 APOE ε4 carriers) and AMC patients (N=19, 75.8 ± 10.2 years old, 8 female, 11 male, 0 APOE ε4 carriers). Fibroblasts were analyzed using immunofluorescent microscopy and Imaris software (v9.7.2, Bitplane, Oxford Instruments) was used to quantify mitochondrial volume (μm^3), abundance, and density (# mitochondria / fibroblast volume). Statistical analyses included 2-way

ANOVA with multiple comparisons in GraphPad Prism and considered significant at $p<0.05$. Imaging analysis revealed abnormal mitochondrial morphology in AD fibroblasts when considering age and female sex as risk factors. Interestingly, *APOE ε4* status did not impact any observed mitochondrial phenotypes in the AD group. Age significantly impacted mitochondrial morphology with older patients (>65 years old) exhibiting decreased mitochondrial volumes and greater abundance in AD than AMC fibroblasts compared to younger patients (<65 years old) suggesting increased mitochondrial fragmentation. Women older than 65 with AD demonstrated an accumulation of smaller mitochondria in their fibroblasts.
Mitochondrial fragmentation associated with AD diagnosis, as well as critical AD risk factors including age and female sex supports the importance of mitochondrial contribution to AD pathobiology. AD-diagnosed patients had exacerbated phenotypes suggesting accelerated aging, impaired mitophagy and fission-fusion events, and may indicate mitochondrial dysfunction intended to compensate for bioenergetic changes in AD pathogenesis. Older women with AD may face a heightened risk of mitochondrial dysfunction. Fibroblasts may offer a promising, patient-specific model for investigating novel and conserved pathological mechanisms of AD and its mitochondrial bioenergetic crises.

Disclosures: M. Bantugan: None. **R.D. Brinton:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.046/LBA44

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

Support: TUBITAK (Scientific and Technological Research Council of Turkey)

Title: Ultrastructural changes and mitochondrial dynamics in mitochondria in an alzheimer's disease model

Authors: E. N. KESKINÖZ[1], ***K. BIRISIK**[1,2], E. S. TOKLUCU[1,2], M. ÇELIK[1], A. ERISIR[2], D. ÖZ ARSLAN[1];
[1]Acibadem Mehmet Ali Aydinlar Univ., Istanbul, Turkey; [2]Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: The pathogenesis of Alzheimer's disease (AD) is recognized to be significantly influenced by mitochondrial dysfunction. However, the precise connection between proteinopathies in AD and mitochondrial dynamics is yet unclear. This study aimed to investigate ultrastructural and molecular changes in mitochondrial dynamics in the 5xFAD transgenic AD model. To identify ultrastructural alterations in the hippocampus, proximal and distal dendrites of CA1 neurons from 9-month-old 5xFAD mice and littermate control brains

were imaged using transmission electron microscopy. Transgenic brains displayed significant alteration in mitochondrial structure including larger mitochondria areas and diameter. In addition, teardrop-shaped mitochondria that connect to others via string-like mitochondrial extensions were observed in CA1 pyramidal dendrites, and these constituted around 30% of all mitochondria encountered in transgenic brains. Strings of the mitochondria display the typical cristae structure, suggesting that mitochondria strings can be a result of an incomplete fission process. Mitochondria-Endoplasmic Reticulum Contact Sites (MERCs) distances measured in CA1 cell bodies revealed a significant increase in the MERCs distance of transgenic mice, suggesting that the short-distance MERCs with vital functions such as lipid transfer and intracellular Ca2+ metabolism may be selectively affected. Similarly, western blot analysis revealed alterations in proteins regulating mitofusion and mitofission: L and S-OPA1 and MFN2 protein levels in the hippocampus of 6- and 9-month transgenic mice were significantly lower than in control mice. DRP1 protein levels, a measure of mitofission, of transgenic mice were significantly lower, providing further evidence that impaired mitochondrial fission mechanisms may underline changes in mitochondrial shape, size, and location detected during ultrastructural analysis. Our study emphasizes that mitochondrial alterations were seen as early as 6 months in 5XFAD mice and are evident in brain tissue, offering potential biomarkers for early diagnosis and therapeutic intervention in AD.

Disclosures: E.N. Keskinöz: None. **K. Birisik:** None. **E.S. Toklucu:** None. **M. Çelik:** None. **A. Erisir:** None. **D. Öz Arslan:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.047/LBA45

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

Support: NIH R01NS089737
NIH R01GM135326

Title: Mitochondrial bioenergetics stimulates autophagy for pathological tau clearance in tauopathy neurons

Authors: *N. JIA[1], D. GANESAN[4], H. GUAN[1], M. NISSENBAUM[1], A. W. KUSNECOV[2], Q. CAI[3];
[2]Psychology, [3]Cell Biol. and Neurosci., [1]Rutgers Univ., Piscataway, NJ; [4]Dept. of Biochem. and Mol. Biol., Augusta Univ., Augusta, GA

Abstract: Hyperphosphorylation and aggregation of microtubule-associated tau is a pathogenic hallmark of tauopathies and a defining feature of Alzheimer disease (AD). Pathological tau is

targeted by autophagy for clearance after sequestration within autophagosomes, but autophagy dysfunction is indicated in tauopathy. While mitochondrial bioenergetic deficits have been shown to precede tau pathology in tauopathy brains, it is unclear whether energy metabolism deficiency is involved in the pathogenesis of autophagy defects. Here, we reveal that stimulation of anaplerotic metabolism restores defective oxidative phosphorylation (OXPHOS) in tauopathy neurons which, strikingly, leads to pronounced tau clearance by boosting autophagy functionality through enhancements of mitochondrial biosynthesis and supply of phosphatidylethanolamine for autophagosome biogenesis. Furthermore, early anaplerotic stimulation of OXPHOS elevates autophagy activity and attenuates tau pathology, thereby counteracting memory impairment in tauopathy mice. Taken together, our study sheds light on a pivotal role of mitochondrial bioenergetic deficiency in tauopathy-related autophagy defects and suggests a new therapeutic strategy to prevent the buildup of pathological tau in AD and other tauopathy diseases.

Disclosures: N. Jia: None. **D. Ganesan:** None. **H. Guan:** None. **M. Nissenbaum:** None. **A.W. Kusnecov:** None. **Q. Cai:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.048/LBA46

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

Title: The Alzheimer’s Disease Panel As A Novel Tool for Accelerating Alzheimer’s Disease Research

Authors: *Y. CHEHREGHANIANZABI, M. RODRIGUEZ, K. TUTTIS RODRIGUES, C. MYERS, B. FRAHER, C. TICAS RODAS, A. SAADIN, D. KURGANOVA, L. AGBOR, A. MANTEY, N. ECKERT;
Elixirgen Scientific Inc., Baltimore, MD

Abstract: We have developed the Alzheimer’s Disease (AD) Panel, an innovative iPSC cell-based model designed to accelerate AD research. Our team has meticulously profiled AD patient-derived iPSC excitatory neurons, microglia, and astrocytes using high-resolution immunofluorescence imaging. This approach has allowed us to gain detailed insights into cellular morphology and the expression of key markers, including vGLUT1, MAP2, TUBB3, Synapsin, IBA1, TMEM119, GFAP, and S100B. Our observations reveal that iPSC-derived excitatory neurons from both AD patients and healthy age and race-matched controls express neuronal markers and exhibit typical neurite growth. These cells, which can be maintained for over 100 days in culture, are also serving as an excellent model for mature neuron studies. Preliminary studies indicate that AD neurons, which exhibit high levels of Amyloidβ42 and pTau, may have detectable but less developed synapses as indicated by Drebrin A and Synapsin

expression and localization. To further validate the utility of the AD Panel, we profiled the expression and release of Amyloid β42, β40, Tau, and pTau in over 10 AD lines and 5 healthy controls. Our findings suggest a slight trend for neurons homozygous for ApoE4 to express higher levels of these markers. Notably, AD-patient derived excitatory neurons present higher levels of Amyloid β42, β40, Tau, and pTau compared to healthy controls. Our preliminary findings suggest that β-secretase inhibitors consistenty decrease Amyloid β42 in AD and healthy lines, while β-secretase inhibitors decrease Amyloid β42 in a more donor-dependent manner.This unique cell-based patient-derived iPSC model, offers invaluable insights into the genetic influences on sporadic AD. We offer to the research community access to numerous neuronal lines and glial cells from AD patients's iPSCs as an advanced cell-based model for tri-culture/organoid studies, target validation, drug discovery and development, biomarker identification, patient stratification, and personalized drug screening in AD research and drug development.

Disclosures: Y. Chehreghanianzabi: A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **M. Rodriguez:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **K. Tuttis Rodrigues:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **C. Myers:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **B. Fraher:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **C. Ticas Rodas:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **A. Saadin:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **D. Kurganova:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **L. Agbor:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc. **A. Mantey:** A. Employment/Salary (full or part-time):; Elixirgen Scientific INC. **N. Eckert:** A. Employment/Salary (full or part-time):; Elixirgen Scientific Inc..

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.049/LBA47

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

Title: Brain-derived neurotrophic factor reduces beta amyloid in three-dimensional cultures of alzheimer's disease

Authors: *M. PANIER, G. BAKIASI, B. GONG, R. E. TANZI, S. CHOI;
Massachusetts Gen. Hospital, Harvard Med. Sch., Charlestown, MA

Abstract: Alzheimer's Disease (AD), the most common form of age-related dementia, is characterized by progressive memory loss and cognitive disturbance. Two of the neuropathological hallmarks of AD include amyloid plaques and neurofibrillary tangles (NFTs). Amyloid plaques result from the aggregation of toxic Aβ peptides, which are produced by

sequential cleavages of the amyloid precursor protein (APP) by β-site APP-cleaving enzyme 1 (BACE1) and γ-secretase. NFTs consist of filamentous accumulations of hyperphosphorylated tau (pTau). Brain-derived neurotrophic factor (BDNF), a nerve growth factor with many diverse functions, has been a focus of intense interest in AD research. While it is known that BDNF plays a role in modulating cognitive function as well as synaptic and neuronal dysfunction, its effects on Aβ and tau pathologies remain poorly understood. Past studies have produced conflicting results, with some showing a reduction in these pathological hallmarks and others indicating no effect on AD pathogenesis, warranting further study. Our study is the first to investigate the effects of BDNF on AD pathology in a three-dimensional (3D) "human" neural cell culture model of AD (3D-AD cultures), which was previously developed by our lab (Choi et al., Nature 2014). These 3D-AD cultures display robust Aβ deposits and tauopathy and more closely model the pathological development of AD, which occurs in humans, as they successfully recapitulate pathological amyloid-driven tau accumulation. We found that BDNF treatment significantly reduced the levels of Aβ40 and Aβ42, as well as the Aβ42/Aβ40 ratio, in the conditioned media of 3D cultures that harbor APP Swedish/London mutations. BDNF also reduced the levels of APP C-terminal fragments α and β (APP-CTFα and APP-CTFβ, respectively), which suggests that BDNF might affect APP processing. Our results demonstrate that BDNF may mediate amyloid and tau pathologies in AD, and these findings, along with insights into its potential mechanisms, warrant further study to better understand how BDNF could serve as a beneficial therapeutic target for AD.

Disclosures: M. Panier: None. **G. Bakiasi:** None. **B. Gong:** None. **R.E. Tanzi:** None. **S. Choi:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.050/LBA48

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

Support: NIA Grant R01AG070873

Title: Protein Kinase G phosphorylates Drp1 at S637 and mediates neuroprotective effects of PDE2A inhibition

Authors: *A. EPP[1], Y. LU[2], Y. XU[3], X. ZHU[2];
[1]Case Western Reserve Univ., University Heights, OH; [2]Dept. of Pathology, Case Western Reserve Univ., Cleveland, OH; [3]Dept. of Anesthesiol., Rutgers Univ., Newark, NJ

Abstract: PDE2A is the major phosphodiesterase expressed in the hippocampus and frontal/temporal cortex which plays an important role in the regulation of memory and cognition

through modulation of cAMP and cGMP(1). Recent studies demonstrated that inhibition of PDE2A affects mitochondrial morphology and cell death, presumably by enhancing cAMP and PKA-dependent phosphorylation of Drp1(2). However, as PDE2 also modulates cGMP levels and PKG activity, it remains to be determined whether cGMP and PKG was involved in PDE2-dependent regulation of mitochondrial morphology. In fact, bioinformatic analysis revealed that PKA and PKG share the same consensus site on Drp1 (S637) in addition to several other putative sites for each. In vitro kinase assay confirmed the direct phosphorylation of Drp1 by PKG. Overexpression of PKG and Drp1 in HEK293T cells led to a robust increase in pS637 Drp1 levels as detected by both immunoblotting and mass spectrometry of IP-enriched Drp1. Moreover, the selective PKG activator, 8-Br-cGMP, induces mitochondrial elongation as well as increased pS637 of endogenous Drp1 level in the M17 neuroblastoma cell line. More importantly, PKG inhibitor KT5823, similar to PKA inhibitor H89, partially blocked the rescuing effect of Bay 60-7550, an inhibitor of PDE2A, on PDE2A overexpression-induced mitochondrial dysfunction and morphology. Taken together, these results demonstrate that PKG phosphorylates Drp1 at Ser637 and that the cGMP-PKG-Drp1 axis is one mechanism via which BAY-60-7550 exhibits its neuroprotective effects.1. Yan, Y. et al. Protective effects of phosphodiesterase 2 inhibitor against Aβ1-42 induced neuronal toxicity. Neuropharmacology 213, 109128 (2022).2. Monterisi, S. et al. PDE2A2 regulates mitochondria morphology and apoptotic cell death via local modulation of cAMP/PKA signalling. eLife 6, e21374 (2017).

Disclosures: A. Epp: None. **Y. Lu:** None. **Y. Xu:** None. **X. Zhu:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.051/LBA49

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

Support: Western Institute of Neuroscience Postdoctoral Fellowship
VAST Postdoctoral Fellowship
Zywie Bio LLC

Title: Ambroxol and its derivatives improve lysosomal function to decrease amyloid burden in Alzheimer's disease neurons

Authors: *M. MEDAPATI[1], A. TSANG[2], S. N. WHITEHEAD[3], V. JACQUES[5], G. J. BROUSSARD[6], S. H. PASTERNAK[4];
[1]Robarts Res. Institute, Mol. Med. Program, [2]Physiol. and Pharmacol., [3]Anat. and Cell Biol., [4]Univ. of Western Ontario, London, ON, Canada; [5]Deuterx, LLC, Bedford, NH; [6]Princeton Univ., Princeton, NJ

Abstract: Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by the accumulation of oligomeric Amyloid Beta (Aβ) and lysosomal dysfunction in neurons. Recent advancements in anti-amyloid antibody therapies have shown efficacy in reducing amyloid plaque burden. However, these treatments are costly and associated with significant side effects, including brain swelling. Consequently, there is a pressing need for novel, cost-effective therapies that can reduce amyloid plaque burden and improve cognitive function in AD patients at an early stage.
Methods: We investigated the effects of Ambroxol and its family of chemically modified dereivatives on lysosomal function and amyloid beta (Aβ) levels in neurons derived from induced pluripotent stem cells (iPSCs) of Alzheimer's disease (AD) patients. Our study utilized iPSCs harboring mutations in the Amyloid Precursor Protein (APP) gene, specifically the Swedish mutation (increasing Aβ production). Lysosomal protein expression was measured via quantitative western blot analysis. Furthermore, the activities of lysosomal cathepsins B and D were assessed using Magic Red substrate and Pepstatin A, along with BODIPY FL conjugates. Aβ40 and Aβ42 levels were quantified using ELISA on neuronal cell culture supernatants and total protein extracts.
Results: Ambroxol and its derivatives improved the expression and activity levels of lysosomal enzymes β-Glucocerebrosidase (GBA), cathepsin D, and cathepsin B in APP neurons upon treatment. The expression of LAMP1, a lysosomal membrane marker, was decreased in APP neurons and restored to normal cellular levels following treatment with ambroxol and its derivatives. There was a significant decrease in Aβ40 and Aβ42 levels in both wild type and APP Swedish mutant neurons following treatment with ambroxol and its modified forms. These findings indicate that ambroxol and its analogues not only reduce Aβ levels but also enhance lysosomal function in AD patient-derived neurons, suggesting a potential therapeutic approach for Alzheimer's disease.

Disclosures: M. Medapati: None. **A. Tsang:** None. **S.N. Whitehead:** None. **V. Jacques:** None. **G.J. Broussard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Drug analogues Patented by Zywie LLC. **S.H. Pasternak:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.052/LBA50

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

Title: Anti-amnesic effect of Agastache rugosa on scopolamine-induced memory impairment in mice

Authors: *S. KANG[1], M. C. ANG[2], J. KIM[3];
[1]Dept. of Anatomy, Col. of Med., Gyeongsang Natl. Univ., Jinju, Korea, Republic of; [2]Basic Vet. Sci., Univ. of the Philippines Los Banos, Los Banos, Philippines; [3]Col. of Vet. Med., Chonnam Natl. Univ., Gwangju, Korea, Republic of

Abstract: *Agastache rugosa*, a traditional herbal medicine of Asia, is commonly utilized for treating digestive problems. Nevertheless, its cognitive benefits have not been investigated. This study aimed to assess the potential of *A. rugosa* extract (ARE) to mitigate scopolamine-induced amnesia in mice and explore processes related to the cholinergic system and antioxidant effects. Mice orally received 100 or 200 mg/kg ARE for 5 days before intraperitoneal injection with scopolamine to induce memory impairment. Learning and memory were then evaluated with the novel object recognition, passive avoidance, and Morris water maze tests. Additionally, ARE effects on hippocampal AchE, ChaT, and mAchR1 mRNA levels and adult neurogenesis modification were evaluated. Antioxidant and anti-inflammatory activities of ARE were assessed using the 2,2-diphenyl-1-picryl-hydrazyl-hydrate and nitric oxide assays. ARE therapy corrected learning and memory deficits caused by scopolamine in the initial learning and long-term retention stages. The scopolamine-induced model showed decreased hippocampal AchE levels, but increased ChaT and mAchR1 levels. These observations were corroborated by elevated doublecortin and KI-67 staining. Additionally, ARE exhibited significant antioxidant and anti-inflammatory properties. In conclusion, these findings indicate that ARE has significant anti-amnesic effects by influencing the cholinergic system and acting as an antioxidant, suggesting ARE could be used as a cognitive enhancer for amnesia.

Disclosures: S. Kang: None. **M.C. Ang:** None. **J. Kim:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.053/LBA51

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

Support: AHA-971566
24TPA1304527

Title: 4 octyl itaconate prevents mitochondrial dysfunction in individuals in alcohol abuse individuals with type 2 diabetes mellitus

Authors: *N. TYAGI;
Univ. of Louisville, Louisville, KY

Abstract: AimsThis study aimed to examine the therapeutic effects and response mechanisms of 4-OI in alcohol abuse individuals with Type 2 diabetes (T2DM+AL). MethodsIn this study,

network pharmacology was used to identify potential targets for individuals with Type 2 diabetes and alcohol abuse (T2DM+AL). Immunofluorescence and Western blot techniques were employed to detect inflammatory phenotypes in a 4-octyl itaconate (4-OI) resistant mouse microglia cell line (BV2). We conducted two behavioral tests the novel object recognition test and the Y-maze test, to evaluate the cognitive impairment of mice before and after 4-OI treatment. Western blotting and immunofluorescence staining were performed to assess mitochondrial dysfunction. To explore the underlying molecular mechanisms of 4-OI treatment, RNA sequencing and transcription factor prediction analyses were conducted. Additionally, Western blot analysis of mouse BV2 cells was performed to further elucidate the potential molecular mechanisms driving the observed effects.ResultsWe found that 4-OI inhibits neuroinflammation by enhancing mitophagy, which is mediated through the activation of the AMPK/mTOR/ULK1 pathway. This is achieved by increased phosphorylation of AMPK and ULK1, along with decreased phosphorylation of mTOR. Additionally, 4-OI markedly improves cognitive function.ConclusionsOverall, this study demonstrated that 4-OI improved mitochondrial dysfunction and cognitive deficits in individuals with Type 2 diabetes and alcohol abuse (T2DM+AL).

Disclosures: N. Tyagi: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.054/LBA52

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

Support: NIH UO1 AG074960

Title: Evaluating the therapeutic efficacy of EcN4R$_{L\text{-}DOPA}$ in Tg344-19 AD rats

Authors: *M. ABDELHAMID[1], M. GIFANI[1], J. BECK[1], P. PADHI[2], G. PHILLIPS[2], A. G. KANTHASAMY[2], S. E. COUNTS[1];
[1]Michigan State Univ., Grand Rapids, MI; [2]Univ. of Georgia, Athens, GA

Abstract: Alzheimer’s disease (AD) is the most prevalent neurodegenerative cause of dementia and is characterized by the presence of amyloid-β plaques and neurofibrillary tangles along with gliosis and synaptic loss. As such, there is an urgent unmet need to develop treatments to slow disease progression. In this regard, it has been shown that restoration of pontine noradrenergic and midbrain dopaminergic systems, which falter very early in mild cognitive impairment and AD, may improve cognitive processes and stabilize activities of daily living. To address this possibility, we leveraged a custom-designed *E. coli* EcN4R probiotic that produces sustained and titratable L-DOPA as a novel gut-brain mechanism to boost norepinephrine and dopamine levels

during the incipient stages of AD. To test the preclinical efficacy of the EcN4R-L-DOPA probiotic, we replicated AD-associated locus coeruleus noradrenergic neurodegeneration by administering a dopamine-β-hydroxylase IgG-saporin immunotoxin into the prefrontal cortex of 6-month-old Tg344-19 AD rats. The animals then received EcN4R-L-DOPA (1.54×10^{11} cfu, plus 40 mg/kg benserazide) or placebo by oral gavage daily for 6 weeks. Cognitive behavioral function was tested at 4 weeks by open field, Barnes maze, and elevated plus maze tests. In addition, amyloid-β plaque load and glial cell activation were evaluated by quantitative immunohistochemical methods. Gut colonization and plasma and brain L-DOPA levels are being evaluated. The EcN4R-L-DOPA and placebo groups performed similarly in the open field and elevated plus maze tests. By contrast, EcN4R-treated rats showed improved spatial and working memory on the Barnes maze ($p < 0.01$). Moreover, the EcN4R L-DOPA probiotic reduced amyloid-β plaque deposition and attenuated MHC-II microglial cell antigen-presentation activity in both the cortex and hippocampus ($p < 0.01$). However, GFAP expression levels were unaffected. We are currently conducting additional experiments to determine neuronal cell counts and synaptic protein levels. These preliminary preclinical studies suggest that a novel, titratable L-DOPA replacement therapy may be a promising therapeutic strategy for AD.

Disclosures: M. Abdelhamid: None. **M. Gifani:** None. **J. Beck:** None. **P. Padhi:** None. **G. Phillips:** None. **A.G. Kanthasamy:** None. **S.E. Counts:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.055/LBA53

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

Support: National Institute of Aging RF1 AG065301
National Institute of General Medical Science R01 GM069819

Title: β-amyloid inhibits 20s proteasome activity and drives 26s proteasome disassembly, proteasome activation mitigates amyloid induced toxicity and cognitive deficits

Authors: *K. DAVIDSON;
Integrative Biol. and Pharmacol., Univ. of Texas Hlth. Sci. Houston, Houston, TX

Abstract: ABSTRACTBackground: Alzheimer’s Disease (AD) is the leading cause of dementia globally, affecting around 50 million people and marked by cognitive decline and the accumulation of β-amyloid plaques and hyperphosphorylated tau. The limited treatment options and numerous failed clinical trials targeting β-amyloid (Aβ) highlight the need for novel approaches. Reduced proteasome activity is a consistent feature in AD, particularly in the hippocampus. β-amyloid and/or hyperphosphorylated tau are hypothesized to impair proteasome

function in AD by disrupting critical neuronal processes such as memory formation and synaptic plasticity.
Objectives: This study hypothesizes that AD-related deficits are driven in part by impaired proteasome function as a consequence of inhibition by Aβ. We investigated the role of Aβ in the modulation of proteasomal function, the capacity of two proteasome-activating compounds, TAT1-8,9-TOD and TAT1-DEN, to rescue Aβ-induced survival deficits in cell culture, and Aβ-induced cognitive deficits in drosophila and mice.**Results:** The study demonstrates that β-amyloid inhibits 20S proteasome function while simultaneously driving disassembly of 26S proteasome into free 20S proteasome. Treatment with proteasome activators TAT1-8,9TOD and TAT1-DEN enhances 20S and 26S proteasome function and reduces cell death caused by Aβ42 toxicity in SK-N-SH cells *(n=15, $p < 0.05$, $p < 0.01$, and $p < 0.001$)*. In Drosophila models overexpressing Aβ42, oral administration of these compounds delayed mortality and restored cognitive function *(n=89-150, $p < 0.05$, $p < 0.01$, and $p < 0.001$)*. Chronic treatment with TAT1-DEN protected against deficits in working memory caused by Aβ42 in mice and in hAPP(J20) mice with established deficits, acute TAT1-DEN treatment significantly improved spatial learning deficits, with treated mice performing comparably to controls *(n=9-11, $p < 0.05$)*.
Conclusions: Aβ has dual impacts on 20S and 26S proteasome function and stability. Proteasome activation using TAT1-8,9TOD and TAT1-DEN shows promise in mitigating AD-like deficits by protecting against amyloid toxicity and enhancing proteasome function. These findings suggest that targeting proteasome activity could be a viable therapeutic approach for AD, warranting further investigation into the broader impacts of proteasome modulation on AD pathology.

Disclosures: K. Davidson: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.056/LBA54

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

Support: Higher Education Grant

Title: New Frontiers in Dementia Treatment: Exploring Acoustic Therapies for Enhancing Alzheimer's Diagnosis and Intervention

Authors: *D. S. AASIM;
Cognitive Musicology/Neuro Acoustics, Kashmir advanced Scientific research Ctr. KASRC Cluster Univ. Srinagar Jammu and Kashmir Indi, Srinagar, India

Abstract: Abstract: This research explores the utilization of targeted acoustic therapies to address Alzheimer's disease (AD) and related dementias. By examining the impact of acoustic stimulation on cognitive function and neuronal health, we aim to establish an innovative, non-pharmacological approach to combatting neurodegeneration.**Objectives**: 1.**Investigate Acoustic Impact**: To evaluate how specific acoustic frequencies influence neuroplasticity, amyloid-beta clearance, and neuroinflammation, we aim to analyze optimal frequencies for neuroprotection.2.**Assess Efficacy**: To conduct clinical trials to measure the therapeutic effects of acoustic therapies in patients with early to moderate AD. Comprehensive evaluations will include cognitive tests, daily functioning assessments, and neuroimaging techniques.3.**Mechanistic Insights**: This research will dissect the biological mechanisms involved, analyzing the modulation of hallmark features of AD, such as amyloid-beta plaques and tau tangles.4.**Protocol Optimization**: Based on gathered data, we will refine therapy protocols to enhance efficacy and patient outcomes.**Theoretical Framework**: Our model postulates that specific acoustic frequencies can modulate amyloid-beta metabolism and enhance synaptic functioning. Using computational simulations, we predict how these therapies interact with AD pathologies.**Experimental Validation**: We will employ in vitro studies with neuronal cultures and in vivo experiments on AD models, analyzing changes in synaptic activity, neuronal health, and behavioral performance following acoustic stimulation.**Clinical Application**: Our multi-phase clinical trial includes a structured acoustic therapy regimen, pairing cognitive assessments and neuroimaging to monitor changes in amyloid burden and cognitive function.**Outcomes:** Our preliminary results revealed significant cognitive improvements and enhanced daily living activities among the majority of participants. Neuroimaging studies showed a marked reduction in amyloid-beta plaque load and improved connectivity in brain regions related to memory and cognition. Behavioural assessments indicated notable enhancements in memory recall, attention, and executive functions. These results suggest that acoustic therapies can positively impact both the pathological and functional dimensions of dementia and AD**Conclusion**: This research underscores the therapeutic promise of acoustic interventions for AD and related dementias, advocating for further exploration into their efficacy and long-term benefits

Disclosures: D.S. Aasim: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.057/LBA55

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

Support: CIHR Grant PJT-178123

Title: Physical exercise upregulates FNDC5/irisin in extracellular vesicles from the serum of humans

Authors: *N. D. SILVA[1], T. RODY[4], T. HUNTER[2], A. DA CONCEICAO[5], E. RANGEL NASCIMENTO[5], J. MARINATTO[5], G. B. DE FREITAS[3], C. FERNANDES[7], V. BODART-SANTOS[9], I. GRENIER-PLEAU[2], B. ARMITAGE-BROWN[2], H. M. MELO[8], S. E. BOEHNKE[3], C. NICOLINI[10], J. HEISZ[10], M. V. LOURENCO[6], S. ABRAHAM[2], D. P. MUNOZ[12], M. FAHNESTOCK[11], S. T. FERREIRA[13], F. DE FELICE[2];
[1]Ctr. for Neurosciences Studies / Biomed. and Mol. Sci., [3]Ctr. for Neurosci. Studies, [2]Queen's Univ., Kingston, ON, Canada; [4]UFRJ, Rio De Janeiro, Brazil; [6]Inst. of Med. Biochem. Leopoldo de Meis, [5]Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [7]Inst. of Med. Biochem., Federal Univ. of Rio De Janeiro, Rio de Janeiro, Brazil; [8]Federal Univ. of Rio De Janeiro, Rio De Janeiro, Brazil; [9]Dept. of Neurosci., Mayo Clin. Florida, Jacksonville, FL; [10]McMaster Univ., Hamilton, ON, Canada; [11]Psychiatry & Behavioural Neurosciences, McMaster Univ., Burlington, ON, Canada; [12]Ctr. for Neurosci. Studies, Queen's Univ. Ctr. For Neurosci. Studies, Kingston, ON, Canada; [13]Fed. Univ. Rio de Janeiro, Rio de Janeiro, Brazil

Abstract: Physical exercise improves overall brain health, cognition, and stimulates the release of extracellular vesicles (EVs) in humans. Exercise upregulates irisin, a myokine derived from fibronectin type III domain-containing protein 5 (FNDC5) previously shown to mediate the beneficial actions of exercise on memory in mouse models of Alzheimer's disease (AD). Here, we investigated if EV's cargo includes FNDC5/irisin and tested whether physical exercise protocols modulate its content in EVs. Method: 14 male participants (aged 18-30 years) underwent a high intensity interval training exercise program. HIIT sessions were performed 3 times a week, over 6 weeks. Serum was collected before and the day after the last exercise session. Plasma from healthy human donors at rest was also collected. Cerebrospinal fluid (CSF) from cynomolgus monkeys at rest was obtained by lumbar punctures. EVs from biofluids were isolated using Exoquick ULTRA (serum and plasma), SEC (plasma) and Exoquick-TC (CSF), followed by nanoparticle tracking analysis. FNDC5/irisin in EVs was detected by Western blotting, and ELISA.Result: Our results indicate that FNDC5/irisin is associated with serum, plasma and CSF EVs from humans, and monkeys. Exercise upregulated EV- FNDC5/irisin in humans, but did not alter circulating EV concentration. EV- FNDC5/irisin correlated positively with BDNF levels in serum obtained from humans post-exercise. Conclusion: These findings indicate that exercise induces upregulation of FNDC5/irisin in EVs, which may be involved with the delivery of this hormone to different organs, including the brain.

Disclosures: N.D. Silva: None. **T. Rody:** None. **T. Hunter:** None. **A. Da Conceicao:** None. **E. Rangel Nascimento:** None. **J. Marinatto:** None. **G.B. De Freitas:** None. **C. Fernandes:** None. **V. Bodart-Santos:** None. **I. Grenier-Pleau:** None. **B. Armitage-Brown:** None. **H.M. Melo:** None. **S.E. Boehnke:** None. **C. Nicolini:** None. **J. Heisz:** None. **M.V. Lourenco:** None. **S. Abraham:** None. **D.P. Munoz:** None. **M. Fahnestock:** None. **S.T. Ferreira:** None. **F. De Felice:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.058/LBA56

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

Support: NIH U24EB028998
NYS SCIRB DOH01-C38328GG
NIH R01AG060981

Title: Towards a detailed mechanistic model of human cortical microcircuits that accurately predicts the cellular- and circuit-level effects of TMS

Authors: F. S. BORGES[1], J. TAJCHMAN[2], T. KHASHAN[1], E. URDAPILLETA[3,1], E. SANTARNECCHI[2], ***S. DURA-BERNAL**[1,4];
[1]SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [2]Harvard Med. Sch., Boston, MA; [3]Ctr. Atómico Bariloche & Inst. Balseiro, Bariloche, Argentina; [4]Nathan Kline Inst. for Psychiatric Res., Orangeburg, NY

Abstract: Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique which alters activity in a relatively small brain region and can treat a range of neurological conditions. TMS parameters, including stimulation location, intensity and frequency, are generally chosen using a “one-size-fits-all” approach. Personalizing TMS to each patient can dramatically enhance target engagement and increase treatment efficacy. This requires accurately predicting how TMS will affect brain circuit dynamics, which remains an unsolved problem. Multiscale mechanistic biophysical simulation of brain circuits offers an unrivaled approach to integrate available experimental data and generate accurate predictions at the molecular, cellular and circuit scales. They can simulate local field potentials (LFP) and electroencephalogram (EEG) recordings and TMS stimulation effects, and can therefore be used to inform TMS optimal parameter selection.
We present preliminary results of simulating TMS effects in a detailed biophysical circuit model of human cortical circuits. Our model, adapted from a previous rat somatosensory cortex model, includes 6796 neurons of 55 cell types distributed across 6 layers. We adapted neuron models to human dimensions and included morphologically and physiologically realistic axons, required to accurately simulate TMS effects. We included distance-dependent connectivity rules, synaptic background stimulation and short-term plasticity to reproduce in vivo-like firing patterns. We implemented the model using the NEURON simulator and NetPyNE modeling tool.
We simulated neuron membrane voltages, spiking activity, LFPs and EEG signals, during baseline and repetitive TMS stimulation. Simulating trains of biphasic TMS pulses at 30 Hz, with 1 sec duration and 60 V/m amplitude, resulted in spiking of layer 5 pyramidal neurons synchronized to individual stimulation pulses. Increasing TMS amplitude to 80 V/m neurons resulted in synchronous firing of neurons across all layers. The same TMS stimulation applied to

disconnected neurons did not elicit spikes, indicating that the circuit synaptic connectivity and ongoing activity lowers the TMS response threshold of neurons.
These results support the need to simulate circuit activity to adequately characterize the effects of TMS. Next steps will include validating against human TMS-EEG clinical data, simulating known electrophysiological biomarkers of diseases such Alzheimer's disease, epilepsy and schizophrenia, and systematically evaluating the effects of TMS parameters aimed at restoring healthy dynamics.

Disclosures: F.S. Borges: None. **J. Tajchman:** None. **T. Khashan:** None. **E. Urdapilleta:** None. **E. Santarnecchi:** None. **S. Dura-Bernal:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.059/LBA57

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

Support: NIH 1R21AG075232
NIH 1R43AG078012
NIH 1R01AG078376

Title: A Multimodal Music-Based Intervention and its Effects on Associative Memory in Mild Cognitive Impairment

Authors: H. WEIBLEY[1], P. LOUI[2], ***E. LARGE**[3];
[1]Harvard Univ., Cambridge, MA; [2]Northeastern Univ., Brookline, MA; [3]Univ. of Connecticut, Storrs Mansfield, CT

Abstract: Music-based interventions (MBIs) have gained popularity as a non-invasive and sustainable approach for managing dementia-related disorders, including Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD). However, evidence regarding effectiveness of MBIs in achieving positive patient outcomes is mixed. Recent research has explored the potential clinical impact of non-invasive Gamma frequency (e.g., 40 Hz) sensory stimulation on dementia. Preliminary findings indicate that such stimulation can address molecular, cellular, and neural systems pathophysiologies associated with dementia, ultimately leading to improvements in cognitive functioning. We are testing a receptive MBI that combines self-selected music with rhythmic light stimulation at delta, theta, and gamma frequencies. We provide preliminary results for older adults with mild-to-moderate cognitive impairment [MCI] (CDR > 0.5) who completed a face-name association task during fMRI scanning before and after either an 8-week MBI (N = 13) or an 8-week control intervention (N=8). Performance improved significantly for MBI participants but not control participants. Moreover, increased activation was observed in

middle temporal gyrus, fusiform gyrus, lateral occipital cortex, parahippocampal gyrus, and dorsolateral prefrontal cortex for MBI participants. Activations in the fusiform face area correlated with associative memory performance, and increased after the MBI intervention. Data collection is ongoing.

Disclosures: H. Weibley: None. **P. Loui:** None. **E. Large:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oscillo Biosciences.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.060/LBA58

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

Support: 1R01 AG062254
I01 BX001655
IK6 BX004851

Title: Ezetimibe lowers risk of Alzheimer's and Related Dementias over 7-fold, reducing aggregation in model systems by inhibiting 14-3-3G::hexokinase interaction

Authors: *S. AYYADEVARA[1], A. GANNE[3], N. MAINALI[2], M. BALASUBRAMANIAM[4], J. ASANTE[1];
[1]Univ. of Arkansas for Med. Sci., LITTLE ROCK, AR; [2]Univ. of Arkansas for Med. Sci., Little Rock, AR; [3]geriatrics, university of arkansas for medical sciences, Little Rock, AR; [4]Univ. of Arkansas for Med. Sci. (UAMS), Little Rock, AR

Abstract: Numerous factors predispose to progression of cognitive impairment to Alzheimer's disease and related dementias (ADRD), most notably age, APOE(ε4) alleles, traumatic brain injury, heart disease, hypertension, obesity/diabetes, and Down's syndrome. Protein aggregation is diagnostic for neurodegenerative diseases, and may be causal through promotion of chronic neuroinflammation. We isolated aggregates from postmortem hippocampi of ADRD patients, heart-disease patients, and age-matched controls. Aggregates, characterized by high-resolution proteomics (with or without crosslinking), were significantly elevated in heart-disease and ADRD hippocampi. Hexokinase-1 (HK1) and 14-3-3G/γ proteins, previously implicated in neuronal signaling and neurodegeneration, are especially enriched in ADRD and heart-disease aggregates vs. controls (each $P<0.008$), and their interaction was implied by extensive crosslinking in both disease groups. Screening the hexokinase-1::14-3-3G interface with FDA-approved drug structures predicted highest affinity for ezetimibe, a benign cholesterol-lowering medication. Diverse cultured human-cell and whole-nematode models of ADRD aggregation

showed that this drug potently disrupts HK1::14-3-3G adhesion, reduces disease-associated aggregation, and activates autophagy. Mining clinical databases supports drug reduction of ADRD risk, decreasing it to 0.14 overall (P<0.0001; 95% C.I. 0.06-0.34), and <0.12 in high-risk heart-disease subjects (P<0.006). These results suggest that drug disruption of the 14-3-3G::HK1 interface blocks an early “lynchpin” adhesion, prospectively reducing aggregate accrual and progression of ADRD.

Disclosures: S. Ayyadevara: None. **A. Ganne:** None. **N. Mainali:** None. **M. Balasubramaniam:** None. **J. Asante:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.061/LBA59

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

Support: NIH NINDS/NIA R01 NS127284-03

Title: Sex differences in learning and memory function during chronic hypertension

Authors: *B. DENG[1], R. KALISH[1], J. C. REULBACH[2], E. J. BAUMOEL[3], A. SHEHRYAR[1], G. M. DEMARCO[1], A. C. CHAPMAN[3];
[1]Binghamton Univ., Binghamton, NY; [2]Neurolog. Sci., Univ. of Vermont Larner Col. of Med., Burlington, VT; [3]Psychology, Binghamton Univ. - SUNY, Binghamton, NY

Abstract: Chronic hypertension is a leading cause of vascular dementia known to damage brain regions involved in learning and memory, such as the hippocampus that accelerates age-related memory decline in men and women. However, whether one sex is more susceptible to hypertension-induced memory deficits remains unclear. Here, we used adult spontaneously hypertensive rats (SHR) of both sexes and compared to normotensive Wistar (Wis) rats (n=6/group). Two hippocampal-dependent tests were used. Spatial memory was tested using a Morris water maze task: three training days of four consecutive 120 sec swim trials where the time to find the hidden platform (escape latency) was measured. Memory was probed the next day by removing the platform and quantifying latency to and crossings through the platform zone. Reference memory was tested using a radial arm maze (RAM) task: the time it took to retrieve rewards from three baited arms during six daily 10-min sessions was measured. Data are mean ± SEM. Comparisons made between groups via a 2-way ANOVA with a post-hoc Tukey test. There were main effects of sex and hypertension on escape latency, with female SHR and male Wis rats finding the platform faster than female Wis rats on training days 1 and 2; however, all rats had similar escape latency on day 3 (Fig 1). There were no differences between groups in latency to the platform zone during the probe, although female rats trended towards crossing the

platform zone fewer times compared to males ($F_{(1,20)}$=3.29; p=0.08). There was a main sex effect on reference memory, as females completed the RAM in less time with each session (e.g., steeper learning curve) with faster retrieval times on the sixth day (Wis: 111±15 sec; SHR: 122±6 sec) versus males (Wis: 570±2 sec; SHR: 297±10 sec; $F_{(1,20)}$=8.05; p=0.01). These data suggest females, regardless of hypertension, have stronger reference memory than males, and may have some degree of disrupted long-term memory. These findings highlight the importance of understanding sex differences in brain region-specific susceptibility to chronic hypertension.

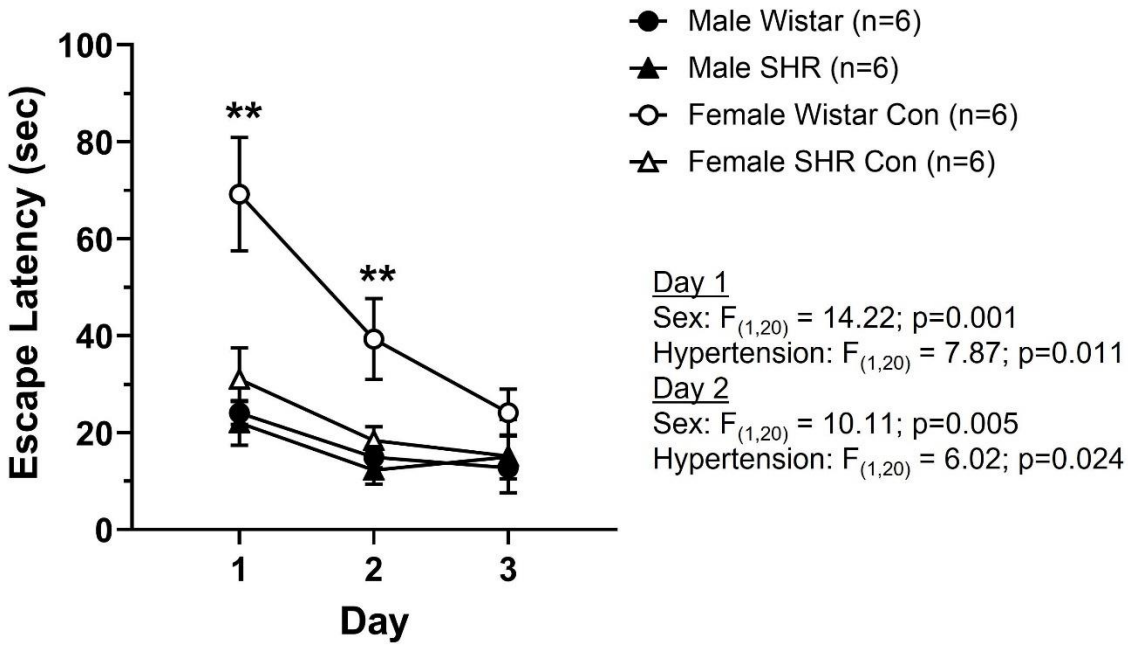

Fig 1. Escape latency of male and female Wistar and SHR rats during a Morris water maze task. **p<0.01 vs. male Wistar rats and female SHR by 2-way ANOVA with post-hoc Tukey test.

Disclosures: B. Deng: None. **R. Kalish:** None. **J.C. Reulbach:** None. **E.J. Baumoel:** None. **A. Shehryar:** None. **G.M. DeMarco:** None. **A.C. Chapman:** None.
Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.062/LBA60

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

Support: NIH Grant R01NS122907

Title: Proteasomal Inhibition Triggers Transactive Response DNA-binding Protein-43 Mislocalization and Enhanced Ubiquitinated Axonal Ribonucleoprotein Condensates in iNeurons

Authors: *S. MATHEW, P. P. GOPAL;
Dept. of Pathology, Yale Sch. of Med., Yale Univ., New Haven, CT

Abstract: Pathologic mislocalization and aggregation of TDP-43, an essential RNA/DNA-binding protein, is central to the pathophysiology of amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), limbic predominant age-related TDP-43 encephalopathy (LATE), and is a feature of Alzheimer's disease and related dementias (AD/ADRDs). The molecular mechanisms underlying TDP-43 redistribution, the variables controlling it, the cellular insult that promotes it and the cellular consequences are poorly understood. We tested the hypothesis that blocking the proteasome causes accumulation of hyperphosphorylated and ubiquitinated TDP-43 condensates in the axon and dendrites. We used human induced pluripotent stem cell derived iNeuron model, in which endogenous *TARDBP* locus has a Dendra2 fluorescent tag and control cell line. iNeurons (DIV14) which are immunopositive for the neuronal markers TuJ1 and MAP2 were treated with proteasomal inhibitor MG132 or DMSO. We then examined how proteasome inhibition affects the localization and trafficking of ubiquitinated TDP-43 in the cytoplasm and TDP-43 distribution in the dendrites and axons of Dendra2 iPSC-derived neurons.The nuclear temporal profile of TDP-43 shifts or has significantly downregulated expression as a result of altered proteostasis. Moreover, upon proteasome inhibition, there is a notable and increased trafficking of ubiquitinated TDP-43 puncta in the dendrites and axons. In DMSO-treated control iNeurons, TDP-43 is restricted to the nucleus. Our data indicate that either local synthesis of TDP-43 or impeded proteolysis may have caused the abnormal spatial mislocalization and ubiquitination of TDP-43. In ongoing work we are examining sequestration of critical cellular constituents by altered proteostasis and the role of lysosomal degradation mechanisms which may have been upregulated by proteasomal suppression.

Disclosures: S. Mathew: A. Employment/Salary (full or part-time):; Yale University, (Full). **P.P. Gopal:** A. Employment/Salary (full or part-time):; Yale University, (Full). 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.; National Institute of Neurological Disorders and Stroke/NIH under Award R01NS122907.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.063/LBA61

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

Title: Role of GFAP in Hypertension-gated Alzheimer's disease

Authors: *K. FATIMA SHAD;
Life Sci., Univ. of Technol. Sydney, Sydney, Australia

Abstract: Introduction: There are over ten million new cases of dementia each year worldwide, implying one new case every 3.2 seconds. The lack of early diagnostic biomarkers highlights the need for accurate tests. Recent focus on Glial fibrillary acid protein (GFAP) and astrocytes suggests their role in cognitive function and dementia. GFAP can influence the onset and progression of Alzheimer's disease (AD). GFAP is a key marker of astrocyte activation. Spontaneous hypertensive rats (SHR) are the unique animal models to study hypertension-gated Alzheimer's disease. **Hypothesis:** GFAP may act as a predictive biomarker for hypertension-gated Alzheimer's Disease, and reactive (A1) Human fetal astrocytes (HFAs) can mimic astrocytes in SHRs. **Aims:1)** Exploring the similarities between the cellular (HFAs) and animal (SHR) models for hypertension and related dementias such as Alzheimer's disease. **2)** To compare the concentration of GFAP in SHR and WKY rat brainstem slices (Samples obtained from **UNSW, animal ethics no. Acec 15/ 49b). 3)** To culture human fetal astrocytes (HFAs) and to differentiate between reactive (A1) and normal (A2) HFAs (Samples acquired from **Biobank of Macquarie University after approval from UTS Ethics no. ETH 17-1883).**4) To estimate and compare the concentrations of calcium-dependent proteins in SHR and HFAs. **Methods:** Spontaneous Hypertensive Rats (SHRs)and Wistar Kyoto (WKY) rats were used as animal models. Normal (A2) and reactive (A1) Human fetal astrocytes as cellular models to test our hypothesis.**Techniques:** Four techniques were used to measure GFAP and other calcium-dependent proteins: Light Microscopy, Confocal Microscopy, LC/MS/MS, and ELISA. **Results:** This study shows for the first time that A1 HFAs resemble astrocytes in SHR, as both have similar concentrations of GFAP mimicking a similar degree of reactivity and hence hypertensive condition. There are significantly higher numbers of GFAP-containing neurons in SHR, compared to WKY rat brain. Longer and thicker processes were observed in both experimental models, indicating higher levels of GFAP in both SHR and A1 HFAs. **Conclusion:** Greater intensity of GFAP in SHR astrocytes and A1 HFAs indicates their involvement in augmented reactivity leading to hypertension-gated Alzheimer's disease. Both S100B and sRAGE proteins were at higher concentrations in A1 than in A2 HFAs. Literature shows that sRAGE concentration is lower in hypertension, suggesting that sRAGE, in addition to GFAP, could be targeted as a therapeutic agent for the treatment of both hypertension and Alzheimer's disease.

Disclosures: K. Fatima Shad: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.064/LBA62

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

Title: Global DNA methylation as an early biomarker for Alzheimer's disease

Authors: *C. CAO[1], F. LAM[2], D. LLANO[3], R. N. DILGER[6], S. SILVERMAN[6], Z.-P. LIANG[4], K. C. LI[7], G. ROBINSON[5];
[1]Univ. of Illinois, Urbana-Champaign, Urbana, IL; [2]Univ. of Illinois at Urbana-Champaign, Champaign, IL; [3]Molec & Integrative Physiol, [4]Electrical and Computer Engin., [5]Univ. of Illinois at Urbana-Champaign, Urbana, IL; [6]Univ. of Illinois Urbana-Champaign, Urbana, IL; [7]Univ. of Illinois Urbana-Champaign, EMERALD HILLS, CA

Abstract: Amyloid β deposition and intracellular aggregation of phosphorylated tau have been the main targets of investigation and therapeutics for Alzheimer's disease (AD). In the meantime, there is increasing interest in alternative diagnostic biomarkers and treatment targets, including AD-associated risk genes, transcriptomics, lipid metabolism and small metabolites, which may also provide a better understanding of the complex etiology of AD. Altered DNA methylation, a key epigenetic mechanism that influences gene expression and exerts long-lasting effects on brain function and disease, has been identified in AD patients and animal models. This presents opportunities for new early biomarker discovery and intervention. However, current methods to measure methylation are destructive and require biopsy. Our team is developing a non-invasive approach known as epigenetic magnetic resonance imaging (eMRI) that has been shown to be able to detect DNA methylation changes in the brain. As a possible prelude to using eMRI to measure and map DNA methylation in AD, our current study aims to explore DNA methylation as an early biomarker by using conventional methods to measure spatiotemporal patterns during AD progression. We used two AD mouse models: a sporadic AD [apolipoprotein E4 (APOE4) knock-in] and a familial AD (5xFAD) model, as well as their respective controls, APOE3 and wild-type (WT). APOE4/APOE3 mice (n = 6) were sampled when 12-13 months old and 5xFAD/WT mice (n = 4) when 2 months old. DNA was extracted from five brain regions (cortex, hippocampus, striatum, midbrain, and cerebellum) and global methylation levels measured using an ELISA kit. APOE4 mice showed lower DNA methylation levels compared to APOE3 mice, with significant differences in the cortex ($t = 2.81$, $df = 8$, $P < 0.05$, Student's t-test), hippocampus ($t = 6.34$, $df = 8$, $P < 0.001$), striatum ($t = 3.01$, $df = 9$, $P < 0.05$), and midbrain ($t = 4.58$, $df = 9$, $P < 0.01$), but not the cerebellum ($t = 1.68$, $df = 9$, $P = 0.13$). The cortex and hippocampus, regions most vulnerable to AD, showed the most striking differences, with the latter exhibiting more than a 2-fold reduction in methylation. 5xFAD mice showed significantly lower DNA methylation across all examined regions relative to WT ($P < 0.05$ or 0.01, $df = 6$ for all brain regions). These findings support the concept that AD is associated with global DNA methylation changes. More importantly, they suggest that DNA methylation differences in the brain could be detected before AD causes significant damage to the brain. This finding encourages further investigation of eMRI for non-invasively mapping this early biomarker for AD.

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Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.065/LBA63

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

Title: Deep learning-based Alzheimer's disease biomarker using FDG-PET

Authors: *J. JANG[1], I. KIM[1], D. T. JONES[2], J. LEE[1];
[1]Hanyang university, Seoul, Korea, Republic of; [2]Mayo Clin., Rochester, MN

Abstract: Alzheimer’s disease (AD) is a prevalent neurodegenerative disorder characterized by gradual memory loss and cognitive decline. Given the irreversible nature of neurodegeneration, clinically reliable methods for early diagnosis and prediction of disease progression before the symptom onset are crucial. This study aims to develop new biomarkers from fluorodeoxyglucose positron emission tomography (FDG-PET) for diagnosing and predicting AD using deep learning models. Initially, we trained a modified 3D-DenseNet model to distinguish between healthy individuals and AD patients. AD probability score value was then extracted from the output of fully connected layer before the classifier, indicating abnormalities in brain metabolism patterns. The clinical implications of the AD probability score derived from the model was validated using a large database (n=4,446) of FDG-PET images from a clinically diverse patient population. The 3D-DenseNet achieved a test accuracy of 95.18% in classifying normal vs. AD using 5-fold cross-validation. AD probability score extracted from the trained model demonstrated statistical significance in differentiating mild cognitive impairment (MCI) from the cognitively unimpaired (CU) group ($p<0.001$, Student’s t-test), suggesting its applicability for early diagnosis of AD continuum. Additionally, we observed statistically significant correlations between the AD probability score and cognitive assessments such as the Clinical Dementia Rating (CDR) and Mini-Mental State Exam (MMSE), as well as other AD neuroimaging biomarkers (e.g., amyloid-beta PET and tau PET scans) ($p<0.001$, Pearson’s correlation). Furthermore, we found that the AD probability score value derived at baseline was associated with the progression of cognitive impairment over time, as evidenced by comparing CU to CU vs. CU to MCI/AD groups, with the latter representing the most recent diagnostic group assignment ($p<0.001$, Student’s t-test). In conclusion, AD probability score derived from FDG-PET data using the CNN model demonstrates significant potential as a reliable biomarker for the early diagnosis and prediction of AD progression.

Disclosures: J. Jang: None. **I. Kim:** None. **D.T. Jones:** None. **J. Lee:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.066/LBA64

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

Title: Advanced Biomarker Analysis for Alzheimer's Disease Diagnosis Using FDG PET: Radiomic Features of Hippocampal Subfields and Amygdala Nuclei

Authors: *R. RASI[1], A. GUVENIS[2];
[1]Bogazici Univ. Inst. of Biomed. Engin., Istanbul, Turkey; [2]Inst. of Biomed. Engin. Boğaziçi Univ., Istanbul, Turkey

Abstract: Advanced Biomarker Analysis for Alzheimer's Disease DiagnosisUsing FDG PET: Radiomic Features of Hippocampal Subfields andAmygdala NucleiAbstractObjective: Our objective is to identify more effective features and regions for describing Mild CognitiveImpairment (MCI) and Alzheimer's Disease (AD) using only FDG PET images.**Method:** We downloaded baseline FDG PET and sMRI data of 555 individuals (189 CN, 201 MCI, and 165AD) from ADNI dataset. The sMRI and FDG PET images were co-registered using the ANTx tool, and thehippocampus and amygdala were extracted utilizing the DKT-Atlas. These structures were furthersegmented into subfields and nuclei with Freesurfer. Using the PyRadiomics tool, we extracted 120radiomic features for each hippocampal subfield and amygdala nucleus. After preprocessing and featurereduction, we applied ANOVA, PCA, and LASSO feature selection methods to identify the most relevantfeatures. Our analysis focused on determining the key features that best describe AD. Finally, weemployed a RandomForestClassifier to test the performance of these features with 100 iterations on a30% independent dataset.**Results:** Our analysis identified two interpretable features in the hippocampus and amygdala thatdemonstrated superior diagnostic efficacy for AD progression. Specifically, glrlm_LongRunEmphasis inthe accessory basal nucleus and gldm_SmallDependenceEmphasis in the presubiculum-head showed aclassification capability with ROC AUC of 0.87 and ACC of 0.78 for AD vs CN, and ROC AUC of 0.80 andACC of 0.75 for AD vs MCI. Additionally, we observed that the average values of these features areassociatewitdh AD progression.**Conclusion:** Our study investigated the subfields of the hippocampus and the nuclei of the amygdala tounderstand AD progression through radiomic analysis. We identified that two specific texture featuresare strongly linked to AD. The glrlm_LongRunEmphasis feature in the accessory basal nucleus effectivelydifferentiates between MCI and AD, suggesting its sensitivity to early AD-associated textural changes.However, our study also revealed a fascinating paradox concerning the presubiculum-head. While thisregion appears remarkably resilient compared to others in terms of severe neurodegeneration, ourfindings suggest it might undergo subtle changes following the MCI stage. This observation adds to thegrowing body of evidence that the presubiculum-head might play a unique role, potentially in the earlystages of AD progression. By focusing on such features in the future, researchers might be able todevelop more precise methods for diagnosing AD earlier and tracking its progression over time.

Disclosures: R. Rasi: None. **A. Guvenis:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.067/LBA65

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

Title: An Automated Assay for Precise and Sensitive Quantification of pTau217 in Plasma and Cerebrospinal Fluid

Authors: S. WILLIS[1], M. CONNOR[1], J. DUNBAR[2], I. O'BRIEN[2], A. JEROMIN[3], ***Y. NOAM**[1];
[1]Bio-Techne, Wallingford, CT; [2]Bio-Techne, Minneapolis, MN; [3]ALZpath, Carlsbad, CA

Abstract: Accurate quantification of fluid biomarkers in blood and cerebrospinal fluid is becoming increasingly important for diagnosis, prognosis, and monitoring of neurodegenerative disease. Growing evidence suggests a strong diagnostic utility for a phosphorylated isoform of the Tau protein (pTau217) as a specific biomarker for Alzheimer's disease. However, many existing methods for detecting and quantifying pTau217 in CSF and blood are time-consuming, expensive, and/or technically complex. This study describes the analytical validation of a novel and fully automated immunoassay for measuring pTau217 in plasma and CSF. The assay utilizes a microfluidics approach (Ella^{TM}) and highly specific pTau antibodies to measure up to 72 samples within 90 minutes, using 25 ul sample volume or less. The limit of detection (defined as three standard deviations above the blank) was determined as 0.49 pg/mL, and the limits of quantitation were determined as 1.5 - 6,000 pg/mL. Intra-assay precision was measured at less than 5% CV using both high- and low-level controls (n=16 replicates per control), and inter-assay precision averaged at 10.0% CV (n=174). Dilutional linearity experiments demonstrated good assay parallelism with recovery rates of 94-106% for plasma and 88-97% for CSF samples. Spike/recovery experiments demonstrated acceptable accuracy with mean recovery values of 86-94% (plasma) and 93-137% (CSF). To assess the biomarker utility of the assay, endogenous plasma levels of pTau217 were measured in a pilot cohort of healthy control donors and Alzheimer's disease patients. Results showed strong elevation of pTau217 in AD samples ($p=0.007$, Mann-Whitney test), consistent with previous reports. In conclusion, this study supports the utility of an automated assay for fast and sensitive pTau217 quantification in plasma and CSF samples of AD patients, while demonstrating robust analytical performance characteristics.

Disclosures: S. Willis: None. **M. Connor:** None. **J. Dunbar:** None. **I. O'Brien:** None. **A. Jeromin:** None. **Y. Noam:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.068/LBA66

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

Title: Plasma ketone bodies as indicators of impaired energy metabolism associated with pre-symptomaticAlzheimer's disease

Authors: *J. JOSE, A. FONTEH, C. MARTINEZ;
Biomarker and Neuro-disease Mechanism Lab., Huntington Med. Res. Inst., Pasadena, CA

Abstract: Introduction: Mitochondrial dysfunction associated with Alzheimer's disease (AD) fails to satisfy the energy requirements of neurons and glia, which contribute to cognitive impairment. Ketone bodies, which are derived from fatty acids through beta-oxidation, are crucial for enhancing mitochondrial efficiency and maintaining sufficient cerebral energy for those who have impaired energy metabolism. Therefore, we hypothesize that plasma ketone body concentrations may be altered in AD patients compared to cognitively healthy individuals.**Method:** Older adults (>65 years) were recruited, and demographic and neurological data were obtained in an ongoing brain-aging project. Participants were classified as cognitively healthy with normal amyloid-tau levels (CH-NAT), cognitively healthy with AD-like pathological amyloid-tau levels having a high risk of cognitive decline (CH-PAT) and AD participants with pathological amyloid-tau levels (AD-PAT). We collected plasma samples from the participants after overnight fasting. Ketone bodies were extracted using ethyl acetate and were derivatized using dimethylaminophenacyl bromide (DmPABr). Derivatized compounds were analyzed using liquid chromatography mass spectrometry with multiple reaction monitoring. The group differences between CH-NAT, CH-PAT and AD-PAT were analyzed.**Results:** Ketone bodies (β-hydroxybutyric acid, acetoacetic acid, and 3-hydroxyvaleric acid) were detected and quantified in plasma samples. The findings indicated a general trend of decreased β-hydroxybutyric acid in AD-PAT plasma as compared to CH-PAT and CH-NAT, and it is in the order CH-NAT>CH-PAT>AD-PAT. Acetoacetic acid and 3-hydroxyvaleric acid levels were found to be increasing in AD-PAT compared to CH-PAT and CH-NAT. The order for both compounds was the same as in the order: AD-PAT>CH-PAT>CH-NAT. Using ROC, acceptable differences in the AUC were shown for each of the ketone bodies comparing CH-NAT with AD-PAT. **Conclusions:** These data suggest that the levels of different ketone bodies are altered in AD patients compared to cognitively healthy people; therefore, plasma levels of ketone bodies can be used as biomarkers of early-stage AD detection.
Fig 1: Derivatization of ketone bodies using DmPABr to enhance the sensitivity of detectionFig.2: Graphs showing the comparison of levels of different plasma ketone bodies between CH-NAT, CH-PAT & AD-PAT. Using ROC, we found all three ketone bodies have an

acceptable difference in the AUC comparing CH-NAT with AD-PAT with a small sample size (each group, n = 4).

Disclosures: J. Jose: None. **A. Fonteh:** None. **C. Martinez:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.069/LBA67

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

Title: Development of a home test for measuring plasma P-tau217 in Alzheimer's disease

Authors: *A. EGHZAWI[1], A. GHARAIBEH[2], R. ABURASHED[3];
[1]Insight Res. Inst., chicago, IL; [2]Insight Inst. of Neurosurg. and Neurosci., Flint, MI; [3]INSIGHT hospital and Med. Ctr. Chicago, Chicago, IL

Abstract: Alzheimer's Disease (AD) is the most common cause of dementia, with an estimated 6.7 million Americans over 65 with AD in 2023. AD is characterized by β-amyloid (Aβ) and phosphorylated tau (p-tau) protein in the brain. Early detection of AD allows for timely intervention to slow disease progression. Blood-based biomarkers provide more accessible and less invasive testing options to help obtain an earlier diagnosis. One such biomarker is p-tau protein at threonine 217 (p-tau217). Plasma p-tau217 are elevated in the mild cognitive impairment (MCI) and dementia stages of AD and are associated with the presence of Aβ and tau pathology as assessed by PET and CSF.
Increased baseline plasma p-tau217 can predict progression of cognitive impairment, and longitudinal increases correlate with declining cognition.
The purpose of this study is to determine if the concentration of p-tau217 measured from blood samples collected using at home blood test is comparable to the results obtained from blood samples collected via venipuncture.
In this study, healthy control subjects and subjects with AD were recruited to obtain blood samples for p-tau217 concentration. Subjects were enrolled to evaluate the alignment between the at home blood test and venipuncture p-tau217 concentration in each subject. Our results showed no significant difference ($p > 0.05$) between p-tau217 concentrations which support that there is an agreement between the concentrations using at home test and venipuncture method. We believe that the at home p-tau217 test will offer an accessible, non-invasive, and convenient method for early evaluation of AD.

Disclosures: A. eghzawi: None. **A. Gharaibeh:** None. **R. Aburashed:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.070/LBA68

Topic: C.03. Parkinson's Disease

Support: NRF-NRFF2016-03
MOE-T2EP30220-0005
MOE-MOET32020-0004
IRB-2016-12-029
IRB-2018-09-052
NREC 08/MRE09/31
NHS REC No 18/SW/0029

Title: Heterogeneity of inflammatory cell death mechanisms involved in neurodegeneration in the post-mortem substantia nigra in Parkinson's disease

Authors: *Y. HENG[1], A. JAYARAMAN[2], R. REYNOLDS[3], J. FOO[1];
[1]Lee Kong Chian Sch. of Med., Nanyang Technological Univ., Singapore, Singapore; [2]Natl. Neurosci. Inst., Singapore, Singapore; [3]Brain Sci., Imperial Col. London, London, United Kingdom

Abstract: Parkinson's disease (PD) is marked by the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) and the presence of Lewy pathology. However, little is known about the precise mechanisms of cell death involved in the neuronal loss, or at which stage such pathways are initiated during PD progression. We examined neuronal loss in SN tissue of 23 PD cases and 12 non-neurological controls. We confirmed a significant loss of tyrosine hydroxylase (TH)-immunoreactive ($p < 0.0001$) and neural Hu (HuC/D)-immunoreactive ($p < 0.0001$) neurons in PD cases compared to controls. Specifically, compared to controls, 46% of total neurons and 54% of DA neurons in the PD SN were lost at the time of post-mortem examination. Furthermore, we found that Lewy pathology, represented by Braak stage, strongly correlated with DA and total neuronal loss (Spearman $r = -0.9014$ and -0.8347, respectively). We also evaluated the mRNA and protein expressions of apoptotic markers (Fas-associated protein with death domain, caspase-8, caspase-3), necroptotic markers (receptor-interacting serine/threonine kinases 1 and 3 [RIPK1/3], mixed lineage kinase domain-like protein [MLKL]), and ferroptotic markers (glutathione peroxidase 4 [GPX4], transferrin receptor [TFR1]) in the same individuals, with an additional 12 controls by reverse transcriptase-PCR, Western blot and immunohistochemical staining. Protein levels were normalized to GAPDH and total neuron counts to account for neuronal loss. The absence of cleaved caspase 3 - the downstream executioner of the terminal apoptotic cascade - either by Western blot or immunohistochemical methods showed that apoptosis is not the main mechanism driving neuronal loss in PD. Instead, activation of inflammatory forms of cell death, namely necroptosis and ferroptosis, were noted by protein expression of specific markers including phosphorylated

MLKL (pMLKL) and TFR1, respectively. When stratifying PD cases by Braak stages, pMLKL level decreased (mean ± SD Intermediate-PD: 0.03 ± 0.03, Late-PD: 0.01 ± 0.02; Dunn's adjusted P = 0.22) and TFR1 level increased (Intermediate-PD: 0.01 ± 0.01, Late-PD: 0.08 ± 0.09; Dunn's adjusted P = 0.0006) in late-stage PD (stages V-IV) compared to intermediate-stage PD (stages III-IV), suggesting that ferroptotic signalling is more prominent in advanced PD. However, further clarification of the molecular underpinnings of ferroptosis, and usage of novel approaches to uncover additional specific ferroptotic molecular markers are required. Our findings have implications for our understanding of the pathological processes underlying neurodegeneration in PD.

Disclosures: Y. Heng: None. **A. Jayaraman:** None. **R. Reynolds:** None. **J. Foo:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.071/LBA69

Topic: C.03. Parkinson's Disease

Support: ASAP-020616

Title: Modulation of Parkinson's Disease-relevant cellular pathophysiology by synaptic surface interactors

Authors: *M. IULIANO[1,2,3], S. SAH[2,3], D. E. PÉREZ-ACUÑA[2,3], P. SHEDGE[2,3], T. BIEDERER[2,3];
[1]Dept. of Neurosci., Tufts Univ. Sch. of Med., Boston, MA; [2]Dept. of Neurol., Yale Sch. of Med., New Haven, CT; [3]Aligning Sci. Across Parkinson's (ASAP) Collaborative Res. Network, Chevy Chase, MD

Abstract: Parkinson's Disease (PD) is a neurodegenerative disease marked by the toxic accumulation of insoluble α-synuclein (α-syn). Pathophysiological progression occurs across synaptically connected neuronal populations, perpetuating α-syn spread and disruption of neuronal and synaptic function. These disturbances suggest synaptic surface interactors are relevant in understanding cellular mechanisms driving PD pathophysiology. Using preformed α-syn fibril (PFF) models, our study aims to define the requirement and/or ability of specific synaptic organizers to facilitate PFF-mediated pathological spread and synaptic disturbances. To modulate candidate expression prior to PFF administration in vitro, we employed a lentiviral short hairpin (shRNA) knockdown approach in aged primary hippocampal cultures (n=3 experimental rounds). Samples were collected and processed 7 days post-PFF treatment for confocal microscopy to examine extent of phosphorylated α-syn (p-α-syn) accumulation and presynaptic vesicular glutamate transporter 1 (VGLUT1) densities. Our evidence suggests a

contribution of synaptic organizers in neuronal pathology and PFF-mediated synapse loss. As a result, we sought to characterize molecular mechanisms directing this process. In addition to identifying the involvement if specific candidate isoforms, we examined whether heparan sulfate (HS) proteoglycan modifications are of relevance, as they have been shown to direct α-syn internalization and are functionally relevant to synaptic organization. Knockdown/selective rescue experiments in vitro suggest the interaction of candidate synaptic proteins with α-syn aggregates can be influenced by HS modifications. Together, our findings identify that synaptic surface interactions are pertinent to understanding molecular mechanisms driving cellular pathophysiology in PD.

Disclosures: M. Iuliano: None. **S. Sah:** None. **D.E. Pérez-Acuña:** None. **P. Shedge:** None. **T. Biederer:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.072/LBA70

Topic: C.03. Parkinson's Disease

Support: Chan Zuckerberg Initiative Grant DAF2018-191999
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NINDS Grant NS072026
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NIA Grant P30AG072980

Title: Astrocytic LRRK2 Controls Astrocyte Morphology and Synaptic Connectivity

Authors: *S. WANG;
Duke Univ., Durham, NC

Abstract: Astrocytes tightly control synapse numbers and function in the brain through their elaborate morphology and direct contact with synapses. Neurodegenerative disorders, including Parkinson's Disease (PD), have astrogliosis and synaptic dysfunction. However, whether astrocytes can be targeted for synaptic dysfunction in PD is unknown. We found that the PD-linked gene Lrrk2 controls astrocyte morphology by regulating the phosphorylation of ERM proteins (Ezrin, Radixin, and Moesin), a structural component of the perisynaptic astrocyte processes. ERM phosphorylation is elevated both in mice and humans carrying the LRRK2 G2019S parkinsonism mutation. We demonstrated that dampening ERM phosphorylation levels

by overexpressing phospho-dead Ezrin in LRRK2 G2019S mouse astrocytes can rescue astrocyte morphology and excitatory synaptic deficits in the anterior cingulate cortex (ACC). Using *in vivo* BioID proximity labeling, we identified Ezrin interactomes in WT and LRRK2 G2019S mouse astrocytes. We found that Ezrin interaction with Autophagy-Related 7 (Atg7), a crucial autophagy regulator, decreased in LRRK2 G2019S astrocytes. Our data showed that astrocytic Atg7 is required for astrocyte morphological complexity in a genotype-dependent manner, and its dysregulation may contribute to the impaired astrocyte morphology in LRRK2 G2019S mice. Our study reveals that astrocyte dysfunction can be targeted to reverse synaptic dysfunction, identifying Lrrk2-ERM-Atg7 signaling pathways for potential therapies.

Disclosures: S. Wang: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.073/LBA71

Topic: C.03. Parkinson's Disease

Title: Species specific difference enhance the human activity of a novel LRRK2 inhibitor, SAR444596

Authors: Y. LI[1], S. BOULARAND[2], H. PARK[1], R. KRISHNAN[1], P. SARDI[1], S. DEPRETS[3], ***C. KAYATEKIN**[1];
[1]Sanofi, Cambridge, MA; [2]Sanofi, Longjumeau, France; [3]Sanofi, Vitry-sur-Seine, France

Abstract: Genetic variants in the *LRRK2* gene, which encodes leucine-rich repeat kinase 2 (LRRK2), are associated with the onset of both familial and idiopathic Parkinson's disease (PD). Pathogenic *LRRK2* variants including the most prevalent G2019S mutant increase LRRK2 kinase activity. Recent observations of increased LRRK2 kinase activity in idiopathic PDs suggest LRRK2 kinase inhibition as a compelling therapeutic approach for both familial and sporadic PD. Here we described a highly brain penetrant small molecule LRRK2 inhibitor, SAR444596, showing potent inhibition of LRRK2 kinase activity in primary cells, rodents, and non-human primates (NHPs). SAR444596 demonstrated functional rescue of lysosomal defects in cellular models. Interestingly, we observed an indirect pharmacokinetic-pharmacodynamic (PK-PD) relationship of SAR444596 in NHPs, but not in rats. Chronic dosing of SAR444596 caused LRRK2 protein depletion, resulting in sustained inhibition of LRRK2 activity in NHPs even after clearance of the compound. We developed an *in vitro* PK-PD model using primary PBMC cultures which recapitulated these cross-species differences and demonstrated a congruous PK-PD relationship between humans and NHPs. Finally, we defined the minimal active dose of SAR444596 in NHP at 5mg/kg twice daily with the inhibitory effect mostly driven

by total LRRK depletion. Our work on SAR444596 provides a roadmap for therapeutic programs targeting LRRK2 inhibition

Disclosures: **Y. Li:** A. Employment/Salary (full or part-time):; Sanofi. **S. Boularand:** A. Employment/Salary (full or part-time):; Sanofi. **H. Park:** A. Employment/Salary (full or part-time):; Sanofi. **R. Krishnan:** A. Employment/Salary (full or part-time):; Sanofi. **P. Sardi:** A. Employment/Salary (full or part-time):; Sanofi. **S. Deprets:** A. Employment/Salary (full or part-time):; Sanofi. **C. Kayatekin:** A. Employment/Salary (full or part-time):; Sanofi.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.074/LBA72

Topic: C.03. Parkinson's Disease

Support: Aligning Science Across Parkinson's ASAP-020495
CZI Neurodegeneration Challenge Network DAF2019-191947

Title: Self-assembling synuclein induces Parkinsonian pathology in vitro and in vivo

Authors: *Y. FAN, V. GRADINARU;
Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: One of the key pathological features of Parkinson's disease (PD) is the abnormal accumulation of alpha-synuclein (αSyn), a protein that aggregates to form Lewy bodies (LB). It remains unclear when, where, and in which cell types αSyn aggregation starts and how it is transmitted between neurons. Inoculation of animal models with αSyn pre-formed fibrils (PFFs) induces aggregation of endogenous αSyn and recapitulates critical aspects of PD pathology. However, this method involves invasive surgeries and lacks cell-type specificity. The PFF model is further hampered in iPSC-derived neuron and organoid systems by limited cellular uptake of PFFs and penetration into organoids. In this study, we therefore aimed to develop a new method to induce temporally controlled, tunable, and cell-type-specific PD pathology that can easily be applied to animal models and cultured cells. First, we designed a library of self-assembling synucleins (SAS) consisting of different types of self-assembling peptides fused to αSyn. The constructs were designed with a Tet response element to allow precise doxycycline-inducible control of the level and duration of expression. *In vitro* screening identified several constructs that not only form αSyn aggregates but also induce substantial Ser129 phosphorylation (pS129), a hallmark of αSyn pathology. We further validated top hits in several modalities of neuronal culture, including murine primary neurons, and human iPSC-derived neurons and organoids. Our top three SAS constructs robustly induced αSyn aggregation and pS129-αSyn pathology in over 90% of neurons. Of these, one construct (SAS3) also induced secondary nucleation of

endogenous αSyn, neuronal axon retraction and neuronal death. Finally, we tested if SAS3 could induce PD-like pathology *in vivo*. By packaging SAS3 into PHP.eB, an adeno-associated viral vector (AAV) engineered by our lab that efficiently transduces the central nervous system in mice, we were able to achieve brain-wide delivery of our construct in C57BL/6J mice. After three weeks of doxycycline treatment, we observed αSyn aggregation and pS129-αSyn pathology across different brain regions, as well as decreased movement in an open field test. In summary, we have developed a genetically-encoded, doxycycline-regulated self-assembling synuclein system to efficiently induce temporal and tunable PD-relevant pathology both *in vitro* and *in vivo.* We expect this to be a valuable tool to study the initiation and spread of pathology in diverse models of PD.

Disclosures: Y. Fan: None. **V. Gradinaru:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C.I.T. filed IP for methods with V.G. as inventor. Capsida Biotherapeutics Cofounder and BoD member..

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.075/LBA73

Topic: C.03. Parkinson's Disease

Support: NIH (KO8 AG071983)
Cognito Therapeutics Inc.
Harry T. Mangurian Jr. Foundation
Norman Fixel Foundation
University of Florida Center for Aging and Memory
McKnight Brain Foundation

Title: Cognitive effects of intra-striatal injection of a-synuclein preformed fibrils in young versus aged rats

Authors: *S. JEYAGOPAL[1], B. SETLOW[2,4], J. L. BIZON[3,4], M. R. BURNS[1,4,5];
[1]Neurol., [2]Psychiatry, [3]Neurosci., Univ. of Florida, Gainesville, FL; [4]Evelyn F. & William L. McKnight Brain Inst., Gainesville, FL; [5]Norman Fixel Inst. for Neurolog. Dis., Gainesville, FL

Abstract: Alpha-synuclein is a protein that has commonly been implicated in Parkinson's disease (PD) and synuclein-associated dementias. This protein aggregates into preformed fibrils (PFFs) and thus contributes to the progression of Parkinson's disease. As a result, many researchers have adopted intra-striatal injections of α-synuclein PFFs in rats to model cognitive and motor symptoms of Parkinson's disease. Despite age being the most significant risk factor contributing to synuclein-associated dementias, aged animal models are rarely used. The focus of

our research is to evaluate the cognitive effects of injecting α-synuclein PFFs into young versus aged rats. Sixty-three male Fischer 344 x Brown Norway F1 hybrid rats, either young (6 months) or aged (20 months), underwent surgery to inject either α-synuclein PFFs (experimental group) or α-synuclein monomers (control group) into the bilateral striatum. Two months post-surgery, rats were food restricted and tested on a delayed response working memory task followed by a probabilistic reversal learning task. Our initial hypothesis was that in comparison to the monomer control group, working memory and cognitive flexibility would deteriorate more rapidly in aged compared to young rats injected with PFFs. Data to date show that aged rats injected with PFF perform numerically worse on the working memory task in comparison to the other groups, especially at long retention delays. Results from the reversal learning task were consistent with the working memory data, and show that aged but not young rats injected with PFFs completed fewer reversals than monomer-injected controls (three-factor, repeated measures ANOVA, group X age interaction, $F(1,16)=8.49$, $p=.01$). Prior work with the PFF model shows that α-synuclein levels peak 2-4 months after injection and decline thereafter, and thus we will evaluate cognition in these rats at these later timepoints, as well as conduct neuroimaging and immunohistochemistry to assess PFF effects on brain structure. The initial results suggest that this aged rat model can replicate the progression of PD and its resulting cognitive deficits.

Disclosures: S. Jeyagopal: None. **B. Setlow:** None. **J.L. Bizon:** None. **M.R. Burns:** 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.; Cognito Therapeutics Inc..

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.076/LBA74

Topic: C.03. Parkinson’s Disease

Title: Progressive cognitive deficits are driven by midbrain alpha-synuclein overexpression in a mouse model of Parkinson's disease

Authors: *B. COUTANT[1], X. ZHUANG[3], J. L. SEILER[4], T. HSIAO[6], G. M. HALLIDAY[7], R. H. EDWARDS[2], T. N. LERNER[5], A. B. NELSON[1];
[1]Neurol., [2]UCSF, San Francisco, CA; [3]Neurol., Univ. of California, San Francisco (UCSF), San Francisco, CA; [5]Neurosci., [4]Northwestern Univ., Chicago, IL; [6]Halliday group, Neurosci. Res. Australia, Randwick, Australia; [7]Sch. of Med. Sci., Univ. of Sydney, Drummoyne, Australia

Abstract: Cognitive deficits, including impaired associative learning and behavioral flexibility, are a disabling and understudied feature of Parkinson’s disease (PD). PD diagnosis is based on motor symptoms, but patients often have mild cognitive impairments at the time of diagnosis.

More recently, cognitive changes have also been reported before PD diagnosis. Understanding the underlying mechanisms of early cognitive impairments represent a major challenge in PD patients and few studies have attempted to link these deficits with circuit dysfunction in PD. Moreover, accumulation of the PD-associated protein alpha-synuclein (αsyn) is correlated with cognitive deficits, but its causal role remains unclear. Here, we combine a progressive mouse model of PD driven by viral overexpression of αsyn in dopamine neurons with cognitive assays to study the impact of αsyn overexpression on cognitive function. We find that overexpressing αsyn drives cognitive impairments even before motor deficits emerge. Specifically, 2 months post-αsyn injection, mice develop severe deficits in basic reward-based action-outcome association, in parallel with a mild motor phenotype. This severe learning deficit prevents study of more complex behavioral flexibility. However, at an earlier timepoint (3 weeks post-injection), αsyn mice are able to learn basic reward-based associations, albeit not as efficiently as control mice. In αsyn mice, a subtle deficit in reversal learning is also observed at this timepoint. To further dissect the circuit mechanisms of cognitive deficits in PD, we investigated the specific role of lateral versus medial substantia nigra *pars compacta* (SNc) in reversal learning at 8 weeks post-injection. Interestingly, mice with αsyn-overexpression in the medial (but not lateral) SNc show deficits in set-switching. Together, these results will provide new insights into circuit-level mechanisms contributing to cognitive dysfunction in PD, as well as potential therapeutic avenues.

Disclosures: B. Coutant: None. **X. Zhuang:** None. **J.L. Seiler:** None. **T. Hsiao:** None. **G.M. Halliday:** None. **R.H. Edwards:** None. **T.N. Lerner:** None. **A.B. Nelson:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.077/LBA75

Topic: C.03. Parkinson’s Disease

Support: Center for Development and Behavioral Neuroscience

Title: Investigating the Role of Dopamine D3 Receptors in Dopamine Dysregulation Syndrome in a Bilateral 6-OHDA Lesion Rat Model of Parkinson’s Disease

Authors: *I. DIROSA, J. MASLINSKI, E. KLAYMAN, N. LIPARI, C. R. BISHOP; Psychology, Binghamton Univ., Vestal, NY

Abstract: Parkinson’s disease (PD) is a progressive neurodegenerative movement disorder caused by the loss of dopamine (DA) neurons in the nigrostriatal pathway. DA replacement therapy (DRT) such as Levodopa (LD) or DA agonists initially improve motor function, but chronic use may result in complications, such as L-DOPA-induced dyskinesia (LID) and

dopamine dysregulation syndrome (DDS). DDS presents as impulsive and compulsive behaviors resulting from patients taking higher and more frequent doses of DRT than necessary yet the mechanisms underlying DDS are not well understood. Previous work from our lab established that LD produces place preference indicating motivational properties driven by progressive DA depletion. Thus, this research aims to clarify the mechanisms underlying DDS by investigating potential reinforcing features of the DA D3R agonist, PD-128907. To test this, 31 male and female Sprague-Dawley rats received bilateral 6-hydroxydopamine (6-OHDA) lesions, sham lesions of the medial forebrain bundle, or no surgical intervention. Parkinsonian phenotype was then assessed 3 weeks post-surgery through validated motor assays such as the forepaw adjusting steps (FAS) test and the rotarod test. Subsequently, the conditioned place preference (CPP) paradigm was utilized to assess whether PD-128907 (vehicle vs. 1 mg/kg) possessed reinforcing properties. To provide further insight, the expression of abnormal involuntary movement (AIMs) and treatment-driven improvements to motor disability were also tested. The current results indicate reinforcing effects of PD-128907 in both sham and parkinsonian rats, with further analyses anticipated to elucidate whether LID is associated with drug preference in DA-lesioned subjects. Further post-mortem analyses will investigate the extent and location of DA loss which could lend insight into a CPP mechanism. Overall, this study aims to provide deeper insights into DA agonist effects in PD, explore the nexus between DDS and LID, and identify potential overlapping and distinct mechanisms that could be targeted for therapeutic interventions.

Disclosures: I. DiRosa: None. **J. Maslinski:** None. **E. Klayman:** None. **N. Lipari:** None. **C.R. Bishop:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.078/LBA76

Topic: C.03. Parkinson’s Disease

Title: Deep Learning Behavioral Phenotyping System in the Diagnosis of Parkinson’s Disease with Drosophila melanogaste

Authors: *K. DONG;
USC, Los Angeles, CA

Abstract: Drosophila melanogaster is widely used as animal models for Parkinson’s disease (PD) research. Because of the complexity of MoCap and quantitative assessment with Drosophila melanogaster, however, there is a technical issue to identify PD symptoms within drosophila based on objective spontaneous behavioral characteristics. In this study, we developed a deep learning framework generated from kinematic features of body posture and motion between wildtype and SNCAE46K mutant drosophila genetically modeled α-Syn,

supporting clustering and classification of PD individuals. We record locomotor activity in a 3D-printed trap, and utilize the pre-analysis pose estimation software DeepLabCut (DLC) to calculate and generate numerical data representing the motion speed, tremor frequency, and limb motion of Drosophila melanogaster. By plugging these data as the input, the diagnosis result (1/0) representing PD or WT as the output. Our result provides a toolbox which would be valuable in the investigation of PD progressing and pharmacotherapeutic drug development. https://www.biorxiv.org/content/10.1101/2024.02.23.581846v1.full

Disclosures: K. Dong: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.079/LBA77

Topic: C.03. Parkinson's Disease

Support: Aligning Science Across Parkinson's (ASAP) grant ASAP-020616

Title: Cortical synaptic vulnerabilities revealed in an a-synuclein aggregation model of Parkinson's disease

Authors: *S. SAH[1,3], A. D. SAUERBECK[4,3], J. GUPTA[2], D. PÉREZ-ACUÑA[1,3], J. E. REIBER[5], V. SINGH[5,3], D. L. RUSSELL[5], T. M. GORALSKI[6,3], M. X. HENDERSON[6,3], L. A. VOLPICELLI-DALEY[5,3], M. J. HIGLEY[2,3], T. T. KUMMER[4,3], T. BIEDERER[1,3,2]; [1]Dept. of Neurol., [2]Dept. of Neurosci., Yale Sch. of Med., New Haven, CT; [3]Aligning Sci. Across Parkinson's (ASAP) Collaborative Res. Network, Chevy Chase, MD; [4]Dept. of Neurol., Washington Univ. Sch. of Med., Saint Louis, MO; [5]Univ. of Alabama at Birmingham, Birmingham, AL; [6]Dept. of Neurodegenerative Sci., Van Andel Inst., Grand Rapids, MI

Abstract: Cognitive impairment is a common non-motor symptom of Parkinson's disease (PD). PD patients experience a loss of synaptic proteins in the cortex, and synaptic dysfunction is likely to impair cortical function. The extent of synapse vulnerability, its temporal profile in the PD cortex, and its spatial relationship to affected areas remain unclear. We used high-resolution mesoscale imaging to examine synaptic abnormalities in the cortex of mice injected with α-synuclein pre-formed fibrils into the striatum, inducing pathological aggregation of endogenous α-synuclein in cortical neurons. α-Synuclein monomer-injected mice served as controls. Our results support that cortical pathology is associated with a progressive loss of excitatory synapses, which is followed by a decline in inhibitory postsynaptic sites. Synapses containing α-synuclein aggregates showed the most significant loss in areas with high pathology levels. Gene ontology analysis of synaptic genes with altered expression in pathology-bearing human and mouse neurons points to specific changes in components of the synaptic vesicle cycle and

postsynaptic proteins and synapse-organizing pathways. Consistent with these findings, we observed ultrastructural changes in excitatory synapses. Additionally, we used electrophysiological measurement to determine that excitatory transmission was compromised in the cortex of our model. Our results provide evidence that α-synuclein aggregation in the cortex is linked to molecular and structural synaptic changes that disrupt connectivity and transmission. These findings provide insights into the progressive vulnerability of cortical synapses and network aberrations in PD.

Disclosures: S. Sah: None. **A.D. Sauerbeck:** None. **J. Gupta:** None. **D. Pérez-Acuña:** None. **J.E. Reiber:** None. **V. Singh:** None. **D.L. Russell:** None. **T.M. Goralski:** None. **M.X. Henderson:** None. **L.A. Volpicelli-Daley:** None. **M.J. Higley:** None. **T.T. Kummer:** None. **T. Biederer:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.080/LBA78

Topic: C.03. Parkinson's Disease

Support: HBC.2020.2901

Title: Combination model for preclinical proof of concept studies targeting human alpha-synuclein pathology

Authors: E. VONCK[1], S. CARMANS[2], W. DEJONCKHEERE[2], V. BAEKELANDT[1], ***T. CORNELISSEN**[2];
[1]Neurosciences, KU Leuven, Lab. for Neurobio. and Gene Therapy, Leuven, Belgium; [2]reMYND, Leuven, Belgium

Abstract: A-synuclein (αSyn) has been identified as a key protein in the pathophysiology of Parkinson's disease (PD). Therefore, this protein has gained a lot of interest as a possible biomarker and therapeutic target. Multiple αSyn-based rodent models have been developed, each reproducing specific features of the disease which are not always as robust. Therefore, a more robust and encompassing model mimicking the full spectrum of pathological and behavioural changes is needed. We aim to create an αSyn-based model with increased construct validity by combining two established approaches to model PD, namely AAV-mediated overexpression of human αSyn with the addition of human αSyn preformed fibrils (hPFFs). To increase translatability for treatments which target human αSyn specifically, administration of **human** PFF's and expression of **human** αSyn via viral vectors is initiated. Young wild-type mice are treated with either AAV2/7-CMVenhSyn-haSyn, recombinant hPFFs (Stressmarq) or the combination of both through unilateral stereotactic injection. We administered human PFF's in

the right striatum after local overexpression of human αSyn by AAV2/7-human-aSyn viral vector injection in the right substantia nigra. Motor performance will be assessed followed by pathologic characterization of the model. Preliminary results of a pilot study showed 25% loss of TH+ cells in the SN and 45% loss of TH+ terminals in the striatum 3 months post injection of AAV. When adding the hPFFs, this loss is increased further to 45% for TH+ cells and 90% of TH+ terminals. Notably, injection of hPFFs alone does not induce dopaminergic cell loss or degeneration of striatal projections, possibly due to the species barrier. These preliminary results suggest that hPFFs do seed the monomeric hαSyn and aggravate the pathology induced by AAV-mediated overexpression of hαSyn. This αSyn-based model can be important to the research field to assess in vivo therapeutic interventions directed against αSyn pathology and more specifically **human** αSyn pathology.

Disclosures: E. Vonck: None. **S. Carmans:** A. Employment/Salary (full or part-time):; reMYND. **W. Dejonckheere:** A. Employment/Salary (full or part-time):; reMYND. **V. Baekelandt:** None. **T. Cornelissen:** A. Employment/Salary (full or part-time):; reMYND.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.081/LBA79

Topic: C.03. Parkinson's Disease

Title: GT-02287, a GCase modulator and Gain Therapeutics' PD drug candidate prevents Tau accumulation in a cellular model

Authors: *N. PEREZ[1], M. CICCALDO[2], S. PAPIN[2], A. GARCIA COLLAZO[1], M. BELLOTTO[3], J. TAYLOR[4], P. PAGANETTI[2];
[1]Gain Therapeutics, Sucursal en España, Barcelona, Spain; [2]Neurocenter of Italian Switzerland (NSI, LRT-EOC), LRT-EOC, BIOS+, Bellinzona, Switzerland; [3]Gain Therapeutics, SA, Lugano, Switzerland; [4]Gain Therapeutics, Inc., Bethesda, MD

Abstract: Neurodegenerative disorders and aging are characterized by brain protein deposition along with deterioration of the autophagy-lysosomal pathway (ALP). Heterozygous mutations of the lysosomal protein GCase is a main risk for synucleinopathies such as Parkinson's disease (PD). The loss of GCase activity leads to a noxious circle whereby accumulation of the GCase substrate, glucosylceramide, and alpha-synuclein ultimately results in neurodegeneration. Recently, it has been shown that this cycle of events can also involve Tau. We have shown previously that inhibition of GCase causes lysosomal dysfunction and contributes to Tau accumulation in degradative organelles of the cell. Additionally, Tau pathology is present in Gaucher disease patients and mice expressing mutant GCase. Moreover, GCase levels and enzyme activity are decreased in Alzheimer's disease where Tau pathology correlates tightly

with disease progression. Therefore, boosting GCase activity may represent a viable therapeutic option to alleviate ALP dysfunction for the treatment of tauopathies.
Gain Therapeutics applied its proprietary drug discovery platform to the identification of the orally bioavailable and brain penetrant GT-02287. Through interaction with GCase, GT-02287 aids correct GCase folding and allows trafficking towards lysosomes, ensuring that glucosylceramide is efficiently processed. In the current study, we show increased seed-induced Tau accumulation in Gaucher-derived fibroblasts carrying a GCase mutation when compared to GCase wild-type fibroblasts. This phenotype was rescued by the presence of GT-02287. Notably, the rescuing effect was also observed on the GCase wild-type background. Based on these findings, GT-02287 shows promise as a potential disease-modifying treatment option for AD and other tauopathies.

Disclosures: **N. Perez:** A. Employment/Salary (full or part-time):; Gain Therapeutics, Sucursal en España, Barcelona, Spain. **M. Ciccaldo:** None. **S. Papin:** None. **A. Garcia Collazo:** A. Employment/Salary (full or part-time):; Gain Therapeutics, Sucursal en España, Barcelona, Spain. **M. Bellotto:** A. Employment/Salary (full or part-time):; Gain Therapeutics, SA. **J. Taylor:** A. Employment/Salary (full or part-time):; Gain Therapeutics, Inc.. **P. Paganetti:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.082/LBA80

Topic: C.03. Parkinson’s Disease

Support: CIHR

Title: Parkinson’s disease relevant cellular stressors differentially impact dopamine neuron axonal release sites.

Authors: *A. TCHUNG[1], N. GIGUERE[2], L.-E. TRUDEAU[3];
[1]Pharmacol. and Physiol., Univ. de Montréal, Montréal, QC, Canada; [2]Dept. of pharmacology and physiology, Dept. of neurosciences and GRSNC, Univ. De Montreal, Montreal, QC, Canada; [3]Dept. of Pharmacol. and Physiol., Univ. of Montreal, Montreal, QC, Canada

Abstract: Increased levels of oxidative stress are often considered as a final common pathway of cellular stressors thought to lead to Parkinson's disease (PD) pathology. While several cellular stressors have been utilized to investigate PD-related pathological signals in cultured neurons, it is unclear to what extent these stressors act through oxidative stress. It is also unclear if these act on axon terminals to induce retrograde degeneration of these neurons, as posited by the dying-back hypothesis of PD. This study aims to address this gap by investigating the effects of various cellular stressors on axonal degeneration. Primary cultures of SNpc neurons from DATIresCre-

Ai9 mice were exposed to increasing doses of cellular stressors. Doses were chosen to test the hypothesis that lower doses would preferentially induce axonal pathology. Subsequently, the impact of these doses on several axonal function parameters was quantified. Among our panel of cellular stressors commonly used in PD studies (1-methyl-4-phenylpyridinium (MPP+), 6-hydroxydopamine (6-OHDA), lactacystine, H_2O_2), we find that only 6-OHDA-induced neuronal loss is reduced by N-acetyl-cysteine (NAC) antioxidant treatment. We further find that all cellular stressors negatively impact axonal functions by reducing mitochondrial density. Morphologically, we observed mitochondrion swelling in the presence of MPP+ and lactacystine and impact in the fission and fusion dynamics in the presence of lactacystine and 6-OHDA showing elongated mitochondrion whereas MPP+ and H_2O_2 show a tendency of increased mitochondrion fragmentation. Furthermore, since mitochondrial integrity is crucial for the function of neurotransmitter release sites, we observed a dose-dependent reduction in synaptotagmin 1-positive release site density for all cellular stressors. Finally, we show that small molecules previously shown to improve mitochondrial efficiency, such as honokiol and dexpramipexole, are protective against 6-OHDA and MPP+, respectively. Unexpectedly, we also uncovered that 6-OHDA exhibits significant non-specific toxic effects on non-dopaminergic neurons. This study demonstrates that cellular stressors have unique effects on axonal release sites, not all of which involve direct oxidative stress mechanisms. These discoveries enhance our comprehension of the mechanism of action of cellular stressors commonly used to model PD pathology and provide new insights into the development of neuroprotective agents through the optimization of bioenergetics and underscore the importance of considering the specificity of these cellular stressors.

Disclosures: A. Tchung: None. **N. Giguere:** None. **L. Trudeau:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.083/LBA81

Topic: C.03. Parkinson’s Disease

Title: GT-02287, a clinical stage GCase regulator, demonstrates disease modifying capacity in both GBA1 and idiopathic Parkinson’s disease models

Authors: B. GUZMAN[1], N. PEREZ[2], A. GARCIA COLLAZO[2], ***J. TAYLOR**[3];
[1]GT Gain Therapeutics, SA, Lugano, Switzerland; [2]Gain Therapeutics, Sucursal En España, Barcelona, Spain; [3]Gain Therapeutics, Inc., Bethesda, MD

Abstract: Heterozygous mutations in the GBA1 gene encoding the lysosomal enzyme glucocerebrosidase (GCase) are the major genetic risk factor for the development of Parkinson’s disease (PD). Interestingly, lowered GCase activity has also been demonstrated in sporadic cases

of the disease, suggesting that restoring GCase activity could be a viable strategy for the treatment of both idiopathic and GBA1-PD. GT-02287 is an orally available and brain penetrant small molecule allosteric regulator of GCase that stabilizes and improves its function in a variety of experimental models. GT-02287 is being developed as a disease-modifying treatment for Parkinson's disease and has recently completed a Phase 1 clinical trial in healthy volunteers. In the current study we employed a GBA1-PD mouse model generated by administering low doses of conduritol beta epoxide (CBE), an irreversible GCase inhibitor, to cause a partial knockdown of GCase activity comparable to that seen in PD patients carrying heterozygous GBA1 mutations, combined with intra-striatal injection of α-synuclein preformed fibrils (PFFs). To model idiopathic PD, we used intra-striatal PFF injection in the absence of CBE administration. Once a clinical phenotype was established, animals began daily GT-02287 treatment. Effect of GT-02287 on neuromuscular function, motor coordination and activities of daily living/cognition was measured in wire hang, beam walk and nest building tests, respectively. GT-02287 was able to rescue deficits in both neuromuscular function and motor coordination in both the GBA1 and idiopathic PD models and to prevent the development of deficits in cognition and activities of daily living, as measured by nest building ability. GT-02287 treatment was then withdrawn from half the treated animals, and we were able to demonstrate that a treatment effect in all three behavioural tests was maintained even in the absence of drug candidate, presumably due to a disease-modifying effect of GT-02287. This study supports the potential of GT-02287 as a disease modifying therapy for both idiopathic and GBA1 Parkinson's disease.

Disclosures: B. Guzman: A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **N. Perez:** A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **A. Garcia Collazo:** A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **J. Taylor:** A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.084/LBA82

Topic: C.03. Parkinson's Disease

Title: A technical platform solution to develop, characterize and implement macaque models of neurodegeneration

Authors: G. WANG, Y. ZHAO, J. GABRIEL, S. WANG, Y. TIAN, R. PEREZ, ***L. YANG**; Kunming Biomed Intl., Kunming, China

Abstract: Development of therapies for neurodegenerative disease often require the use of non-human primates (NHP) to best position the candidate for clinical trial success. Here we show a series of technical assays we employ in developing and utilizing NHP models of two of the most prevalent neurodegenerative diseases, Alzheimer's (AD) and Parkinson's (PD). Animals (cynomolgus macaque) for each model were selected from a large cohort to ensure future access of similar age and sex. Biomarkers (catecholamine metabolites, blood chemistry, immune markers), behavior (cognition and motor performance) and neuroimaging (PET: AV45 [18F-florbetapir], for beta-amyloid and AV133 [FP-(+)-DTBZ], for VMAT-2) were assessed at baseline and at multiple timepoints from model creation (MPTP or AAV9-hA53T-aSyn for PD and increasing age for AD). In the AD model, we show clear age-related (young; 5-6 yrs vs. middle-age; 17-20 yrs vs. old; >25 yrs) increases in cortical and hippocampal beta-amyloid[1-42] by AV45-PET and tissue immunofluorescence. In the PD model, we show reduced striatal VMAT-2 by AV133-PET and degeneration in the substantia nigra by T1-FLAIR-MRI, supported by tyrosine hydroxylase immunohistochemistry. Behaviorally, macaques display reduced performance in gross and fine motor movement. Using our biomarkers platform, we show a significant reduction in CSF-HVA (by HPLC) in the PD and AD-aging models. Cognition is currently being assessed in the aging AD model and will be reported on. In conclusion, we demonstrate that the use of a battery of assays can be used to optimize model development, identify in-life and post-mortem endpoints and ready a complete technical platform for preclinical evaluation of candidate therapeutics in NHP.

Disclosures: G. Wang: None. **Y. Zhao:** None. **J. Gabriel:** None. **S. Wang:** None. **Y. Tian:** None. **R. Perez:** None. **L. Yang:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.085/LBA83

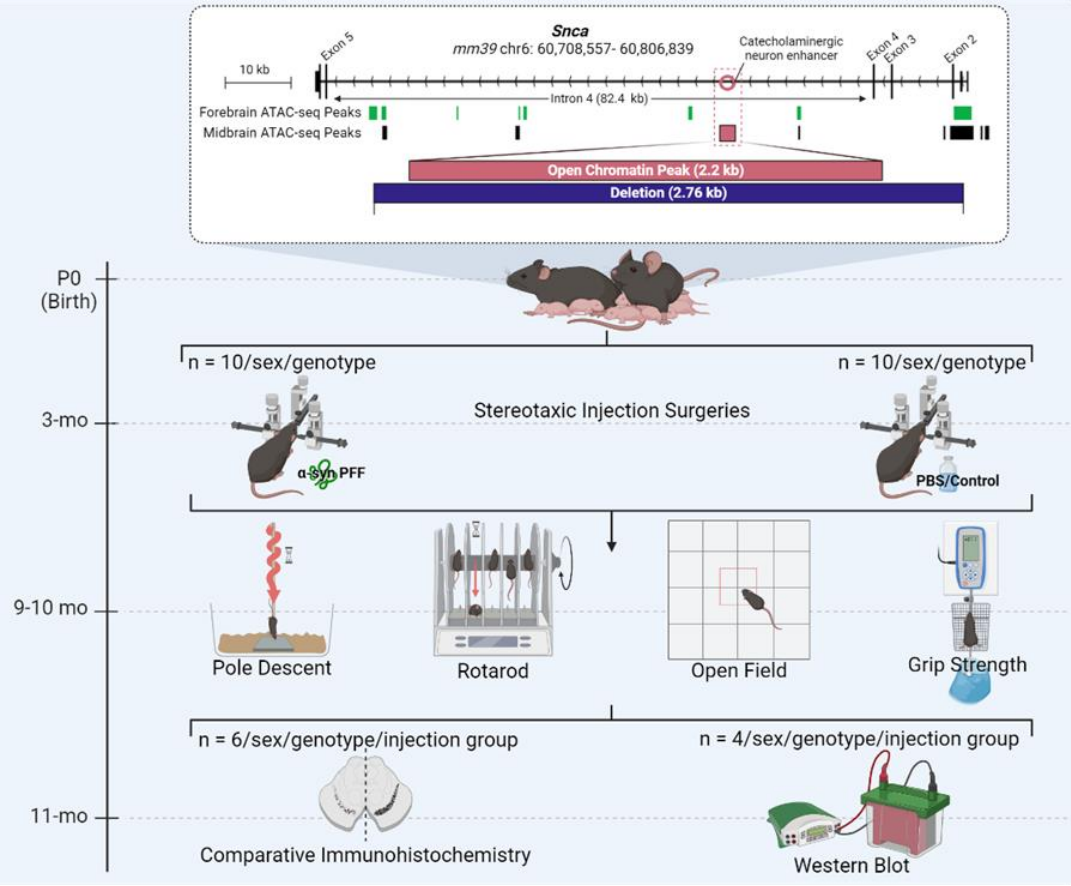
Topic: C.03. Parkinson's Disease

Support: Canadian Institutes of Health Research (DFD-181599)
National Institutes of Health (R01HG010480)
National Institutes of Health (R21NS128604)
National Institutes of Health (T32GM007814-40)

Title: Neuronal titration of Snca via enhancer disruption mitigates disease onset in a Parkinson's disease mouse model

Authors: *R. J. BOYD[1], A. KHO[2], H. KO[3], A. S. MCCALLION[1];
[1]Genet. Med., [2]Dept. of Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Dept. of Neurol., Inst. for Cell Engineering, Johns hopkins university, Baltimore, MD

Abstract: α-synuclein/*SNCA* is consistently identified as the greatest genetic risk factor for Parkinson's disease/PD. SNCA misfolding and overexpression is linked to pathognomonic features of PD, including SNCA aggregates, Lewy Bodies, and progressive midbrain dopaminergic neurodegeneration. We recently identified an intronic sequence at SNCA that harbors two variants significantly associated with PD risk, demonstrating it to be a neuron-dependent, cis-regulatory element. We have engineered a mouse model lacking this sequence and demonstrate that its removal significantly reduces *Snca* transcription in the midbrain dopaminergic neurons of heterozygous and homozygous deletion mice (2.98-3.52 fewer copies; $p < 0.01$) compared to wild-type littermates. In an established PD mouse model, a battery of motor, molecular, and histological assays further reveal that mice lacking this *Snca* enhancer are protected against PD-relevant histopathology and motor impairments. By targeting a cell-dependent regulatory element to diminish PD onset/progression in mice, we initiate a new generation of potential therapeutic strategies against PD and other synucleinopathies.



Disclosures: **R.J. Boyd:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Application No. 63/662,938. Filed: 21-Jun-2024. **A. Kho:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Application No. 63/662,938. Filed: 21-Jun-2024. **H. Ko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Application No. 63/662,938. Filed: 21-Jun-2024. **A.S. McCallion:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Application No. 63/662,938. Filed: 21-Jun-2024..
Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.086/LBA84

Topic: C.03. Parkinson's Disease

Title: Systemic AAV gene therapy with CNS-targeted engineered capsids achieves significant GCase activity increases in the primate brain to support the potential treatment of PD-GBA

Authors: *R. L. RESSLER[1], K. MCDOWELL[1], N. GOEDEN[2];
[1]Capsida Biotherapeutics, Newbury Park, CA; [2]Capsida Biotherapeutics, Thousand Oaks, CA.

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder with an estimated prevalence of over 1.2 million people in the United States by 2030 and no approved disease modifying treatments today. While there are several genetic risk factors associated with PD, mutations within the GBA1 gene have been shown to be the most significant, and current evidence suggests up to 15% of PD patients have GBA1 mutations.
Capsida is developing a gene supplementation therapy candidate (CAP-003) to be administered as a single intravenous (IV) infusion to PD-GBA patients. CAP-003 consists of an engineered AAV capsid that is designed to deliver the functional human GBA1 gene broadly across the CNS while de-targeting the liver, thereby providing a permanent source of the GBA1 protein to the brain and allowing for long term correction of GCase activity. Substantial clinical and preclinical evidence suggests that interventions targeted to normalize GCase activity in the brain would enable long-term disease modification and substantially slow or stop the disease progression of PD-GBA. Using a GCase loss-of-function mouse model we provide proof of concept pharmacology demonstrating that administration of the intended clinical cargo results in dose-dependent increases in GCase activity that coincide with dose dependent decreases in glycolipid accumulation. Importantly, normalization of GCase activity to wild-type levels resulted in significant reductions in glycolipid species that are thought to contribute either directly or indirectly to α-synuclein pathology in PD-GBA patients. In non-human primates, we show that at low to moderate doses administration of CAP-003 results in robust neuronal transduction across

the entire CNS, with particularly high levels in disease relevant brain regions such as the substantia nigra and putamen. These levels of transduction resulted in increases in bulk GCase activity that exceeded levels expected to normalize GCase activity in the patient population. Importantly, these levels of GCase supplementation are achieved at doses that are well tolerated and without any clinical pathology or immunogenicity findings, including a lack of histopathology in the liver and dorsal root ganglia, that are associated with higher-dose systemic gene therapies. Taken together, CAP-003 is being advanced with the ultimate goal of achieving disease modifying clinical benefit for patients with PD-GBA through a convenient single dose IV administration.

Disclosures: R.L. Ressler: A. Employment/Salary (full or part-time):; Capsida Biotherapeutics. **K. McDowell:** A. Employment/Salary (full or part-time):; Capsida Biotherapeutics.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.087/LBA85

Topic: C.03. Parkinson's Disease

Title: Longitudinal Studies of LFP Activities During Acute and Chronic DBS Stimulation in PD Patients

Authors: *Y. ZHAO[1], M. G. VARGA[2], S. R. SANTACRUZ[3];
[1]Biomed. Engin., Univ. of Texas at Austin, Austin, TX; [2]Dept. of Neurol., The university of Texas at Austin, Dell Med. Sch., Austin, TX; [3]Biomed. Engin., The Univ. of Texas at Austin, Austin, TX

Abstract: While DBS has been recognized for its clinical benefits in the treatment of PD patients, its mechanism of action has not been elucidated yet, and DBS programming is still a trial and error. DBS long-term stimulation effects imply neuroplastic-induced changes. This effect has been studied in animal models but is still poorly understood in patients with Parkinson's disease. This study investigates the changes in local field potential (LFP) during acute and chronic deep brain stimulation (DBS) in patients with Parkinson's disease (PD) due to the direct DBS effect on brain circuits and neuroplastic changes induced by chronic DBS stimulation.We conducted a longitudinal study involving eight PD patients who underwent acute and chronic DBS implantation. Following their initial implant surgery, patients were scheduled for LFP data collection monthly for the first 4 months post-implant and then every 3 months after that. Prior to each session, patients were off PD medication for 12 hours, with DBS devices active. During the one-hour data collection sessions, DBS was temporarily turned off, and LFP data was recorded at 5, 10, 15, 30, 45, and 60-minute intervals. Each recording lasted 20 seconds while patients maintained a rest posture, and we recorded three trials for each interval. After data

collection, DBS devices were turned back on to their original settings.Our findings reveal that beta power remains suppressed even after 1-hour off stimulation, and the broadness of beta power decreases with longer implant duration. This study provides high temporal resolution, allowing us to capture dynamic brain changes post-stimulation. Understanding these changes can inform the optimization of DBS parameters and advance the development of adaptive, closed-loop brain stimulation therapies.

Disclosures: Y. Zhao: None. **M.G. Varga:** None. **S.R. Santacruz:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.088/LBA86

Topic: C.03. Parkinson’s Disease

Title: Recent advancements and updates in the management of Parkinson's disease

Authors: *K. KHATRI[1], R. AHMED[3], P. PRAJJWAL[2], Y. KANCHARLA[4], P. .[5], A. BISEN[2], A. ASHIQ[6];
[2]Neurol., [1]Bharati Vidyapeeth Univ. Med. College, Pune, India, Pune, India; [3]Dow Univ. Of Hlth. Sci., Pakistan, Pakistan; [4]Kamineni academy of medical sciences and research centre, Hyderabad, India; [5]Government Med. College, Patiala, Punjab, India, Nakodar, District Jalandhar, India; [6]Hillcrest Health System, Tulsa, OK

Abstract: Background Parkinson's disease (PD) is caused due to degeneration of dopamine-secreting neurons in the substantia nigra of the brain. The most widely accepted pharmacological treatment is a combination of Levodopa and Carbidopa. Dopamine agonists, MAO-B inhibitors, and deep brain stimulation (DBS) are some of the other therapies that help improve motor control by increasing dopamine levels directly or sometimes by mimicking the effects of dopamine. Current ongoing research has shown promising clinical improvement with newer treatment modalities such as gene therapy and stem cell therapy in PD. **Rationale** Our study aims to shed light on the safety and efficacy of newer modalities in the management of PD drawing insights from a comprehensive analysis of several promising randomized clinical trials. **Methods** We conducted a systematic search across PubMed/Medline for articles published from 2020-2024, selecting randomized controlled trials by using a combination of keywords and MeSH terms. The search terms focussed on newer pharmacologic interventions being studied in PD, including Safinamide, Levodopa-Carbidopa Intestinal Gel (LCIG), and various newer dopamine agonists. The primary outcomes included the motor symptoms scale, dyskinesia rating, PD Rating Scale, and Quality of Life metrics. Thirteen studies were included in the final analysis. **Results** Levodopa/Carbidopa subcutaneous infusion (ND0612), Opicapone, Safinamide, and LCIG were effective in reducing OFF time and dyskinesias, improving motor

function and Quality of Life. ND0612 showed a mean change in the Unified PD Rating Scale (UPDRS) total score of -11.7 ± 14.5, and dyskinesia scores improved by -0.7 ± 1.4. Opicapone addition to Levodopa reduced the time to ON and improved the mean UPDRS Part III scores. Safinamide demonstrated a significant improvement in the UPDRS total scores by -5.99 points ($p < 0.0001$) and in the PD Questionnaire summary index by -3.36 points ($p = 0.0033$). LCIG led to a reduction in dyskinesia scores by -15.05 ± 3.20 (95% CI -21.47 to -8.63, $p < 0.0001$). Subthalamic nucleus DBS was beneficial in controlling motor symptoms. Dyskinesia was significantly decreased in the studies of immediate-release/extended-release amantadine (OS320) with treatment differences of ≥8. **Conclusion** Pharmacological therapies such as ND0612, Opicapone, Safinamide, and LCIG have the potential to improve the Quality of Life in PD by decreasing motor symptoms and dyskinesias. STN-DBS can also be a cutting-edge measure in the overall management of patients. Further studies should be directed toward the use of combination therapies and precision-based treatment regimens for refractory cases.

Disclosures: K. Khatri: None. **R. Ahmed:** None. **P. Prajjwal:** None. **Y. Kancharla:** None. **P. .:** None. **A. Bisen:** None. **A. Ashiq:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.089/Web Only

Topic: C.03. Parkinson’s Disease

Title: Tissue-specific gene co-expression of SNCA supports the gut-brain axis in Parkinson's disease

Authors: E. HAN, *X. MAO;
Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: The SNCA gene, which encodes alpha-synuclein, was the first gene discovered for Parkinson’s disease (PD). While alpha-synuclein plays a central role in PD, the function of SNCA is not fully understood. We examined its gene expression patterns across various tissues using the Genotype-Tissue Expression dataset, to understand in which brain regions and non-brain tissues SNCA may exert a larger impact. We hypothesize that the functional impact of SNCA in a tissue is related to both its expression levels and the number of genes whose expression levels covary with SNCA (co-expression), as SNCA dysfunction could influence co-expressed genes and their related biological pathways. Among brain tissues, SNCA showed the highest expression level in the cerebellar hemisphere, followed by the frontal cortex and anterior cingulate cortex, with the lowest level in putamen. In non-brain tissues, the highest expression was observed in whole blood, even higher than in several brain tissues. In terms of gene co-expression, we observed the largest number of co-expressed genes (Pearson correlation > 0.8) in

the putamen (3,871), followed by the anterior cingulate cortex (3,673), nucleus accumbens (3,084), frontal cortex (3,032), caudate (2,214), substantia nigra (1,614), amygdala (1,572), and hippocampus (875). Despite its highest expression level in the cerebellar hemisphere, SNCA had a much smaller number of co-expressed genes in this tissue (304), and similarly in blood (2). Notably, despite relatively low expression levels, SNCA displayed many co-expressed genes in the small intestine (700), colon (671), and stomach (445), with more than half of these genes not co-expressed in brain tissues (Figure 1). Finally, we examined the enrichment of co-expressed genes in each tissue for PD-associated genes from the GWAS catalog and observed significant enrichment in seven brain tissues and the stomach. Our findings suggest the functional role of SNCA across brain and non-brain tissues, particularly in the intestine, colon, and stomach, providing further evidence supporting the gut-brain axis in PD.

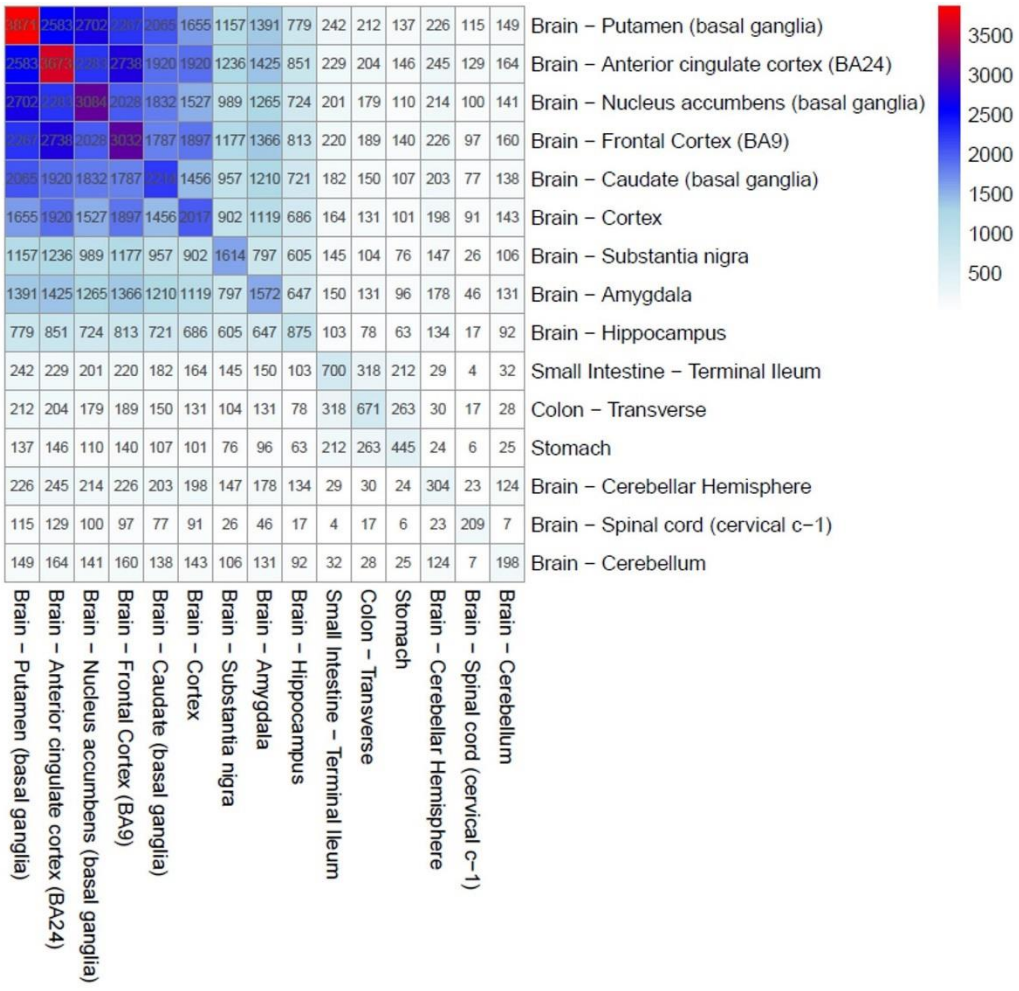


Figure 1. Pairwise Overlap of SNCA Co-Expressed Genes Among Tissues. Numbers on the diagonal indicate the number of co-expressed genes in each tissue, while numbers off the diagonal indicate the number of overlapping co-expressed genes between two tissues.

Disclosures: E. Han: None. **X. Mao:** None.
Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.090/LBA87

Topic: C.03. Parkinson's Disease

Title: Hub genes in Parkinson's disease and melanoma influence GDNF-RET signaling

Authors: *R. LOGAN;
Eastern Nazarene Col., Quincy, MA

Abstract: Neurodegeneration involves neuronal death, whereas cancer involves rapid and abnormal cell replication. People with cancer usually do not get neurodegeneration, and vice versa, confirming the biological opposite nature of these diseases. However, people with Parkinson's disease are at an increased risk for melanoma, and vice versa. The molecular pathways shared between these diseases might provide insight into the pathogenesis of these seemingly disparate diseases and the possibility of developing novel treatments. Here, we searched for hub genes common among the GSE7621 and GSE238207 datasets from Gene Expression Omnibus (GEO), which include Parkinson's disease and melanoma samples, respectively. Both datasets were generated using the [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array platform and had 107 shared differentially expressed genes (83 upregulated, 24 downregulated). GO term and KEGG analysis revealed upregulated functions related to metal and calcium ion transport as well as neural communication. Downregulated functions include NOTCH4 signaling, proteolysis regulation, and metalloendopeptidase regulation. Protein-to-protein interaction networks revealed the top hub genes: RET, GFRA1, PSPN, ARTN, GFRA4, SRC, DOK6, EDN3, AGTR1, and SSTR1. These hub genes play significant roles in neuronal survival, maintaining neuronal integrity, cancer progression, and cancer metastasis, highlighting their dual involvement in Parkinson's disease and melanoma. These findings underscore the importance of GDNF-RET signaling pathways in both diseases and could offer a novel therapeutic target for Parkinson's disease and melanoma. This connection provides promising direction for future research.

Disclosures: R. Logan: None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.091/LBA88

Topic: C.03. Parkinson's Disease

Support: MJFF Grant 019562
NIH Grant R25AG076396

Title: Identifying Peripheral Immune Response Signature Dependent on Parkinson's Disease Progression

Authors: *A. TITUS[1], J. MARK[1], H. STALEY[1], N. R. MCFARLAND[2], R. WALLINGS[1], M. G. TANSEY[1,2];
[1]Dept. of Neurosci., Univ. of Florida, Gainesville, FL; [2]Fixel Inst. for Neurolog. Dis., Gainesville, FL

Abstract: Disrupted immune function is a significant component of Parkinson's disease (PD) and inflammatory cytokines in the blood may serve as biomarkers to identify early PD. However, there is significant variability in circulating cytokine levels due to circadian rhythm, diet, and environmental exposures. Stimulation-based assays may be more sensitive to underlying immune dysfunction, potentially allowing us to observe immune deficits in patients prior to the development of motor symptoms in PD. To investigate this, peripheral blood mononuclear cells were collected from healthy controls, early and moderate PD, and prodromal PD individuals with REM sleep behavior disorder who are likely to convert to PD. Monocytes and T-cells were isolated, plated, and treated with vehicle or a stimulation paradigm (interferon gamma for monocytes, CD3/CD28 beads for T cells) for 72 hours to assess stimulation-based responses rather than baseline differences. Flow cytometry was used to analyze monocyte and T-cell subtypes, activation, mitochondrial health, and lysosomal activity. The cultured media was analyzed for cytokine secretion using Meso Scale Discovery assay. We observed that later stages of PD are associated with a more proinflammatory monocyte composition, and T-cells from later stage PD patients showed lower fractions of functional mitochondria after stimulation. Prodromal PD cells exhibited higher stimulation-dependent secretion of TNF, IL-1β, and IL-8 relative to early and moderate PD, as well as a distinct signature of immune activation relative to healthy controls. These findings reflect observable immune dysfunction based on PD progression, indicating potential in blood stimulation-based assays as biomarkers for early PD identification.

Disclosures: A. Titus: None. **J. Mark:** None. **H. Staley:** None. **N.R. McFarland:** None. **R. Wallings:** None. **M.G. Tansey:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.092/LBA89

Topic: C.03. Parkinson's Disease

Support: Canadian Institutes of Health Research (CIHR)

Title: Freezing in Parkinson's Disease: An exploratory reaching study

Authors: *J. STEVENSON[1], L. J. STEINKE[1], L. E. BROWN[2];
[2]Psychology, [1]Trent Univ., Peterborough, ON, Canada

Abstract: A particularly debilitating manifestation of dysfunction in Parkinson's Disease (PD) is freezing of gait (FOG), which affects approximately 50% of individuals with PD. There are specific scenarios known to elicit FOG, such as turning a corner, initiating a reversal (walking away from and back to a starting position) and navigating through narrow spaces like doorways. Freezing-like episodes have also been observed in the upper limbs during finger-tapping and writing tasks. Although the complexities of freezing are not well understood, there may be a visual component. Researchers have observed that people with PD (PwPD) can be released from FOG in the presence of patterns, like stripes on the floor and laser beams, which is interesting, as there is evidence that PwPD experience changes in their visual-spatial frequency sensitivity. ***Objective:*** Here we asked whether freezing of upper limbs (FOUL) can be induced by these same movement tasks (reversals, corners, and narrows) and if FOUL is also sensitive to background patterns with different spatial frequencies. ***Method:*** PwPD and age-matched healthy control participants completed a reaching task to a target and quickly returned to the start position (reversal) or made a 90° turn to a target presented on their dominant side (corner) or moved to the same target while passing through virtual "doorway" presented at 75% of total distance. They completed these tasks while viewing targets presented on a random-dot background or a high- or low-spatial-frequency gaussian horizontal stripe pattern. Participants were instructed to complete each trial as quickly as possible. They also completed the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Freezing of Gait questionnaire. ***Results:*** Compared to control participants, PwPD's movements were significantly shorter and less accurate than controls when approaching the target in all tasks. The movement times of PwPD were markedly longer, particularly when navigating through the tunnel. We did not find any effect of background pattern on these measures. ***Conclusions:*** These findings support the notion that freezing-like behaviours may be studied using an upper-limb task.

Disclosures: J. Stevenson: None. **L.J. Steinke:** None. **L.E. Brown:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.093/LBA90

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: National Key R&D Program of China 2021YFA0805200
National Natural Science Foundation of China 31970954
Guangdong Science and Technology Department 2021ZT09Y007

Title: Using non-human primate brain to study HTT degradation and HTT interacting proteins

Authors: Y. QIN, J. LIN, S.-H. LI, X. LI, ***S. YANG**;
Jinan Univ., Guangzhou, China

Abstract: Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by the CAG trinucleotide expansion in the coding region of Huntingtin (*HTT*) gene. Rodents are the most common animal models used in HD research, but they cannot fully recapitulate HD neuropathology in human. In the present study, we utilized cynomolgus monkey (*Macaca fascicularis*) as a model to study primate-specific HD pathogenic mechanisms. We found that the primate brain has distinct HTT degradation kinetics and mechanisms compared with the mouse brain. Inspired by these findings, we performed an unbiased proteomic screening of HTT interacting proteins in the monkey brain. Our preliminary analysis showed that while some important HTT interacting proteins are shared between monkey and mouse, there are certain proteins that specifically interact with primate HTT, such as spliceosomal proteins. These results demonstrate that non-human primate is an important animal model to study HD pathogenic mechanisms.

Disclosures: Y. Qin: None. **J. Lin:** None. **S. Li:** None. **X. Li:** None. **S. Yang:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.094/LBA91

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: R01NS110943 (NIH/NINDS)
TL1TR003169 (NIH/NCATS)
Presidents Research Excellence Award (UT-GSBS)
Dr. John J. Kopchick Fellowship Award (UT-GSBS)

Title: Identification of a Highly Conserved Functional Motif in the Huntington's Disease-Associated HTT/HAP40 Core Complex

Authors: ***S. FARMER**[1], A. SOLBACH[1], S. XU[1], B. RIOS[1], X. YE[1], A. GAO[2], D. COVARRUBIAS[3], Y. YU[1], S. ZHANG[1];

[1]Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [2]Univ. of Texas at Austin, Austin, TX; [3]Rice Univ., Houston, TX

Abstract: Huntington's disease (HD) is a hereditary neurodegenerative disorder caused by an abnormal CAG repeat expansion encoding a polyglutamine (polyQ) tract in the Huntingtin (HTT) protein. This polyQ expansion contributes to HD pathogenesis, but its precise effect on HTT's full-length structure and function remains unclear. Previous cryo-EM studies have shown that HTT primarily exists in a core complex with HAP40, forming a highly ordered globular conformation with repeating alpha helices and several invisible regions of unknown importance. Using AlphaFold3, we generated full-length models of human HTT-HAP40 and its Drosophila ortholog dHtt-dHap40, which demonstrated similar topologies, thus enabling us to perform in-depth structure-function analysis and use evolution as a basis to elucidate function. Co-immunoprecipitation (co-IP) validated the interaction between HTT/HAP40 in human cells and dHtt/dHap40 in flies. Protein-contact maps revealed 463 stabilizing residue-residue pairs in humans and 412 in flies, primarily localized to HTT's C-terminal domain (CTD), accounting for 55% of binding free energy in humans and 70% in flies. Molecular dynamics simulations showed that HTT's CTD significantly stabilizes HAP40 in both species, underscoring its importance for complex stability. Molecular modeling further identified ten essential bonds at the HTT/HAP40 interface conserved in Drosophila. Deletion of these bonds abolished HTT/HAP40 binding in co-IP assays and failed to restore HTT levels, indicating their critical role in maintaining core complex integrity. Further structural analyses revealed a conserved motif, BΦ, within HAP40 that is solvent-exposed and not directly involved in HTT binding. Overexpression of HTT/HAP40 induced neurotoxicity in Drosophila, a phenotype suppressed in HAP40-BΦ mutants, suggesting that this motif is functionally important in vivo. However, HAP40-BΦ mutants restored HTT levels in HAP40-KO human cells and flies but did not restore lifespan or autophagy defects, indicating the core complex is stable but functionally inhibited. Understanding HTT-HAP40 stabilization and function sheds light on potential HD therapies. Future work will determine if BΦ deletion is disease-modifying in HD models.

Disclosures: S. Farmer: None. **A. Solbach:** None. **S. Xu:** None. **B. Rios:** None. **X. Ye:** None. **A. Gao:** None. **D. Covarrubias:** None. **Y. Yu:** None. **S. Zhang:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.095/Web Only

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Psd-95 as a potential developmental drug target for huntington's disease: a bioinformatics and immunohistochemistry approach

Authors: S. Q. RICHARDS[1], *C. CROFT[2];
[1]Penn State Univ., State College, PA; [2]Fauquier High Sch., Warrenton, VA

Abstract: Interacting proteins have been suggested as potential drug targets for Huntington's disease (HD) but have yet to be extensively explored for a developmental application. Here we applied a two-pronged approach with developmental brain tissue to identify likely candidates for drug targets. First, we extracted interacting proteins for huntingtin (htt) from PubMed and analyzed data from the Allen Brain Atlas at P4, P14, P28, P56. Expression profiles were utilized to determine the timelines of expression within the striatum and the cerebellum, informing us of potential correlations between the functions of target proteins and htt through different stages of postnatal development. These methods revealed PSD-95 and β-Catenin to be the most likely drug targets of the 467 proteins examined, and β-Catenin has already been linked to developmental defects in htt (Godin, et al 2010). We therefore focused on PSD-95, and cerebellar profiles were used in further exploration into the significance of the cerebellum in HD patients, as the striatum is typically the focal point of these experiments. In our second phase, we used immunohistochemistry to analyze cerebellar tissue of huntingtin KO mouse models. We found that purkinje cell death increased in the KO, suggesting that htt sequesters PSD-95 during development. Overall our results suggest that PSD-95 should be further explored as a potential drug target during development of HD. Developmental drug targets leave room for potential alleviation of neurodegeneration by preventing symptoms prior to onset.

Disclosures: S.Q. Richards: None. **C. Croft:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.096/LBA92

Topic: C.04. Movement Disorders other than Parkinson's Disease

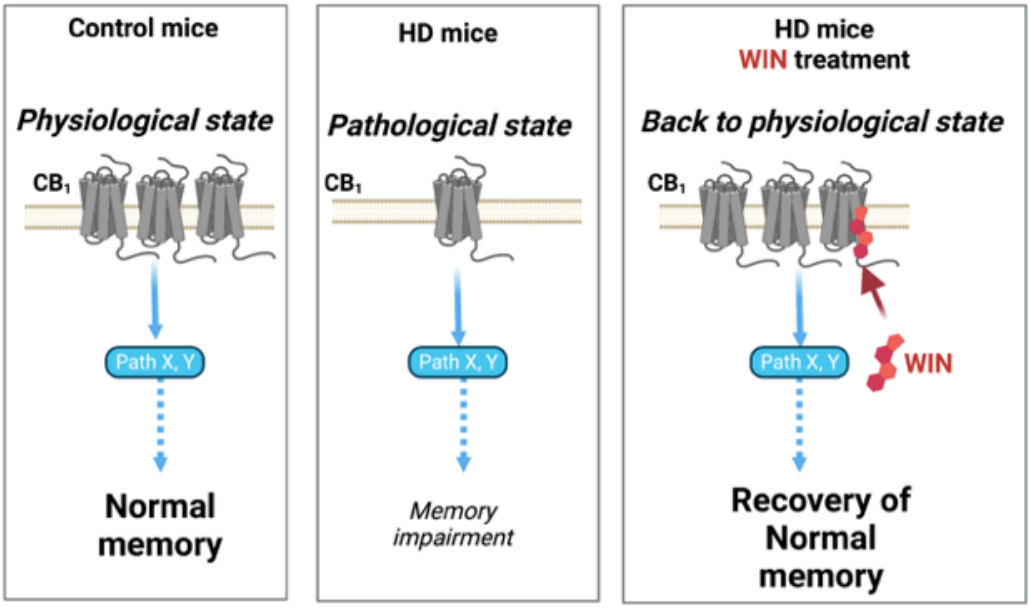
Support: Marato TV3 202013

Title: Cannabinoid receptor type-1 triggers hippocampal GABAergic dysfunction leading to cognitive decline in Huntington's disease

Authors: *N. DI FRANCO[1,2,3], I. BENGOETXEA DE TENA[4], A. SÁNCHEZ-RUIZ[5], R. RODRIGUEZ-PUERTAS[6], G. PEREA[7], M. GUZMÁN[8], S. GINES-PADROS[9];
[1]universitat de barcelona, Barcelona, Spain; [2]Inst. d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [3]Ctr. de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain; [4]Pharmacol., Univ. of the Basque Country (UPV-EHU), Leioa, Spain; [5]Instituo Cajal, Spanish Res. Council (CSIC), Madrid, Spain; [6]VAT Q4018001B, Univ. of the Basque Country, Leioa, Spain; [7]Cajal Inst.,

Madrid, Spain; [8]Dept. of Biochem. and Mol. Biol. I, Complutense Univ. Madrid, Madrid, Spain; [9]CRAI Univ. de Barcelona, Barcelona, Spain

Abstract: Huntington's disease (HD) is a rare genetic disease caused by the abnormal repeat expansion of the trinucleotide CAG in the Huntingtin gene. Despite the motor symptoms are the most studied, the onset of cognitive deficits (CD) appears largely before and is the most limiting factor for patients' everyday life. Molecular mechanisms leading to CD are still unknown, and the hippocampus remains an underexplored region. The scarcity of knowledge causes the need for innovative molecular targets, and emerge in the absence of treatments for CD. Recently, evidences emphasized CB1R importance in cognition and CD. CB1R is one of the most expressed GPCR receptors in the brain, widely in the hippocampus. Its cell specific expression in GABAergic and glutamatergic cells is essential for cognition. Consequently, the project propose CB1R as a crucial target for CD in HD. Particularly, we aim to:1) characterize CB1R expression and functions in the hippocampal neurons of HD mouse models R6/1,2) explore CB1R in the hippocampal neuron dysfunction,3) manipulate the receptor in GABAergic/glutamatergic populations,4) assess CB1R agonist WIN 55,212-2(WIN) effect as a possible therapeutic compound for CD in HD. As results, we found that CB1R decreases in the hippocampus of R6/1 mice, at different time points and in both genders, specifically in GABAergic cells. Moreover, GABAergic transmission is altered in R6/1 and viral CB1R increase in GABAergic cells ameliorate CD. Finally, WIN treatment rescues CD, ameliorates CB1R levels, synaptic density and GABAergic transmission in R6/1 mice hippocampus. In conclusion, the current work confirms CB1R as crucial target for CD in HD, showing that CB1R functional activation in GABAergic cells rescues CD in mice and cannabinoid compounds assume a benefic role on CD.



Disclosures: N. Di franco: None. **I. Bengoetxea de Tena:** None. **A. Sánchez-Ruiz:** None. **R. Rodriguez-Puertas:** None. **G. Perea:** None. **M. Guzmán:** None. **S. Gines-Padros:** None.
Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.097/LBA93

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant NS116883
NIH Grant NS105839

Title: Patients with cerebellar ataxia exhibit deficiencies in simulating dynamic events in the physical world.

Authors: *T. WANG[1], R. IVRY[2];
[1]Univ. of California, Berkeley, BERKELEY, CA; [2]Psychology, Univ. California, El Cerrito, CA

Abstract: Patients with cerebellar ataxia face significant challenges in interacting with the physical world, historically attributed to deficits in motor control. However, recent research suggests that the cerebellum plays a crucial role in many non-motor cognitive functions, such as visual perception and language processing. Particularly, it has been proposed that a domain-general function of the cerebellum might be dynamically manipulating mental representations, which is critical for making physical inferences. As such, we hypothesize that patients with cerebellar ataxia also exhibit impairments in predicting the dynamics of physical events independently of making motor responses.

We conducted a physical inference task in which participants watched a pendulum swing on a screen, with a marked point indicating where the pendulum's string would be cut. Several baskets were positioned beneath the pendulum, and participants were required to verbally predict which basket would catch the ball. The task varied the pendulum's cut point and the distance between the falling ball and the baskets to challenge mental simulation abilities. We compared the performance of 14 cerebellar ataxia patients with 14 age-matched controls and evaluated their responses against several null models where agents applied simple, explicit response strategies instead of trajectory simulation. We also tested the participants' physical knowledge of the pendulum, and performance was matched across groups.

Patients outperformed the null models but performed slightly worse than the control group, indicating deficits in physical inference. A model-based analysis dissected these deficits into inaccuracies in depth perception of the pendulum, biases in timing the cut of the ball, and increased noise in trajectory simulation. The full model fitted the performances of both groups well. Both groups exhibited similar errors in depth perception. Patients showed larger timing biases; However, this cannot be attributed to a larger perceptual error since patients showed perfect performance in a control task for visual perception. As such, this timing bias suggests the patients may have suffered a deficiency in simulating the temporal dynamics of the pendulum. Moreover, the simulation noise in patients increased more rapidly with simulation distance compared to controls, further supporting the idea that the patients had deficiencies in

continuously simulating the trajectory of the ball.
Our findings indicate that cerebellar ataxia impairs physical inference abilities, supporting the hypothesis that continuous mental manipulation might be a domain-general function of the cerebellum.

Disclosures: T. Wang: None. **R. Ivry:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Richard Ivry is a co-founder with equity in Magnetic Tides, Inc..

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.098/LBA94

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH/NINDS Grant 1R01NS109077-01A1

Title: Mutant ATXN1 expression in microglia impacts Spinocerebellar Ataxia Type 1 phenotypes in mice

Authors: *A. SELIMOVIC[1], H. T. ORR[2], M. CVETANOVIC[3];
[1]Univ. of Minnesota Grad. Program In Neurosci., St Paul, MN; [2]Univesity of Minnesota, Minneapolis, MN; [3]Univ. of Minnesota, Minneapolis, MN

Abstract: Spinocerebellar Ataxia Type 1 (SCA1) is an autosomal dominant inherited neurodegenerative disease caused by a CAG trinucleotide repeat expansion in the *ATXN1(ATAXIN1)* gene. SCA1 is characterized by progressive motor and cognitive dysfunction, and premature death. Microglia are the resident immune cells in the brain that play key roles in the healthy brain and in many neurodegenerative diseases. While activated microglia are present in SCA1 mouse models, and microglia gene expression is profoundly altered in both patients and mouse models, causes and effects of microglial activation in SCA1 remain poorly understood. Our objective is to understand how mutant *ATXN1* (*mATXN1*) expression in microglia contributes to microglial activation and disease pathogenesis in SCA1. To address this question, we crossed conditional SCA1 model, *f-ATXN1*$^{146Q;2Q}$ mice with microglia and macrophage specific Cre line, *Lyve1*^{CRE} mice to delete *mATXN1* expression in microglia. We enriched microglia using magnetic bead isolation (Miltenyi) and used RT-qPCR to validate selective depletion of *mATXN1* in microglia. Rotarod and Barnes maze were used to assess motor and cognitive phenotypes in WT, *f-ATXN1*$^{146Q;2Q}$ and *f-ATXN1*$^{146Q;2Q}$;*Lyve1*^{CRE} mice. Barnes maze unbiased strategy analysis (BUNS) provided insight into strategy development. To determine how *mATXN1* in microglia impacts synaptic perturbations, we quantified synaptic density using immunohistochemistry and the Puncta Analyzer ImageJ plugin. We confirmed reduction of

mATXN1 in isolated microglia in *f-ATXN1*$^{146Q/2Q}$*;Lyve1*^{Cre} mice but not in other cell-types. We found ameliorated performance on rotarod and in Barnes maze and improved strategy development in *f-ATXN1*$^{146Q/2Q}$*;Lyve1*^{Cre} mice. We are currently quantifying inhibitory and excitatory synapses. Our work highlights the impacts of *mATXN1* expression in microglia on SCA1 behavioral phenotypes. Further investigation into the role of SCA1 microglia is necessary to understand the mechanism underlying these behavioral outcomes. These results implicate microglia as contributors to motor and cognitive phenotypes seen in SCA1 mice.

Disclosures: A. Selimovic: None. **H.T. Orr:** None. **M. Cvetanovic:** None.

Late-Breaking Poster

LBA003: Theme C Late-Breaking Posters

Location: MCP Hall A

Time: Sunday, October 6, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA003.099/LBA95

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: ARSACS Foundation

Title: Cerebellum single-nucleus RNA sequencing along disease progression of the neurodegenerative ataxia ARSACS

Authors: *E. M. KING[1], S. BOESHORE[1], S. LAMBERTI[2], J. WOLTER[1];
[1]Univ. of Wisconsin, Madison, Madison, WI; [2]UNC-CH, Cary, NC

Abstract: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is the second most common recessive ataxia and is caused by a mutation in the neuronal gene *SACS*. It is a progressive spinocerebellar ataxia characterized by spasticity and death of cerebellar Purkinje neurons. Previous studies in the ARSACS mouse model demonstrate that molecular, cellular and behavioral deficits emerge first in the first months of life, prior to the onset of neurodegeneration. However, the neurodevelopmental origins of ARSACS, and the molecular characteristics that allow some neurons to survive while others die, remain unknown. Here we employ single-nuclei RNA sequencing (snRNA-seq) on the cerebellums of ARSACS mice during cerebellar development through activation of the neurodegenerative cascade (p5, p30, p60, p120) with 2-2.5k cells per animal, 5-7 animals per condition and 72 animals in total. These results reveal molecular and cellular phenotypes at the earliest stages of cerebellar development, suggesting that this neurodegenerative disease has neurodevelopmental origins. These early deficits involve migrating granule cells, differentiating Purkinje neurons, and the emergence of glial cell types. Following the conclusion of cerebellar development Purkinje neurons remain significantly affected, with Purkinje cell death occurring earlier than previously believed. Subclustering and anatomical dissection of specific cerebellar regions identifies Purkinje neuron subtypes that are susceptible and resilient to neurodegeneration. Differential

gene expression suggests that survival is dictated by the activation of specific molecular pathways in resilient Purkinje neurons. We also find unexpected roles for non-neuronal cell types across disease progression, including astrocytes and endothelial cells. Ongoing studies aim to clarify the molecular relationship between these cell types, specifically the breakdown of the blood-brain barrier, synaptic pruning pathways, and the emergence of neuroinflammation.
In all, this study expands the relevant cell types in ARSACS, informs the neurodevelopment precedents of Purkinje neuron death, and lays the foundation for ongoing mechanistic studies aimed at identifying molecular pathways that can be activated to delay or prevent the progression of this neurodegenerative ataxia. More broadly, this data has implications for the relationship between neurodevelopmental processes and the initiation of neurodegeneration.

Disclosures: E.M. King: None. **S. Boeshore:** None. **S. Lamberti:** None. **J. Wolter:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.001/LBA1

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant P20GM121176

Title: Temporal Transcriptomic Changes in Human Nociceptors Following Repeated Opioid Exposure

Authors: *M. R. KOCH[1], J. DEMETER[1], D. JONES[1], K. WESTLUND HIGH[3], S. R. ALLES[4], J. I. DE LA PENA[2];
[1]Dept. of Anesthesiol., [2]Anesthesiol., Univ. of New Mexico, Albuquerque, NM; [3]Anesthesiol., Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [4]Anesthesiol., Univ. of New Mexico HSC, Albuquerque, NM

Abstract: Chronic pain affects more than 50 million adults and is the leading cause of disability in the US. Opioids are one of the most effective treatments for pain and are heavily prescribed; however, their prolonged use carries high risk of adverse outcomes including reduced analgesic response (tolerance) and nociceptive sensitization that causes paradoxically increased pain (hyperalgesia). The dorsal root ganglion is home to cell bodies of pain-sensing neurons (nociceptors) and contributes to opioid analgesia, tolerance, and opioid-induced hyperalgesia. However, the direct effects of opioids on human nociceptors are understudied. Here we developed an *in vitro* model of opioid treatment by exposing human induced pluripotent stem cell (hiPSC)-derived nociceptors to morphine (10 μM) for 1 hour (acute exposure) or 1, 2, or 3 days (repeated exposure). Calcium imaging, immunocytochemistry, and RNA sequencing were performed to characterize the dynamics of neuronal activity, mu-type opioid receptor (MOR)

expression, and transcriptomic profile, respectively, at each timepoint. Capsaicin-evoked calcium responses were attenuated after 1 hour of morphine treatment but returned to baseline levels after 1 day of treatment, suggesting a tolerance and/or hypersensitivity phenotype at this timepoint. Repeated morphine exposure altered MOR expression in a time-dependent manner, with a delayed response in axons compared to soma. Finally, the expression of genes associated with sensory perception and GPCR activity were altered across timepoints relative to baseline, supporting the validity of our model and providing potential mechanistic insights. Thus our model begins to shed light on mechanisms of the beneficial and adverse effects of opioids on nociceptors, prompting and allowing deeper investigation.

Disclosures: M.R. Koch: None. **J. Demeter:** None. **D. Jones:** None. **K. Westlund High:** None. **S.R. Alles:** None. **J.I. De La Pena:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.002/LBA2

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant

Title: Chorda tympani geniculate ganglion innervation of oral cancer

Authors: *A. AGYEMANG;
Col. of Dent., NEW YORK UNIVERSITY, NEW YORK CITY, NY

Abstract: Background and Aims: Patients with oral cancer, one of the group of head and neck cancers, suffer pain at the site of the cancer. Tongue is the most common site of oral cancer. Oral cancer pain is attributed to the release of mediators that sensitize sensory neurons. In addition, cancers induce reprogramming of the nerves innervating the cancer. The anterior two-thirds of the tongue is innervated by sensory, sympathetic and parasympathetic neurons carried by the lingual and chorda tympani nerves that arise from the trigeminal and geniculate ganglia, respectively. Most research on oral cancer pain has focused on the trigeminal sensory afferents. The geniculate ganglion contains chemosensory (gustatory) and somatosensory neurons that innervate the tongue papillae. The aims of this research are to map the connectome between oral tongue cancers and the geniculate ganglion, identify the involved neuronal cell types and assess variations associated with the site of the cancer on the tongue.**Methods:** Oral cancer tongue allograft mouse cancer models were generated by injecting 4MOSC2 oral cancer cells in a diluent of a 1:1 mixture of saline and Matrigel into the anterior tongue (right and left) of C57BL/6 mice. Control mice were injected with 1:1 saline-Matrigel only. Neurons innervating the cancers were identified by injecting the neural tracer 4% fluorogold (no transcytosis) into the

cancers. The incubation time for the tracer was 7 days. Geniculate ganglia were harvested from the mice, fixed, embedded in OCT, sectioned and sections stained with antibodies to neuronal markers.**Results:** There are two populations of neurons in the geniculate ganglion that can be distinguished by expression of transcription factors. The presence of the tracer injected into the tumor was found in the Phox2b+ chemosensory neurons that project to the oral cavity. By contrast, Phox2b- BRN3A+ neurons that project to the pinna were not labeled. Expression of TRPV1 and SCN10A was observed in the Phox2b+ neurons. Expression of TRPV1 and SCN10A is reprogrammed in the trigeminal ganglia of tongue cancer mouse models. Reprogramming of these sensory receptors in both the trigeminal and geniculate ganglia are being evaluated in cancer mice.**Conclusion:** The presence of the neural tracer in the geniculate ganglia is consistent with innervation of oral tongue cancer allograft tumors by chorda tympani afferents. This observation opens the possibility of cancer-induced reprogramming of chorda tympani neurons, similar to the demonstrated cancer-induced reprogramming of trigeminal neurons to promote oral cancer and oral cancer pain.

Disclosures: A. Agyemang: None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.003/LBA3

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH/NEI Grant EY034680-01

Title: Behavioral and physiological markers of photophobia during a cortical spreading depression model of migraine

Authors: *N. WARD[1], M. KAUR[1], K. KARLAGE[1], S. A. AICHER[2], C. W. MORGANS[2], T. M. LARGENT-MILNES[1];
[1]Med. Pharmacol., Univ. of Arizona Col. of Med. - Tucson, Tucson, AZ; [2]Chem. Physiol. & Biochem., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Intro/Objective: Migraine is characterized by unilateral, episodic headaches accompanied by sensory disturbances. In approximately 14% of cases, this manifests as migraine with aura (MA), which physiologically correlates with cortical spreading depression (CSD). Nearly 86% of MA patients experience light sensitivity (photophobia) which is classified as pain upon exposure to light or substantial discomfort due to glare. Despite its prevalence, photophobia mechanisms are still poorly understood. Therefore, we examined a chemically induced CSD model in male and female rats to determine the time-course of onset, severity, and sex differences of migraine pathophysiology.

Methods: Rodents were surgically cannulated to allow for subsequent cortical injection. Upon recovery from anesthesia, they were injected with (a) KCl to induce migraine, (b) aCSF as a positive control, or (c) nothing (n=6-9/condition/experiment). Rats were then exposed to either periorbital von Frey testing and/or light/dark box behavioral assays. Vertical palpebral aperture and pupil constriction measurements were calculated during peak pain/photophobia time points.
Results: Female rats developed significant photophobia following injection with KCl, with light aversion being detected at 60 min ($p=0.007$) and peaking at 180 min ($p=0.003$), and dark seeking being detected at 120 min ($p=0.01$) and peaking at 180 min ($p=0.001$). Male rats did not develop photophobic behaviors. In females, photophobia was accompanied by significant periorbital allodynia across multiple timepoints (60, 90, 120, and 180 min, $p < 0.05$). Both sexes showed significant pupil constriction 60 min post-injection, while KCl-injected females exhibited sustained narrowing of the vertical palpebral aperture at 180 min ($p=0.01$) suggesting eyelid closure.
Conclusion: Our results suggest sexually dimorphic photophobic and periorbital allodynia behaviors in a CSD model of MA. These results reflect current clinical data, with females having higher migraine prevalence and exhibiting more severe symptoms. Photophobia symptoms also manifest over a similar timeframe as other migraine symptoms, suggesting common mechanisms. Future studies will examine proteomic and electrophysiological characteristics to determine changes in the trigeminal ganglia.

Disclosures: N. Ward: None. **M. Kaur:** None. **K. Karlage:** None. **S.A. Aicher:** None. **C.W. Morgans:** None. **T.M. Largent-Milnes:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.004/LBA4

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH/NEI 1U01EY034680-01

Title: Efficacy of Rimegepant in Reversing Photophobic Behaviors in a Rat Model of Migraine with Aura

Authors: *M. KAUR[1], N. A. WARD[2], S. A. AICHER[4], C. W. MORGANS[5], T. M. LARGENT-MILNES[3];
[2]Med. Pharmacol., [3]Pharmacol., [1]Univ. of Arizona, Tucson, AZ; [4]Chem. Physiol. & Biochem. L334, [5]Dept. of Physiol. & Pharmacol., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Intro/Objective: Rimegepant is a clinically approved migraine medication that acts through calcitonin gene-related peptide (CGRP) antagonism. The drug is effective in treating

both migraines with aura (MA) and without aura (MO), and it can be taken prior to or shortly after symptom initiation, yet the full efficacy and mechanisms are not well described. Using a rat model of MA induced by cortical spreading depression (CSD), we investigated the efficacy and time course of rimegepant in mitigating photophobia in female rats. **Methods:** Rats were surgically cannulated to allow for subsequent injection with either KCl, aCSF, or no injection. Cortical injection served as t = 0 across all assays. Migraine-like pain behaviors were assessed via periorbital von Frey thresholds, while photophobia was examined using a three-chamber light-dark assay, pupil constriction, and vertical palpebral aperture measures. After induction of headache-like behaviors, rimegepant was dosed at 1ml/kg, and behaviors reevaluated. **Results:** CSD induced periorbital allodynia, light aversion, and dark seeking behaviors. Rimegepant did not prevent CSD induced by KCl, as there was no significant difference in light aversion and dark seeking between treated and untreated groups. Initial data suggest no impact on behavioral outcomes, indicating that clinical reports on photophobia may differ in preclinical models. **Conclusions:** These data suggest that rimegepant does not limit the severity of MA-like behaviors in a rat CSD model, indicating potential differences between clinical and preclinical models in the efficacy of rimegepant for photophobia. Future investigations will explore the role of CGRP in both peripheral and central regions related to eye physiology to understand the molecular mechanisms by which CGRP and its antagonism by rimegepant influence photophobia

Disclosures: M. Kaur: None. **N.A. Ward:** None. **S.A. Aicher:** None. **C.W. Morgans:** None. **T.M. Largent-Milnes:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.005/LBA5

Topic: D.01. Somatosensation – Pain and Itch

Support: National Natural Science Foundation of China NO.82222020
National Natural Science Foundation of China NO.31825013

Title: The sp5c^{Glu}-pbn^{Tac1} pathway contributes to trigeminal neuropathic pain

Authors: *J. WANG, L. SUN, X. LI, X. LIN, J. DENG;
Fudan Univ., Shanghai, China

Abstract: Trigeminal neuropathic pain (TNP) is a severe form of orofacial pain characterized by recurrent brief unilateral electric shock-like pain triggered by innocuous stimuli. The efficacy of current drug treatment for TNP is limited, indicating the importance of fully understanding the underlying mechanisms of TNP. Since parabrachial nucleus (PBN) neuron activation was reported in inflammatory pain and neuropathic pain, we aim to identify whether PBN neurons

and related circuits contribute to TNP. We applied constriction injury of the infraorbital nerve (CION) model to mimic the TNP, confirmed PBN Tac1 and Sp5C glutamatergic neurons are involved through c-fos staining and RNAscope *in situ* hybridization, and evaluated their roles by monitoring the alterations in mechanical and thermal threshold in the whisker pad before and after treatment till day 14 after CION in transgenic reporter mice. We identified inhibition of PBN Tac1 neurons, which receive inputs from Sp5C glutamatergic neurons attenuated the TNP development. Also, inhibition of Sp5C PBN projection neurons, which receive input from GABAergic interneurons, alleviated the mechanical and thermal allodynia in TNP mice. Moreover, chemogenetic activation of Sp5C GABAergic neurons hindered TNP development. Thus, our study discovered a $Sp5C^{GABA}$-$Sp5C^{Glu}$-PBN^{Tac1} pathway participates in TNP development, and sheds light on novel therapeutic targets for TNP treatment.

Disclosures: J. Wang: None. **L. Sun:** None. **X. Li:** None. **X. Lin:** None. **J. deng:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.006/LBA6

Topic: D.01. Somatosensation – Pain and Itch

Support: R01 NS108414

Title: Neural correlates of nociception in primary somatosensory cortex precede operantly conditioned behavior in self-report paradigm

Authors: *K.-S. JEONG[1], D. A. BORTON[2], C. Y. SAAB[3];
[1]Biomed. Engin., Cleveland Clin. Lerner Res. Inst., Cleveland, OH; [2]Neuroengineering, Brown Univ., Providence, RI; [3]Biomed. Engin., Cleveland Clin. / Case Wester/ Brown, Cleveland, OH

Abstract: Decoding the neural correlates of nociception in primary somatosensory cortex (S1) remains a critical challenge for understanding the neural mechanisms of pain. We have previously demonstrated that transgenic Trpv1-ChR2-EYFP mice, whereby optogenetic stimulation of peripheral skin elicits a nociceptive behavior, can be trained on a sensory detection assay to perform lick behavior in response to optogenetic activation of peripheral nociceptive fibers versus tactile stimuli (Black et al., 2020). In this study, electrodes implanted into superficial laminae of S1 of head-restrained transgenic mice (n=3) enabled us to record local field potentials during the sensory discrimination task. Subtraction of the power spectra between optogenetic nociceptive stimulation versus tactile stimulation of hindpaw shows a contralateral increase in low gamma power (30-60 Hz) with a latency of 400-450 ms as well as increases in theta (4-8 Hz) and beta (13-30 Hz) power with a latency of 150 ms and 250 ms, respectively,

prior to lick behavior. These results suggest distinct spectral events discriminating pain from touch in S1 preceding a conscious report of sensory stimulation in the hindpaw.

Disclosures: K. Jeong: None. **D.A. Borton:** None. **C.Y. Saab:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.007/LBA7

Topic: D.01. Somatosensation – Pain and Itch

Support: T32: DA007261

Title: The Thalamic Ventral Posterior Lateral Nucleus is Functionally Connected with Action Networks

Authors: *S. R. KRIMMEL[1], R. CHAUVIN[2], A. WANG[2], N. DOSENBACH[3];
[1]Neurol., [2]Washington Univ. in St. Louis, St. Louis, MO; [3]Neurol., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: The ventral posterior lateral nucleus (VPL) of the thalamus relays sensory information from the medial lemniscus and spinothalamic tract to the somatosensory cortex. The VPL is clinically relevant, as lesions can lead to chronic pain. VPL activity, influenced by task goals, encodes mismatches between expected and actual movement, critical for updating action plans. This suggests VPL involvement in networks essential for developing and executing action plans, including the Action-Mode Network (AMN; anterior cingulate and posterior insula) and the Somato-Cognitive Action Network (SCAN; pre- and post-central gyrus). This study aims to determine the VPL's functional connectivity using fMRI. We combined dense sampling of participants (Precision Functional Mapping - PFM; n=20) with three large group-averaged datasets (Human Connectome Project, Adolescent Brain Cognitive Development, and UK Biobank; n~45,000). This captures individual variability from PFM and ensures generalizability to larger datasets. We identified the VPL using anatomical segmentation for PFM data and probabilistic atlases for group-averaged data. Neural networks were identified for each participant/group-dataset. We used decoding methods based on over 10,000 studies via Neuroimaging Meta-Analysis Research Environment (NiMARE). Consistent with tract tracing, we observed connectivity to networks associated with the postcentral gyrus, including somatomotor networks. The VPL was strongly functionally connected to the SCAN, often more than any somatomotor network, with smaller but consistent connectivity to the AMN. NiMARE decoding indicated pain and movement as terms most associated with the AMN, consistent with VPL relayed information. The connectivity between the VPL and SCAN/AMN is a novel finding with significant theoretical implications. VPL neurons respond to external perturbations during

goal-directed movement, and its connectivity with SCAN and AMN may integrate these perturbations into high-level action networks, enabling dynamic adjustments. The link between movement and pain at neural and thalamic levels suggests pain is a critical signal for modifying action, more associated with action-related networks (AMN, SCAN) than with arousal or motivated behavior networks like the salience network. The connectivity patterns observed at individual and group levels can aid efforts to functionally localize thalamic nuclei.

Disclosures: S.R. Krimmel: None. **R. Chauvin:** None. **A. Wang:** None. **N. Dosenbach:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.008/LBA8

Topic: D.01. Somatosensation – Pain and Itch

Support: UVA Brain Institute

Title: Conditioned Pain Modulation - A Multimodal Cortical Investigation

Authors: X. ZHANG[1], **S. YE**[2], D. WANG[3], *C.-C. LIU[4];
[1]Neurosci., [2]Univ. of Virginia, Charlottesville, VA; [3]Dept. of Neurolog. Surgery, Univ. of Virgina, Charlottesville, VA; [4]Univ. of Virginia Sch. of Med., Charlottesville, VA

Abstract: Conditioned pain modulation (CPM) is a psychophysical assessment used to estimate the efficiency of the body's inherent pain relief mechanisms. While spinal cord mechanisms of descending pain modulation are well understood, the contributions of cortical regions in CPM are less clear.
In this study, we used a multimodal approach (EEG and fMRI) to investigate differential neural responses in pain-related cortical regions during CPM in healthy controls (N = 38). During CPM assessment, ice water (0°C) was used to elicit long-lasting pain (>60/100) as the conditioning stimulus, while a computer-controlled infrared laser (neodymium: yttrium-aluminum-perovskite, Nd:YAP) was used to deliver acute painful stimulation (50/100) as the test stimulus. Thirty laser stimulations (4ms duration, 5mm spot diameter, 6-8s inter-stimulus interval) were delivered during CPM assessment. Brief laser stimulation has been shown to mainly activate pain-related A-delta and C-fibers in the superficial layer of the skin. Brain responses to painful laser stimulation were recorded using a 3T MRI scanner and a 32-channel MRI-compatible EEG system.
Our results showed that both laser pain intensity (i.e., test stimulus) and vertex evoked potential elicited by painful laser (LEP_N2P2) were significantly reduced in our CPM paradigm (n = 34, 23.9±10.2 yrs., 19 females, paired t-test, $p < 0.0001$). Furthermore, the decrease in laser pain intensity (CPM efficiency) significantly correlated with a reduction in LEP_N2P2 ($r = 0.42$, $p <$

0.01, Spearman's correlation). Decreased brain connectivity measured with fMRI and current source density (CSD) were observed among cortical areas involved in the sensory and modulatory components of pain processing, such as the primary somatosensory cortices, insula, anterior cingulate cortex, and dorsolateral prefrontal cortex (n = 4 for fMRI, 25.4±5.6 yrs.,4 females; n = 34 for CSD, paired t-test, $p < 0.05$).
Our preliminary results support multimodal development of brain-based biomarkers for conditioned pain modulation.

Disclosures: X. Zhang: None. **S. Ye:** None. **D. Wang:** None. **C. Liu:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.009/LBA9

Topic: D.01. Somatosensation – Pain and Itch

Title: Anti-nociceptive Activity of 80% Methanolic Leaf Extract of Pterolobium stellatum (Forssk.) Brenan (Fabaceae) in Mice

Authors: *S. S. SALILE[1], A. ABIYE[2], T. E. KEDISO[3], H. ZEWDIE[2], H. ALI[2], B. WOLDAMO[2], B. AYSA[4], T. ABULA[2];
[1]Pharm., Arba Minch University, Col. of Med. and Hlth. Sci., Arba Minch, Ethiopia; [2]Pharmacol. and Clin. pharmacy, Addis Ababa Univ., Addis Ababa, Ethiopia; [3]Biomed. Sci., [4]Pharm., Arba Minch Univ. Col. of Med. and Hlth. Sci., Arba Minch, Ethiopia

Abstract: Pterolobium stellatum is claimed in Ethiopia for neuralgia. However, the analgesic potential was not studied. This study was designed to investigate its anti-pain potential. The 80% methanol extract of P. stellatum leaves was used to investigate analgesic potential. Mice divided into five groups were given extract (100, 200, 400 mg/kg) with negative control and positive control. The Hot Plate Test and Formalin test were used as analgesic models. The results were expressed as mean ± SEM and analyzed using ANOVA with $\alpha=0.05$ using SPSS version 25. In the hot plate test, compared to the negative control, the 80% methanol extract of P. stellatum leaves at three test doses (100, 200, 400 mg/kg) and the standard drug morphine (5 mg/kg, s.c.) showed a statistically significant delay in response time for pain ($p < 0.05$) at 30, 60, 90, and 120 min after drug administration. In the formalin-induced paw-licking pain test ,at the late phase doses of 200 mg/kg and 400 mg/kg showed statistically significant pain inhibition ($p < 0.05$versus control), but the extract dose group of 100 mg/kg did not show statistically significant pain inhibition ($p >0.05$) compared with control. None of the extract dose groups studied showed statistically significant pain inhibition in the early phase ($p > 0.05$). At a dose of 4 mg/kg s.c., morphine had a statistically significant effect ($p < 0.05$) in both phases compared with the control. The plant contains some secondary metabolites such as alkaloids, coumarins, fats and

oils, flavonoids, phenols, saponins, sterols, tannins and terpenoids. The analgesic effect can be attributed to the presence of these secondary metabolites, as shown by other studies. The UPLC-MS analysis by the same author indicated the presence of gallic acid, ellagic acid, kaempferol, myricitrin, isoquercitrin and quercitirin in the crude extract(Salile et al., 2023). Gallic acid has shown to possess antinociceptive action on neuropathic pain (Yang et al., 2021). The antinociceptive effect of ellagic acid was demonstrated in hyperglycemic rats via attenuating oxidative stress (Shahidi et al. 2021). Ellagic acid alleviates also inflammatory pain and paclitaxel-induced neuropathic pain in other study(Liu et al., 2016). Kaempferol which was component of *P. stellatum* significantly decreased pain in the acute pain models in other study (Zarei et al., 2023). The present study demonstrated that the extract is harmless in mice, and the data suggest that Pterolobium stellatum leaves hydroalcoholic extract has antinociceptive activity in the hot plate test and formalin test mouse models.

Disclosures: S.S. Salile: None. **A. Abiye:** None. **T.E. Kediso:** None. **H. Zewdie:** None. **H. Ali:** None. **B. Woldamo:** None. **B. Aysa:** None. **T. Abula:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.010/LBA10

Topic: D.01. Somatosensation – Pain and Itch

Title: Novel cannabichromene derivatives effectively reduce pain in mice

Authors: *R. E. OZBORN[1], M. A. DE LEON[1], H. M. HARRIS[2], W. GUL[2], M. ELSOHLY[2], N. M. ASHPOLE[1];
[1]Biomolecular Sci., [2]Univ. of Mississippi, Oxford, MS

Abstract: Pain is the primary cause of disability in the United States. Non-addictive pain management strategies are needed to reduce the use of opioids. Many studies suggest cannabinoid-based therapies as *Cannabis sativa L.* is reported to relieve pain in over 60% of medical marijuana users. While most studies examine the effects of Δ9-tetrahydrocannabinol (Δ^9-THC) the therapeutic potential of Δ^9-THC is limited due to its psychoactive effects and potential abuse liability. Therefore, a cannabinoid devoid of these limitations would be a better therapeutic candidate. Cannabichromene (CBC) has been shown to have non-psychoactive and anti-inflammatory effects in animals, leading our team to develop novel derivatives of CBC that could enhance bioavailability and therapeutic potential. The current study evaluates the effectiveness of a novel CBC derivative, CBC-Val-HS, compared to the naturally occurring CBC against multiple pain modalities.To assess the efficacy of CBC-Val-HS compared to CBC against inflammatory pain, an abdominal writhing assay was conducted. Male and female mice were administered increasing doses of CBC or CBC-Val-HS (0.1mg/kg- 50mg/kg, i.p.) 30

minutes prior to administration of 0.7% acetic acid. Separately, the two stereoisomers of CBC-Val-HS were assessed within this assay (10mg/kg, i.p.). The number of abdominal writhes associated with inflammatory pain was measured for 30 minutes. To assess the bioavailability of these two compounds, a pharmacokinetic study was conducted (10mg/kg, i.v., po), and blood concentrations were measured at varying timepoints (e.g., 30 min, 60 min, 2 hrs). The efficacy of CBC-Val-HS against cisplatin-induced neuropathic pain was also assessed using the electronic Von Frey test, and the psychoactive potential of CBC-Val-HS was evaluated in the classic tetrad assay. Administration of CBC and CBC-Val-HS decreased the number of abdominal writhes in a dose-dependent manner with 10mg/kg or higher fully blocking inflammatory writhing. No differences in the efficacy of the stereoisomers was detected. CBC-Val-HS showed greater bioavailability than CBC with both IV and oral administration. Similar to CBC, 10mg/kg CBC-Val-HS alleviated cisplatin-induced neuropathic pain, and reduced tail flick and hot plate latencies in the tetrad assay, without reducing locomotion or dropping core body temperature. Together, these data indicate that CBC-Val-HS can attenuate inflammatory, chemotherapy-induced, and thermal pain as effectively as CBC. Importantly, CBC-Val-HS has greater bioavailability than CBC and lacks psychoactive effects, suggesting greater therapeutic and commercialization potential.

Disclosures: R.E. Ozborn: None. **M.A. De Leon:** None. **H.M. Harris:** None. **W. Gul:** None. **M. ElSohly:** None. **N.M. Ashpole:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.011/LBA11

Topic: D.01. Somatosensation – Pain and Itch

Support: National Research Foundation of Korea (NRF) grant funded by the Korea government (MIST) (RS-2024-00347913)
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National Research Foundation of Korea (NRF) grant funded by the Korea government (MIST) (2022M3C1A3081359)

Title: Role of voltage-gated sodium channel in neuroma pain severity: Difference in neuroma pain severity result from Nav1.7 and Nav1.8 distribution peripherally

Authors: *J. KWON[1,2,3], J. KIM[2,3,4];
[1]Korea university, Seoul, Korea, Republic of; [2]Dept. of Hlth. Sci., Korea Univ. Grad. Sch., Seoul, Korea, Republic of; [3]Dept. of Healthcare Sci., Transdisciplinary Major in Learning Hlth.

System, Korea Univ., Seoul, Korea, Republic of; [4]Dept. of Hlth. and Envrn. Sci., Korea Univ. Undergrad. Sch., Seoul, Korea, Republic of

Abstract: The formation of the neuroma following peripheral nerve injury cause painful condition and considered as a primary onset of neuropathic pain. The sodium channels accumulation in the terminal neuroma may generates ectopic neuronal firings, which contributes to central sensitization. However, the underlying mechanism of neuroma-related pain are not fully understood. In the present study, we investigated the alterations in different types of voltage-gated sodium channel (Nav1.7 and Nav1.8) expression in the neuroma according to pain severity. To develop an animal model for neuroma pain, the tibial nerve was ligated and completely transected in rats. Behavioral tests to measure pain severity was quantified by using paw withdrawal threshold to mechanical stimulation, latency to noxious heat stimulation (Hargreaves test) and duration of spontaneous foot lifting for 4 months. Four months after nerve injury, the diameter of neuroma was measured, and correlations between the size of the neuroma and the pain severity were analyzed using Spearman's rank correlation test. Immunohistochemistry to quantify the calcitonin gene-related peptide (CGRP) expression was performed in the L4-6 segments of the spinal cord. The changes in the expression of axonal sodium channels (Nav1.7 and Nav1.8) in the neuroma were measured through western blot at 7 and 28 days after nerve injury. In vivo dorsal root single-unit recordings from the spinal nerve at the L4-6 segments were performed to record ongoing spontaneous activity (SA) at 7 and 28 days after nerve injury. We found that about 20% of rats showed less painful like behavior (less-pain group) than the other rats (pain group). However, the formation of the neuroma was all presented regardless of pain severity. The size of the neuroma showed any significance with the neuroma pain severity. In the less-pain group, the CGRP expression level in the spinal dorsal horn was lower than the pain group. The decreased regular/irregular SA was shown in the less-pain group when it compared to the pain group. In addition, the greater density of Nav1.7 and Nav1.8 channels was observed in the neuroma of the pain group than neuroma of the less-pain group at both 7 and 28 days after nerve injury. The present data demonstrate that the alteration in the Nav1.7 and Nav1.8 channels expression play a crucial role in the development and persistence of neuroma pain. In addition, the spontaneous firings from the neuroma contribute to difference in neuroma pain severity in both acute and chronic phases. Our results suggest that the voltage-gated sodium channels could be an important role in the mechanism underlying neuroma pain and may be a potential therapeutic target.

Disclosures: J. Kwon: None. **J. Kim:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.012/LBA12

Topic: D.01. Somatosensation – Pain and Itch

Support: NSFC Grant 82222020
NSFC Grant 31825013

Title: Tac1-tacr1 signaling in the right-sided parabrachial nucleus mediates early-phase neuropathic pain development

Authors: *Y. LI, N. HA, J. LI, Y.-X. YAN, J. DENG;
Fudan university, Shang hai, China

Abstract: The lateral parabrachial nucleus (PBN) is critically involved in neuropathic pain modulation. However, the cellular and molecular mechanisms of this process are largely unknown. Here, we report that in mice, the right-sided PBN, but not the left-sided, plays an essential role in the development of hyperalgesia following nerve injury, regardless of the injury side. Spino-parabrachial pathways targeting the right PBN display short-term facilitation, and right-sided PBN neurons exhibit an increase in excitability and activity after nerve injury. Inhibiting tachykinins receptor 1 (Tacr1) positive neurons, blocking Tacr1, or knocking-down the Tacr1 gene in the right-sided PBN reduced hypersensitivity of neuropathic pain development. Additionally, the right PBN modulates pain hypersensitivity during the early-phase, but not the late-phase of neuropathic pain. These results highlight the critical role of Tacr1 in driving the lateralized modulation of neuropathic pain by the PBN, which provide new insight to mechanisms underlying neuropathic pain.

Disclosures: Y. Li: None. **N. ha:** None. **J. Li:** None. **Y. Yan:** None. **J. deng:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.013/LBA13

Topic: D.01. Somatosensation – Pain and Itch

Support: Cumming School of Medicine Graduate Scholarship (MSc)
Spinal Cord Nerve Injury and Pain Graduate Scholarship (MSc)

Title: The impact of morphine on nerve injury recovery and lipid metabolism

Authors: *S. STOKES-HECK[1], T. TRANG[2];
[2]Comparative Biol. & Exptl. Med., [1]Univ. of Calgary, Calgary, AB, Canada

Abstract: Neuropathic pain resulting from peripheral nerve injury is among the most debilitating types of chronic pain conditions. Opioid medications are often used despite their poor efficacy in treating neuropathic pain symptoms and concerns about adverse effects. Notably, emerging

evidence suggests that rather than alleviating neuropathic pain, opioids may worsen mechanical allodynia, wherein innocuous stimuli elicit pain. Morphine has been shown to exacerbate nerve injury-induced mechanical allodynia, but the cause is not understood. Both morphine and nerve injury have been implicated in myelin and oligodendrocytes perturbations. As myelin is primarily composed of lipids, here we determine whether lipid metabolism alterations are a potential mechanism underlying morphine exacerbated neuropathic pain. Chronic constriction injury (CCI), consisting of three sutures around the sciatic nerve, was performed on eight-week-old female and male C57/B6J mice. Development of mechanical allodynia was followed until return to baseline paw withdrawal threshold using the von Frey filament test. RNA extracted from lumbar spinal cord tissue was profiled using lipid metabolism arrays. Validation of genetic targets were performed at the RNA and protein level, using qPCR and Western Blot. We found that morphine treatment of CCI prolonged mechanical allodynia and recovery from nerve injury. This effect of morphine prolonged pain is further delayed by two weeks in female mice. RNA profiling arrays for lipid metabolism revealed gene candidates in male mice that were further validated at the RNA and protein levels in both sexes. These results suggest that morphine delays recovery from CCI by dysregulating lipid metabolism at the spinal cord level. As oligodendrocytes are the myelinating cells of the CNS, we propose that alterations in lipid metabolism are linked to changes in this cell type. The potential findings could help mitigate adverse opioid effects and improve treatment for people suffering from neuropathic pain.

Disclosures: S. Stokes-Heck: A. Employment/Salary (full or part-time):; University of Calglary. **T. Trang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); co-founder of AphioTx.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.014/LBA14

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH/NIDA P50 DA044121-01A1

Title: Multi-receptor whole-cortex adaptations with long-term opioid use in chronic pain

Authors: *M. N. BALIKI[1], A. VIGOTSKY[2], L. HUANG[2], R. JABAKHANJI[2], J. BARROSO[2], P. BRANCO[2], A. V. APKARIAN[2];
[1]PM&R, [2]Neurosci., Northwestern Univ., Chicago, IL

Abstract: Chronic back pain (CBP) is commonly treated with opioids, but its neurobiological consequences with stable long-duration use remain unknown. Here, we compared the clinical, psychological, and brain properties of CBP on long-term stable doses of opioids (CBP+O, n=70;

mean = 7.8 years of opioid consumption) and patients managing their pain without opioids (CBP−O, n=70), and matched healthy subjects (n = 39). Various physical function, pain, and mental health outcomes were assessed and compared between the groups. We first performed a principal components analysis (PCA) to reduce the dimensional of these outcomes. Three principal components (PC1-3) explained 69% of the total variance: PC1 (*functional disability*) included decreased physical function, less social activity, increased general disability and greater pain interference; PC2 (*pain quality*) was mainly composed of pain properties, including sensory and affective pain scales, and pain catastrophizing; PC3 (*negative affect*) included increased depression, anxiety, negative affect, decreased mental well-being. Compared to CBP-O, CBP+O exhibited worse outcomes for functional disability ($p < 0.0001$) and pain quality ($p = 0.007$), but not negative affect ($p = 0.28$). Furthermore, in CBP+O patients worse functional disability was associated with higher opioid blood levels ($R = 0.49$, $p< 0.001$). Differences in brain anatomical properties were assessed using standardized FSL pipelines. CBP+O exhibited decreased gray matter density in 2 localized clusters within the cingulum and S1/M1 region ($p<0.01$, TFCE corrected). There were no differences in white matter properties as well as cortical and sub-cortical volumes between the groups. CBP+O showed starkly different spontaneous brain activity, assessed using amplitude of low frequency fluctuations (ALFF) during resting state fMRI. ALFF differences strongly reflected cortical mu-opioid (MOR) and serotonin receptors ($5HT_{1a}R$ and $5HT_{1b}R$) distribution in the brain. We then derived a per-subject whole-cortex activity for each receptor of interest (MOR*ALFF, $5HT_{1a}R$*ALFF, and $5HT_{1b}R$*ALFF). These metrics differentiated between groups and reflected 2 of the 3 principal components that defined CBP, functional disability and negative affect. They also strongly differentiated between CBP+O on high or low doses of opioid use, between before and after short-duration opioid abstinence, and between success or failed opioid tapering. Overall our results provide a novel multi-dimensional receptor-related brain adaptations with opioid exposure and identify specific receptors the modulation of which may aid opioid tapering.

Disclosures: M.N. Baliki: None. **A. Vigotsky:** None. **L. Huang:** None. **R. Jabakhanji:** None. **J. Barroso:** None. **P. Branco:** None. **A.V. Apkarian:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.015/LBA15

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH F31NS126012
NIH 1P50DA044121
NSF DGE-1324585

Title: The Effect of Dopamine Reuptake Inhibition on Offset Analgesia

Authors: *A. VIGOTSKY[1], R. JABAKHANJI[2], A. ENGLE[4], M. N. BALIKI[3], A. V. APKARIAN[5];
[1]Departments of Biomed. Engin. and Statistics & Data Sci., [2]Neurosci., [3]PM&R, Northwestern Univ., Chicago, IL; [4]Integrated Pain Mgmt., Chicago, IL; [5]Neurosci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Pain psychophysics protocols commonly rely on quasi-static perceptual ratings, wherein a single pain rating is obtained each time a noxious stimulus is applied. These quasi-static accounts ignore perceptual dynamics, such as pain's seemingly complicated temporal fluctuations in response to a changing noxious stimulus. Pain's temporal dynamics are well-illustrated by "offset analgesia" - a pain psychophysics phenomenon whereby a slight decrease in the intensity of a noxious stimulus produces a disproportionately large decrease in pain. Since its discovery 12 years ago, offset analgesia's mechanism has remained elusive. In previous work, our group has demonstrated that offset analgesia's dynamics can be captured by a "valence competition model," consisting of two opponent nodes—positive and negative valence—that were assumed to be dopaminergic, arising from two distinct subtypes of VTA dopamine neurons and their interaction. This work assessed how modulating dopamine availability via a dopamine reuptake inhibitor (methylphenidate, 0.35 mg/kg) would perturb offset analgesia dynamics. We recruited 14 young (26 ± 4 years) healthy human participants to participate. Participants attended the lab twice for a randomized, double-blinded, placebo-controlled crossover trial. In one session, participants received 0.35 mg/kg methylphenidate; in the other, participants received a placebo. The order of the sessions was randomized and counterbalanced. In each session, the participants received four 10-minute stimulus trains, each of which contained four offset analgesia trials—two stimulus trains before the pills were consumed and two stimulus trains ~50 min after the pills were consumed. Preliminary results indicate that the drug did not have a salient effect on offset analgesia dynamics, diminishing the likelihood that offset analgesia is a dopaminergic phenomenon. Future work will quantify methylphenidate's effects and their uncertainty using a Bayesian hierarchical model of coupled differential equations derived from the valence competition model.

Disclosures: A. Vigotsky: None. **R. Jabakhanji:** None. **A. Engle:** None. **M.N. Baliki:** None. **A.V. Apkarian:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.016/LBA16

Topic: D.01. Somatosensation – Pain and Itch

Support: P50 DA044121

Title: Multi-receptor, whole-brain adaptations in mice with neuropathic pain during fentanyl vaping task

Authors: *S. CERMAK[1], M. N. BALIKI[2], A. V. APKARIAN[3];
[1]Northwestern Univ., chicago, IL; [2]PM&R, Northwestern Univ., Chicago, IL; [3]Neurosci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Introduction: Many individuals with opioid use disorder experience chronic pain. Despite concerns about its efficacy, side effects, and addiction potential, opioids continue to be the leading prescription treatment for chronic pain. However, whether shared neurobiological mechanisms may contribute to increased opioid risk in chronic pain is poorly understood. **Methods:** Given the interplay between chronic pain and opioid use, we investigated the dynamics of multi-receptor activity in the whole-brain during a fMRI study. We evaluated changes to brain circuitry in mice with or without neuropathic pain over the course of a fentanyl-vapor self-administration paradigm, in which mice were trained to self-administer fentanyl daily in 2-hour periods. Sessions took place for 1 week on a fixed-ratio 1 (FR) schedule, followed by 1 week on a FR5 schedule. We scanned mice at baseline (BL)-- prior to fentanyl exposure, and at the conclusion of the first week (T1) and second week (T2) of fentanyl self-administration. We scanned both male and female C57/Bl6J mice with either spared-nerve injury (SNI) (n=11) or sham (n=9). We collected two subsequent scans: one resting state, and one fentanyl task, in which fentanyl was presented in a block design. We also collected mechanical allodynia data. We calculated the amplitude of low frequency fluctuations (ALFF) for each resting state and fentanyl task. We conducted a paired t-test to assess differences in ALFF between BL versus T1 and T2 for each SNI and sham. We extracted *in situ* hybridization data from the Allen Brain Institute to spatially map receptor gene expression intensity for neurotransmitters, including HT1A, D1, D2, GABA-1A, GLUR5, averaged by brain region. Then, we predicted ALFF changes from receptor intensities for SNI and sham groups. **Results:** We found the models showed a significant relationship between receptor intensities and ALFF at T2 compared to BL for SNI (R^2=.49) and sham (R^2=.40). In both groups, we found that regions with high MOR and NET ($p<.05$) receptor intensity predicted resting state ALFF changes. Mice with SNI, but not sham, also showed significant changes in regions with D1 and D2 at both T1 ($p<.05$) and T2 ($p<.01$) compared to BL. During the first exposure to fentanyl at BL, fentanyl task-related ALFF changes in SNI and sham were both predicted by HTT ($p<.01$). Mice with SNI also showed engagement of D2 and HT4 ($p<.05$). **Conclusion:** These results show multi-receptor adaptations in the whole brain concurrent with fentanyl use, particularly in mice with neuropathic pain. These data may indicate potential mechanisms contributing to opioid risk in chronic pain and promote the use of nonaddictive alternatives.

Disclosures: S. Cermak: None. **M.N. Baliki:** None. **A.V. Apkarian:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.017/LBA17

Topic: D.01. Somatosensation – Pain and Itch

Support: R01DA054583
New York Stem Cell Foundation

Title: Establishing the functional arrangement of the opioid system in neural circuits using novel Cre- and Flp-expressing mouse lines

Authors: *K. HUANG[1], W. MCCALLUM[2], A. SHUSTER[3], D. WANG[4], G. SCHERRER[5]; [1]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Cell Biol., Emory Univ. Neurosci. PhD Program, Atlanta, GA; [3]Stanford Univ., Fremont, CA; [4]Nevro Corp, Redwood City, CA; [5]UNC Neurosci. Center, Dept of Cell Biol. and Physiol., Univ. of North Carolina, Chapel Hill, NC

Abstract: The delta, kappa, and mu (DOR, KOR, MOR) opioid receptors and endogenous opioid peptides enkephalin and dynorphin are broadly expressed by distinct types of neurons throughout the nervous system. Establishing which neuron types mediate the analgesic versus detrimental effects of opioids such as addiction has been hampered by the lack of tools to gain specific genetic access to cell types expressing each opioid receptor or peptide. To address this issue, we generated knockin mouse lines in which we targeted the *Oprd1*, *Oprk1*, *Oprm1*, *Penk*, and *Pdyn* genes that encode DOR, KOR, MOR, enkephalin and dynorphin to express the DNA recombinases Cre or Flp. These mouse lines can be used independently, or combinatorially, to selectively manipulate neurons expressing one, or coexpressing two, opioid receptor(s) or peptide(s). Here, we describe the characterization of $Oprd1^{ECE}$, $Oprd1^{Flp}$, $Oprm1^{ECE}$, $Oprm1^{Flp}$, $Penk^{Cre}$, $Penk^{Flp}$. We crossed these novel mouse lines with a variety a mouse lines, including Ai14, $Rosa26^{Sun1\text{-}sfGFP}$, $Rosa26^{VFRL\text{-}eGFP}$, Ai65D, or injected them with different viruses to label neurons (co-)expressing DOR, MOR or their high affinity agonist enkephalin. This approach confirmed the largely segregated expression of DOR and MOR, provides genetic access to the discrete neuron types co-expressing DOR and MOR to study the functional interactions between these receptors in vivo, and revealed the organizational logic of enkephalinergic signaling at DOR and MOR. For example, we found that DOR, MOR, and enkephalin are expressed by largely distinct neuron types in the cerebral cortex cortex and dorsal root ganglia, while co-expression and enkephalinergic auto-signaling increases in other regions of the forebrain such as the striatum and in the brainstem and spinal cord. Collectively, these findings validate the expression patterns of Cre and/or Flp in these novel mouse lines and demonstrate their utility as novel genetic tools to resolve the organization of the endogenous and mechanism of action of opioid drugs.

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Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

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Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.018/LBA18

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant R01DA054583

Title: Molecular identity, distribution across layers, and connectivity of prefrontal and sensorimotor Oprm1+ cortical neurons in mice

Authors: *N. E. OCHANDARENA[1], J. K. NIEHAUS[2], N. MERCER LINDSAY[3], C. CHEN[4], H. ZENG[5], G. SCHERRER[6];
[1]UNC Chapel Hill, Chapel Hill, NC; [2]Neurosci. Ctr., Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [3]Biol., Stanford Univ., Palo Alto, CA; [4]Neuronscience, UNC-CH, CHAPEL HILL, NC; [5]Allen Inst. for Brain Sci., Seattle, WA; [6]UNC Neurosci. Center, Dept of Cell Biol. and Physiol., Univ. of North Carolina, Chapel Hill, NC

Abstract: Although mu opioid receptor (MOR) agonists provide potent pain relief clinically, identifying and separating the mechanisms underlying opioid analgesia and addiction remains a challenge. Elucidating the molecular identity of MOR-expressing neurons may allow for the development of more precise therapeutics to manage chronic pain and opioid use disorders. Here, we combine intersectional mouse genetic tools, viral circuit tracing, slice electrophysiology, and *in vivo* calcium imaging studies to clarify the mechanism of action of MOR agonists in the cerebral cortex. First, we quantified the expression pattern of cortical neurons expressing the gene encoding MOR, *Oprm1*, using semi-automated whole-brain quantification of molecularly defined neuronal populations. We found that for excitatory neurons, the number of *Oprm1*+ cells differed greatly between cortical regions and layers. Almost universally, the density of *Oprm1*+ excitatory neurons increased with cortical depth. Surprisingly, prefrontal regions thought to underlie opioids' effects on affective responses and decision making during pain and addiction demonstrated a lower density of excitatory *Oprm1*+ cells compared to somatosensory cortices. Visualization of inhibitory cortical cell types also revealed a specific architecture to *Oprm1* expression. Layer-specific expression occurred in *Oprm1*+ *Sst*+ cells, while other *Oprm1*+ cell types, including *Pvalb*+ and *Lamp5*+ cells demonstrated striking differences between prefrontal and sensorimotor cortical regions. Next, we leveraged mouse genetic tools to investigate the connectivity and dynamics of *Oprm1*+ cortical neurons. These experiments revealed key differences in thalamocortical connectivity between prefrontal and sensorimotor cortical regions. Together, these findings characterize molecularly defined *Oprm1*-expressing cell types and reveal a divergence in the functional organization of MOR-mediated neuromodulation between sensorimotor and prefrontal cortical regions.

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Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.019/LBA19

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant R01NS118504
UNC Eshelman Innovation Grant
Brain Research Foundation Grant
McKnight Endowment Fund for Neuroscience

Title: Molecular profiling of amygdalar nociceptive neurons enables the discovery of non-opioid analgesics

Authors: *D. F. LEE[1], D. J. BERG[3], X. JIANG[4], N. MERCER LINDSAY[4], A. TASSOU[5], M. J. SCHNITZER[6], G. SCHERRER[2];
[1]Pharmacol., [2]UNC Neurosci. Center, Dept of Cell Biol. and Physiol., Univ. of North Carolina, Chapel Hill, NC; [4]Biol., [3]Stanford Univ., Palo Alto, CA; [5]Neurosci., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [6]Depts. Biol. & Applied Physics, Stanford University, Dept. of Biol., Stanford, CA

Abstract: Pain is a complex experience with sensory, emotional, and cognitive dimensions. We previously described an ensemble of neurons in the amygdala that encodes, and is necessary for, the unpleasant quality of pain. To determine the molecular identity of nociceptive amygdalar neurons, we combined activity-dependent fluorescent labeling (TRAP2) and single-cell RNA sequencing (scRNA-seq) to profile the gene expression of individual neurons active during pain. These analyses revealed 17 types and 28 subtypes of amygdalar neurons. By mapping the spatial organization of the marker genes defining these amygdalar cell types, we established a comprehensive neuron atlas of the mouse amygdala. Next, we utilized this resource to guide the discovery of drugs that could exert an analgesic effect by modulating amygdala circuits. Specifically, we searched for G protein-coupled receptors (GPCRs) that were enriched in amygdalar neuron types involved in pain processing. We identified more than a dozen G protein-coupled receptors differentially expressed by distinct nociceptive amygdalar neuron types, including neurotransmitter and neuropeptide receptors. Using preclinical pain assays and acute and chronic pain models, we then tested drugs engaging these GPCR targets and identified multiple amygdalar GPCR agonists with antinociceptive properties. We devised non-opioid precision pharmacological approaches to identify analgesics with improved side effect profiles compared to opioids. Biased allosteric modulators provided potent analgesia with reduced sedation compared to unbiased agonism. Combination therapy of three amygdalar analgesics at subthreshold doses enhanced analgesia selectively against pain unpleasantness across acute pain models and in a preclinical model of chronic orofacial neuropathic pain without promoting

motivated behaviors induced by addictive drugs. Together, these findings establish the molecular structure of the amygdala and identify highly druggable targets to treat pain unpleasantness across pain types.

Disclosures: D.F. Lee: None. **D.J. Berg:** None. **X. Jiang:** None. **N. Mercer Lindsay:** None. **A. Tassou:** None. **M.J. Schnitzer:** None. **G. Scherrer:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.020/LBA20

Topic: D.01. Somatosensation – Pain and Itch

Title: Gabapentin-induced changes in electrophysiological properties and transcriptomic profiles of human dorsal root ganglion neurons

Authors: *J. DEMETER, N. A. ZUREK, M. R. KOCH, M. W. SHILLING, K. N. WESTLUND, R. EHSANIAN, S. R. A. ALLES, J. I. DE LA PENA;
The Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM

Abstract: Neuropathic pain affects around one-tenth of the general population, and gabapentin is its first-line treatment. Despite gabapentin's widespread use in the clinic, its functional and molecular effects on human sensory neurons remain poorly understood. Therefore, we sought to characterize the electrophysiological and transcriptomic impacts of gabapentin on neurons harvested from the dorsal root ganglia (DRGs) of ethically consented human donors. We treated primary human DRG cultures with gabapentin and performed patch-clamp electrophysiology and RNA-sequencing analyses. Exposure to gabapentin altered the electrophysiological properties of DRG neurons, often in a manner specific to either single- or multi-firing neurons. In single-firing neurons, gabapentin decreased input resistance, particularly after 3-hour treatment. In multi-firing neurons, there was a positive linear trend between maximum rise slope and gabapentin treatment duration, and overnight gabapentin exposure decreased resting membrane potential. In all DRG neurons, there was a positive linear trend between rheobase and gabapentin treatment duration. As potential contributing mechanisms, 3-hour gabapentin treatment regulated the expression of genes associated with transporter and ion channel activities, including the regulation of calcium ion transport. Overnight gabapentin exposure similarly altered genes associated with plasma membrane calcium ion import as well as genes involved in phosphatidylinositol phosphate binding. Key genes modulated by overnight gabapentin exposure have been recognized to regulate neuronal functions such as synaptic transmission, nociception, and neuroendocrine peptide generation. This study presents an opportunity for further investigation into potential analgesic targets and provides a richer mechanistic understanding of gabapentin's effects. Ultimately, these insights into the peripheral impacts of gabapentin in a

human context may be harnessed to optimize gabapentin's use for the treatment of neuropathic pain.

Disclosures: J. Demeter: A. Employment/Salary (full or part-time):; The University of New Mexico Health Sciences Center. **N.A. Zurek:** A. Employment/Salary (full or part-time):; The University of New Mexico Health Sciences Center. **M.R. Koch:** None. **M.W. Shilling:** A. Employment/Salary (full or part-time):; The University of New Mexico Health Sciences Center. **K.N. Westlund:** A. Employment/Salary (full or part-time):; The University of New Mexico Health Sciences Center. **R. Ehsanian:** A. Employment/Salary (full or part-time):; The University of New Mexico Health Sciences Center. **S.R.A. Alles:** A. Employment/Salary (full or part-time):; The University of New Mexico Health Sciences Center. **J.I. De La Pena:** A. Employment/Salary (full or part-time):; The University of New Mexico Health Sciences Center.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.021/LBA21

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH/NINDS Grant NS125413

Title: Compartmentalized signaling of MrGPRX1 and TRPV channels in pain and itch pathways

Authors: *P. DURAN[1], J. RETAMAL[2], D. D. JENSEN[3];
[1]New York Univ., New York, NY; [2]Univ. of Santiago of Chile, Santiago, Chile; [3]Translational Res. Ctr., NYU Col. of Dent., New York City, NY

Abstract: G protein-coupled receptors (GPCRs) and TRPV (transient receptor potential vanilloid) channels are crucial for signal transduction in various physiological processes, including neurotransmission, pain perception, and itch. Downstream effectors of GPCR signaling can either directly stimulate TRPV channels or enhance their sensitivity to activating stimuli, a process known as TRPV sensitization. Traditionally, GPCRs are activated at the cell surface by extracellular agonists, triggering signaling cascades. Recent evidence suggests compartmentalized signaling of GPCRs from intracellular organelles. The human Mas-related G-protein coupled receptor X1 (MrGPRX1) is a GPCR expressed in primary sensory neurons involved in nociception and pruritus. However, there is no evidence that MrGPRX1 can signal from intracellular compartments. In this study, we characterized MrGPRX1 signaling within the endosomal network and its role in sensitizing TRPV channels to enhance pain and itch signaling. Utilizing recently developed cellular biosensors, we demonstrated MrGPRX1's ability to traffic and signal from endosomes. Immunofluorescence analysis showed that MrGPRX1 internalizes following BAM8-22 stimulation. BRET assays revealed that MrGPRX1 activation induces Gαq

and β-arrestin-1 protein recruitment to the plasma membrane and early endosomes. Pharmacological and genetic inhibition of dynamin or clathrin blocked BAM8-22-induced MrGPRX1 endocytosis and decreased activation of nuclear extracellular signal-regulated kinase. Additionally, calcium imaging assays confirmed that MrGPRX1-mediated TRPV sensitization is protein kinase C dependent. Our findings reveal a novel role for MrGPRX1 endosomal signaling in TRPV sensitization. Understanding the mechanisms of MrGPRX1 signaling offers valuable insights into differentiating between pain and itch pathways, aiding in the development of targeted therapies for chronic pain and persistent itch.

Disclosures: P. Duran: None. **J. Retamal:** None. **D.D. Jensen:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.022/LBA22

Topic: D.02. Somatosensation – Touch

Support: Case-Coulter Translational Research Partnership PY23-P651

Title: Acute Placement and Selectivity of a Novel Interfascicular Electrode for Peripheral Nerve Stimulation

Authors: *M. RANDOLPH[1], D. J. TYLER[2];
[1]Biomed. Engin., Case Western Reserve Univ., CLEVELAND HEIGHTS, OH; [2]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: Background: Peripheral nerve stimulation (PNS) has been implemented for various clinical applications including the alleviation of chronic neuropathic pain and sensory restoration following amputation. The therapeutic benefit of peripheral nerve interfaces relies on the selectivity of the interface, which refers to its capability to activate specific axonal populations while avoiding activation of others. However, there is a tradeoff between selectivity and invasiveness. Invasiveness refers to the extent of physical interaction between the interface and the axonal population, which is characterized by the protective nerve membranes that are interrupted, namely the perineurium. We hypothesize that peripheral nerve electrodes that are placed between the fascicles- *inter*fascicularly may balance the tradeoff between invasiveness and selectivity by allowing access to central axon populations while leaving the perineurium intact. Here we outline and characterize the development, placement and selectivity of multi-contact interfascicular electrode placement into porcine peripheral nerves. **Methods:** Multiple microwire interfascicular contacts were implanted acutely into the median or ulnar nerves of N=6 anesthetized pigs. Electromyography (EMG) signals were recorded from downstream muscles via needle electrodes in response to stimulation of each interfascicular contact to

quantify the recruitment behavior and selectivity of the interfascicular electrodes. The nerve was then excised, and micro-computed tomography was performed to visualize the relative positions of the microwires and fascicles. **Results:** *Selectivity:* Multiple muscles across the implants were able to be independently recruited using interfascicular electrical stimulation, as defined by their recruitment curves. Additionally, comparable or higher levels of muscle activation were observed with interfascicular electrical stimulation as compared to whole nerve extraneural stimulation suggesting functional feasibility. *Placement:* Across the total of N=30 placements, 24 (80%) of them appeared interfascicular as shown on the micro-computed tomography, while the remaining 7 (20%) were found to be intra-fascicular. Additionally, in each nerve, interfascicular electrodes were successfully placed centrally in the nerve, and were placed in unique locations in the nerve. These results suggest that interfascicular implantation is feasible and may allow for further access to central axonal populations.

Disclosures: M. Randolph: None. **D.J. Tyler:** A. Employment/Salary (full or part-time):; Afference INC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Barologics, INC, Afference INC.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.023/LBA23

Topic: D.02. Somatosensation – Touch

Support: NINDS 5R01NS118769
NINDS 1R01NS109170

Title: A skin-to-brain circuit dedicated to transmitting cool sensation

Authors: *H. LEE[1,2], X. SU[3], H. CHA[4], B. DUAN[2], X. XU[5], L. R. HORWITZ[2];
[1]MCDB, [2]Dept. of Molecular, Cell. and Developmental Biol., Univ. of Michigan, Ann Arbor, MI; [3]Dept. of Molecular, Cell. and Developmental Biol., [4]Molecular, Cellular, and Developmental Biol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [5]Dept. of Molecular, Cell. and Developmental Biol., Univ. Michigan, Ann Arbor, MI

Abstract: External temperature perception is crucial for maintaining homeostasis and preventing temperature-related injuries. While progress has been made in identifying molecular thermosensors, the neural circuits involved in temperature signaling remain largely unknown. Here we unveil the spinal circuit transmitting skin-to-brain cool signals. Excitatory interneurons in the dorsal horn, co-expressing Calbindin1 and Thyrotropin-releasing hormone receptor ($Calb1^{Trhr}$), act as a central hub for cool sensation. $Calb1^{Trhr}$ neurons receive inputs from

Transient receptor potential melastatin type 8-positive ($TRPM8^{+}$) sensory afferents in the dorsal root ganglion. Genetic ablation or silencing of $Calb1^{Trhr}$ neurons results in the loss of cool sensation. Calcitonin receptor-like receptor ($Calcrl^{+}$) expressing spinal projection neurons receive inputs from both $Calb1^{Trhr}$ neurons and $TRPM8^{+}$ afferents and transmit cool signals to the parabrachial nucleus in the brain. $Calb1^{Trhr}$ neuron absence impedes activation of $Calcrl^{+}$ neurons, preventing cool transmission. Our study has provided a comprehensive depiction of the neural architecture for temperature sensation.

Disclosures: H. Lee: None. **X. Su:** None. **H. Cha:** None. **B. Duan:** None. **X. Xu:** None. **L.R. Horwitz:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.024/LBA24

Topic: D.02. Somatosensation – Touch

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BBSRC BB/V005405/1

Title: Repetitive sensory stimulation potentiates and recruits sensory-evoked cortical population activity

Authors: *L. E. WILLIAMS[1], L. KÜFFER BUSSIEN[2], T. BAWA[3], E. HUSI[2], S. PAGES[4], A. HOLTMAAT[5];
[1]Ctr. for Brain Discovery Sci., Univ. of Edinburgh, Edinburgh, United Kingdom; [2]Univ. of Geneva, Geneva, Switzerland; [3]Dept. of Fundamental Neurosci., Univ. de Geneve, Carouge GE, Switzerland; [4]Wyss Ctr. For Bio and Neuroengineering, Geneve, Switzerland; [5]Neurosci., Univ. Hosp. of Geneva, Geneva, Switzerland

Abstract: Sensory experience and learning are thought to be associated with plasticity of neocortical circuits. Repetitive sensory stimulation can induce long-term potentiation (LTP) of cortical excitatory synapses in anesthetized mice; however, it is unclear if these phenomena are associated with sustained changes in activity during wakefulness. Here we used time-lapse, calcium imaging of layer (L) 2/3 neurons in the primary somatosensory cortex (S1), in awake male mice, to assess the effects of a bout of rhythmic whisker stimulation (RWS) at a frequency by which rodents sample objects. We found that RWS induced a 1h-increase in whisker-evoked L2/3 neuronal activity. This was not observed for whiskers functionally connected to distant

cortical columns. We also found that RWS altered whether individual neurons encoded subsequent stimulus representation by either being recruited or suppressed. Vasoactive intestinal-peptide-expressing (VIP) interneurons, which promote plasticity through disinhibition of pyramidal neurons, were found to exclusively elevate activity during RWS. These findings indicate that cortical neurons' representation of sensory input can be modulated over hours through repetitive sensory stimulation, which may be gated by activation of disinhibitory circuits.

Disclosures: L.E. Williams: None. **L. Küffer Bussien:** None. **T. Bawa:** None. **E. Husi:** None. **S. Pages:** None. **A. Holtmaat:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.025/LBA25

Topic: D.02. Somatosensation – Touch

Support: The National Institutes of Health (NIH) award P41 EB018783 (Wolpaw)
NYS Spinal Cord Injury Research Board C37714GG (Gupta)
NYS SCIRB C38338GG (Wolpaw)
Stratton Veterans Affairs Medical Center
NIH Grant R01HD062744 (Reinkensmeyer)

Title: Relationship between cortical mechanoreceptive processing and finger proprioception in stroke rehabilitation

Authors: *D. GUPTA[1,2], C. JOHNSON[3], L. GARCIA[4], V. CHAN[5], R. D. ROJAS[4], D. J. REINKENSMEYER[6,7,8,9], A. J. FARRENS[10];
[1]Natl. Ctr. for Adaptive Neurotechnologies, Stratton VA Med. Center, Albany, NY, Albany, NY; [2]Electrical and Computer Engin., Univ. at Albany, State Univ. of New York, Albany, NY; [3]Rancho Res. Inst., Irvine, CA; [4]Mechanical and Aerospace Engin., [6]Dept. of Mechanical and Aerospace Engin., [7]Dept. of Anat. and Neurobio., [8]Dept. of Physical Med. and Rehabil, [9]Dept. of Biomed. Engin., [10]Biomed. Engin., [5]Univ. of California, Irvine, CA

Abstract: Objective: Brain injury such as a stroke frequently leads to impairment of hand sensation as well as motor function. Recent studies have indicated that damaged somatosensory connections in the brain, evidenced as altered cutaneous mechanoreceptive processing, is associated with impairments in both touch sensation and movement execution (Gupta et al., 2017). However, it is unclear how impaired cortical mechanoreceptive processing relates to another key aspect of somatosensation - proprioception - as well as to somatosensory plasticity driven by rehabilitative movement training. Using vibration-evoked somatosensory evoked potentials (SEPs), we examined the relationship between cortical mechanoreceptive processing

and finger proprioception after chronic stroke, as well as its ability to predict improvements in finger proprioception following robot-based hand therapy.
Method: Thirty-five adults with stroke participated in a 3-week robot-based therapy (3 sessions/week). At pre- and post-therapy, we measured: i) Somatosensory evoked potentials (SEPs) with 19 channel referential electroencephalography (EEG) (DSI-24, Wearable Sensing; BCI2000 software), elicited by trains of vibrotactile stimuli delivered at the index fingers, and ii) Proprioception error via a finger crisscross task with the Finger Individuating Grasp Exercise Robot (Ingemanson et al., 2016). All data was collected with informed consent; study was IRB approved (University of California, Irvine, #476). This is part of a randomized control trial dataset (NCT04818073).
Results: Vibration-induced SEP (P50 component) at the contralateral parietal cortex of the affected hand was found to be significantly correlated with the proprioceptive errors at pre-therapy ($rho= -0.33$, $p< 0.05$), as well as post-therapy ($rho= -0.44$, $p< 0.05$). The dichotomized baseline SEP (i.e. absent / present), also showed a significant relationship with proprioceptive errors at both pre-therapy ($p= 0.0064$) and post-therapy ($p= 0.0061$)- indicating that absence of SEP at baseline is associated with larger proprioceptive errors pre- and post-therapy. Baseline SEP response predicted proprioceptive gains post therapy ($rho= 0.34$, $p< 0.05$), demonstrating the association of damage to mechanoreceptive processing and proprioceptive functional gain in people with stroke.
Conclusion: The study demonstrates a potential non-invasive EEG-based marker that can be easily assessed passively and rapidly, with potential to guide the rehabilitation of somatosensation in chronic stroke.

Disclosures: D. Gupta: None. **C. Johnson:** None. **L. Garcia:** None. **V. Chan:** None. **R.D. Rojas:** None. **D.J. Reinkensmeyer:** None. **A.J. Farrens:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.026/LBA26

Topic: D.02. Somatosensation – Touch

Support: JSPS KAKENHI JP 23K28420
JSPS KAKENHI JP 21H03312
JSPS KAKENHI JP 19K07798
JST CREST JPMJCR186
NICT Commissioned Research (No. 22801)

Title: The cortical representation of fingers: a high-resolution electrocorticography study in nonhuman primates.

Authors: *T. KAIJU[1,2], T. ASAHINA[1,2], M. INOUE[1,2], M. HIRATA[3], T. SUZUKI[1,2];
[1]Natl. Inst. of Information and Communications Technol., Suita, Japan; [2]Grad. Sch. of Frontier Biosci., [3]Dept. of Neurolog. Diagnosis and Restoration, Osaka Univ., Suita, Japan

Abstract: Sensory perception in the fingers is essential for everyday activities such as tool use. To gain insight into the underlying mechanisms, researchers have employed a range of techniques, including single-unit recordings, optical imaging, and functional MRI, to map the finger representation in the primary somatosensory cortex. However, micro-electrocorticography (μECoG), a powerful tool for electrophysiological mapping at a mesoscale, has not been extensively used in this field. The objective of this study is to investigate the finger representations in multiple nonhuman primates using μECoG in order to identify consistent patterns of cortical activity.
Intraoperative or immediate postoperative recordings were performed on 11 hemispheres of seven Japanese macaques under general anesthesia. A μECoG array (72 or 128 channels; contact size 300 × 300 μm², 1 mm intervals) composed of parylene C and gold was utilized. Ring electrodes were placed on the fingers, and constant current stimulation was applied to record somatosensory evoked potentials (SEPs).
The positive peak amplitude of the SEP (2 mA stimulation) was 1003±423 μV, with the minimum observed in D1 (thumb) stimulation and the maximum in D4 (ring). The maximum peak amplitude, the minimum stimulation intensity, and the 90% activation intensity were estimated to be 1196 μV, 858 μA, and 1765 μA, respectively. The activated region was depicted as an elliptical area with a surrounding negative potential, arranged from the outside to the inside in the order of D1 to D5. The distance between response areas in the fingers was found to be largest between D1 and D2 (2.2 mm) and smallest between D4 and D5 (1.1 mm).
We were able to collect consistent finger representations from multiple animals. The results are generally consistent with previous studies but have a high signal-to-noise ratio and time resolution. In addition, we were able to capture negative potential changes, indicative of lateral inhibition at the finger level, which are difficult to obtain directly from BOLD signals or intrinsic optical imaging. The results of this study will accelerate our understanding of the advanced mechanisms of finger somatosensory processing in primates. We also expect that the results will serve as a comparative dataset for the development of advanced neural imaging techniques.

Disclosures: T. Kaiju: None. **T. Asahina:** None. **M. Inoue:** None. **M. Hirata:** None. **T. Suzuki:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

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Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.027/LBA27

Topic: D.02. Somatosensation – Touch

Support: BBSRC Grant BB/V009680/1
MSCA Grant No 873178
Weizmann UK Making Connections

Title: Barrel cortex encodes body state during freely moving behaviour

Authors: *M. BURGESS, L. GANTAR, N. MANSOUR, D. GILL, A. NAMESNA, J. RUSCO-PORTABELLA, A. EBRAHIMI, R. STORCHI, R. S. PETERSEN;
The Univ. of Manchester, Manchester, United Kingdom

Abstract: Through decades of research on anaesthetised preparations, much is known about how neurons in the brain's ascending sensory pathways respond to stimulation of their associated sense organs. However, due to technical challenges, little is known about the function of sensory cortices in the natural setting when animals are awake, unconstrained and free to move around. To investigate this, we chronically implanted mice with Neuropixels probes into the barrel cortex and recorded neural activity whilst the mice explored objects in a dark arena under IR illumination. Mouse behaviour was imaged using four cameras. 11 body landmarks were tracked with DeepLabCut and their 3D coordinates were derived by a custom triangulation algorithm. The surfaces of the object and of the arena were reconstructed in 3D, allowing us to measure the distance of the mouse's snout to the closest 3D surface (snout-to-surface distance; SSD), from which we derived a proxy for whisker-surface touch. Additionally, to describe the mouse's body state, we extracted various parameters from the body landmarks, including 3D whole body velocity and 3D allocentric head angles, as well as their temporal derivatives. We also described non-rigid body shape changes by their first three Principal Components. We then trained a supervised learning algorithm (XGBoost) to predict the firing rate of each well-isolated neuron (n=439 neurons from 6 mice) from SSD. SSD was a statistically significant predictor of firing rate for 92% of the recorded neurons and on average explained 11% of their firing rate variance. However, when the algorithm was trained to predict firing rate from both SSD and body state parameters, the variance explained was substantially higher (18% mean variance explained; 84% neurons significant). To control for the possibility that this result might reflect a correlation between body state and whisker touch, we repeated the experiment in mice where whisker afferent input was removed by infra-orbital nerve transection (n=123 neurons from 2 mice). In these mice, 93% of neurons significantly encoded body state (14% mean variance explained). We also examined which body state parameters were the best encoded. We found that, on average, neurons encoded 2.7 body state parameters, with egocentric head pitch and forward velocity being most prevalent. In conclusion, these results suggest that, during natural exploratory free movement, neurons in the barrel cortex reliably encode body state regardless of afferent whisker input.

Disclosures: M. Burgess: None. **L. Gantar:** None. **N. Mansour:** None. **D. Gill:** None. **A. Namesna:** None. **J. Rusco-Portabella:** None. **A. Ebrahimi:** None. **R. Storchi:** None. **R.S. Petersen:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.028/LBA28

Topic: D.02. Somatosensation – Touch

Support: NSF OIA 2242771 to AA
JSPS KAKENHI Grant 23H04689, 24H02314 to YK

Title: Myelination and branching patterns of thalamocortical axons in layer 4 of mouse barrel cortex

Authors: *A. AGMON[1,2,3], T. MIYAZAKI[3,4], N. EGAWA[3], T. ETO[3], Y. KUBOTA[3,4,5];
[1]Neurosci., West Virginia Univ., Morgantown, WV; [2]Rockefeller Neurosci. Inst., Morgantown, WV; [3]Section of Electron Microscopy, Natl. Inst. for Physiological Sci., Okazaki, Japan; [4]RIKEN Ctr. for Brain Sci., Wako, Japan; [5]The Grad. Univ. for Advanced Studies (SOKENDAI), Okazaki, Japan

Abstract: Nearly all sensory information on our external or internal environment is conveyed via the thalamocortical pathway to the neocortex, where it gives rise to conscious perception. A well-studied model system for sensory processing is the rodent somatosensory cortex, in which thalamocortical terminations in layer 4 are clustered into segregated “barrels” corresponding to individual facial whiskers. Thalamocortical axons and terminals in barrel cortex have been studied extensively using both light and electron microscopy, but their myelination patterns as they enter layer 4 have not been described previously. To address this gap we used correlated light- and electron-microscopy (CLEM) to image genetically labeled thalamocortical axons in mouse barrel cortex. The brain of a 3-month-old female KN282 mouse (GENSAT) crossed with a tdTomato reporter line was perfusion-fixed and imaged on a confocal microscope at 0.5-μm Z-steps. A tissue block (330x155x50 micrometer) from layer 4 of barrel cortex was then processed histologically, cut into 850 60-nm sections and imaged serially on a scanning electron microscope. By following identified thalamocortical axons through serial sections we found that, contrary to the implicit assumption in the literature, most ascending thalamocortical axons crossing the layers 5/4 boundary are myelinated, and retain their myelin sheath at least 50-100 μm into layer 4. The myelinated segments are relatively thick (typically over 1 μm in diameter) as they enter layer 4, tapering somewhat within the layer, and rarely extend side branches. The transition to a non-myelinated segment occurs smoothly and with nearly no change in internal axon diameter. The unmyelinated main segment continues its pia-directed course while sending out multiple thin (typically less than 0.2 μm) unmyelinated branches laterally. Synapses (mostly on spines, a small number on smooth dendritic shafts) are made both by the unmyelinated main trunk and by en-passant large varicosities on the thin side branches. We hypothesize that maintaining a myelin sheath within layer 4 not only reduces conduction time but also enhances synaptic transmission synchrony between thalamocortical terminals within a barrel, contributing to the generation of the 400 Hz “ripplet” oscillations we previously described. The

developmental molecular signals for termination of myelination within layer 4 are yet to be determined.

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Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.029/LBA29

Topic: D.02. Somatosensation – Touch

Support: Blue Brain Project, EPFL, Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: How are simple pieces of information encoded by cortical cell assemblies? Do latent factors and spike sorting obscure a precise neural code?

Authors: *J. B. ISBISTER[1], S. LAQUITAINE[2], M. W. REIMANN[2];
[1]The Blue Brain Project, EPFL, Geneva, Switzerland; [2]The Blue Brain Project, EPFL, Geneva, Switzerland

Abstract: Cell assemblies transmit information through sequences of spikes. The form of these spike sequences determine the subsequent response of a downstream cell assembly. As such, characterizing such spike sequences is critical to understanding how information is successively transformed in the brain. We present new results characterizing how in vivo cortical cell assemblies represent simple units of information at a single stage of processing.
In particular, we considered why millisecond precise spike time patterns are rarely reported in abundance through-out the cortex. We hypothesized that low-dimensional fluctuations in cortical excitability might stretch / compress (i.e. time-warp) spike time patterns. Extending our previous work in the barrel cortex [1], our new results demonstrate that spike time patterns for larger cell assemblies (up to 12 neurons) are time-warped on single trials depending on a single dimensional latent factor. We next compare this single dimensional latent factor with the main dimensions of trial-to-trial variability obtained from different dimensionality reduction techniques applied to multi-unit activity. In doing so, we aim to understand the relation between variability in trial-to-trial population dynamics and precise spike time patterns. In the future, this might illuminate how behavioral variability modulates spike time patterns.
Secondly, we characterized how biases from extracellular recording and spike sorting hide and distort spike time patterns by leveraging our recent large-scale biophysically-detailed model of the rodent non-barrel primary somatosensory cortex [2]. In particular, we inserted a virtual Neuropixels 1.0 probe into the model and characterized how different spike sorting biases (i.e.

spike collision, overmerging) lead to specific types of artifacts in extracted spike time patterns.
[1] Isbister, J. B., Reyes-Puerta, V., Sun, J. J., Horenko, I., & Luhmann, H. J. Clustering and control for adaptation uncovers time-warped spike time patterns in cortical networks in vivo. Scientific Reports 2021.
[2] Isbister, J. B., Ecker, A., Pokorny, C., Bolaños-Puchet, S., Egas Santander, D., ..., Reimann, M. W. Modeling and Simulation of Neocortical Micro- and Mesocircuitry. Part II: Physiology and Experimentation. bioRxiv 2023.

Disclosures: J.B. Isbister: None. **S. Laquitaine:** None. **M.W. Reimann:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.030/LBA30

Topic: D.03. The Chemical Senses

Support: NIDCD ROO DC017754
NIDDK T32 DK128782

Title: Loss of the calcium gated Cl- channel TMEM16B alters odor coding and induces homeostatic plasticity in olfactory bulb circuits

Authors: *Z. FYKE, E. HAILE, V. KONANUR, K. BELONIO, L. VIVONA, J. D. ZAK; Biol. Sci., Univ. of Illinois at Chicago, Chicago, IL

Abstract: The olfactory signaling cascade contains two ion channels that generate transduction currents. Following olfactory receptor-ligand binding, cAMP-dependent cyclic-nucleotide-gated channels open to generate a non-selective inward cation current that results in a modest olfactory sensory neuron (OSN) membrane depolarization. An increased abundance of intracellular calcium then activates the second phase of the transduction current, the opening of the calcium-activated chloride channels (TMEM16B), leading to an efflux of intracellular Cl^-. The chloride current dominates the transduction current, accounting for ~90% of the total current (Pietra et al 2016). While TMEM16B amplifies the CNG-mediated current, it paradoxically limits OSN spike output via voltage-inactivation of sodium channels. Past work has largely focused on characterizing the electrophysiological properties of Cl^--currents using dissociated OSNs or *ex-vivo* preparations. Here, we studied how TMEM16B contributes to population activity and stimulus coding properties of OSNs in live mice. We used calcium imaging to measure the odorant response properties of individual OSNs within their native environment of the main olfactory epithelium (MOE) in WT and *Tmem16b*$^{-/-}$ mice. Using a panel of 32 odorants, we found that the loss of TMEM16B increased OSN odorant responses (mean $dF/F = 0.16 \pm 0.01$ in WT and 0.22 ± 0.01 in *Tmem16b*$^{-/-}$; $P < 0.001$), decreased sparseness (mean population

sparseness = 0.02 ± 0.002 in WT, 0.06 ± 0.007 in *Tmem16b*$^{-/-}$; P < 0.001), and reconfigured odorant-odorant relationships in OSN populations. We next considered how altered OSN coding properties may affect olfactory-guided behavior. In a navigation task, we found a strong relationship between the concentration of an odorant and the latency to localize its source in *Tmem16b*$^{-/-}$ mice, while WT mice efficiently localized the odorant regardless of its concentration. Next, we tested whether downstream circuits in the olfactory bulb homeostatically compensate for increased OSN excitability. Using whole-cell patch-clamp recordings from WT and *Tmem16b*$^{-/-}$ brain slices, we recorded spontaneous excitatory postsynaptic currents (sEPSC) from external tufted cells, which receive direct synaptic input from OSNs, but not other glomerular cells. Our recordings revealed a 27.36% decrease in OSN-to-eTC sEPSC amplitudes in *Tmem16b*$^{-/-}$slices. These data suggest that TMEM16B plays a critical role in sensory coding at the level of OSNs in the MOE and that its loss results in olfactory behavioral deficits and OB-circuit homeostatic plasticity.

Disclosures: Z. Fyke: None. **E. Haile:** None. **V. Konanur:** None. **K. Belonio:** None. **L. Vivona:** None. **J.D. Zak:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.031/LBA31

Topic: D.03. The Chemical Senses

Support: NIH R01DC020528

Title: Pharmacological inhibition of FAK following acute inflammation improves neuroregeneration and smell function recovery through CNTF in olfactory epithelium

Authors: *D. COX[1], B. WANG[1], J. PYBURN[1], D. RODRIGUEZ-GIL[1], T. HAGG[2], C. JIA[3]; [2]Dept. of Biomed. Sci., [3]Biomed. Sci., [1]East Tennessee State Univ., Johnson City, TN

Abstract: Acute olfactory epithelial (OE) inflammation destroys olfactory sensory neurons, leading to olfactory dysfunction, such as anosmia and hyposmia. Adult neurogenesis in the OE, i.e., globose basal cell (GBC) proliferation and regeneration of new olfactory sensory neurons, maintains the sense of smell. Manipulation of signaling pathways to promote OE neuroregeneration would reveal new therapeutic strategies for treating olfactory deficits. Our previous study demonstrates that ciliary neurotrophic factor (CNTF) expressed in horizontal basal cells (HBCs) of the OE is required for neuroregeneration and olfactory function recovery following methimazole-induced acute OE inflammation. Inhibition of focal adhesion kinase (FAK) upregulates CNTF expression in the OE of naïve mice. Here, we investigate whether pharmacological inhibition of FAK improves OE neuroregeneration and smell function recovery

following methimazole in mice. A water-soluble FAK inhibitor, FAK14, was given intranasally or intraperitoneally at 3-5 days when methimazole-induced inflammation is gradually increased and maximized. Intranasal FAK14 upregulated expression of CNTF and Mash1, a GBC marker, and enhanced methimazole-induced basal cell proliferation. FAK14 did not alter TNFα and IL-1β, suggesting that the effect of FAK14 is not through modifying methimazole-induced inflammation. In contrast, systemic FAK14 treatment affected neither CNTF nor basal cell proliferation. Intranasal FAK14 treatment also increased regeneration of new olfactory sensory neurons and recovery of the smell function measured 3 weeks post-methimazole in C57BL/6 and CNTF+/+ mice but not CNTF-/- mice. These data indicate that intranasal treatment with FAK inhibitor following methimazole promotes OE neuroregeneration and olfactory function recovery through CNTF. We next determined whether HBCs produce CNTF upon FAK inhibition in methimazole-treated mice. In vitro, incubation of FAK inhibitor with primary HBCs isolated from methimazole-treated mice increased CNTF mRNA and protein in cell lysates and culture media, respectively. This study demonstrates that inhibition of FAK following acute inflammation boosts OE neuroregeneration and accelerates olfactory function recovery via upregulation of CNTF in HBCs. It highlights the therapeutic potential of intranasal application of FAK inhibitors to improve olfactory neurogenesis and function after injury.

Disclosures: D. Cox: None. **B. Wang:** None. **J. Pyburn:** None. **D. Rodriguez-Gil:** None. **T. Hagg:** None. **C. Jia:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.032/LBA32

Topic: D.03. The Chemical Senses

Support: Wellcome Trust

Title: Multisensory processing of social information in the medial amygdala

Authors: *S. BAILEY[1], D. REGESTER[2], M. EDWARDS[2], Y. ISOGAI[2];
[1]Sainsbury Wellcome Ctr., London, United Kingdom; [2]Sainsbury Wellcome Centre, UCL, London, United Kingdom

Abstract: Instinctive social behaviours such as mating, aggression, and parenting, are crucial to survival. However, it remains unclear how the brain interprets the wide range of social sensory stimuli that drive ethologically appropriate actions. In mice, which depend heavily on the vomeronasal pathway to identify conspecifics through non-volatile signals, the medial amygdala (MeA) is a primary candidate for coordinating social responses, since this area receives dense vomeronasal inputs. Previous studies have also shown that activation of genetically defined

subpopulations in MeA are sufficient to drive various innate social behaviours, many of which are strongly associated to brain regions directly downstream of MeA. Using Neuropixels probes, we recorded extracellular activity from the MeA in awake head-fixed CD1 male mice (n=12) and presented social cues in volatile, non-volatile, and tactile forms. We found that MeA neurons (n=833) respond reliably to all three sensory modalities, and stimulus identity could be decoded from population activity. Interestingly, k-means clustering revealed distinct temporal patterns (early and delayed firing) in the population response to co-presentations of volatile and non-volatile cues. To identify the origin of the different phases of the response, we delivered methimazole to eliminate sensory neurons from the main olfactory pathway before recording single unit MeA activity (n=546). We found that main olfactory inputs are essential for early population responses and decoding volatile information, but play a minor role in decoding co-presented stimuli. We then explored how differential processing of volatile and non-volatile inputs in the MeA contribute to naturalistic behaviour by chronically recording from the MeA in virgin CD1 males (n=4) during freely moving interactions with male, female and infant C57BL/6 mice. We leveraged the clustering results obtained from head-fixed recordings, and found neuronal ensembles that responded selectively to conspecific types and phases of social behaviour. Altogether we propose that olfactory information, represented as biphasic responses in the MeA, is flexibly processed and selectively integrated with multimodal sensory inputs to coordinate the expression of different social behaviours.

Disclosures: S. Bailey: A. Employment/Salary (full or part-time):; University College London. **D. Regester:** A. Employment/Salary (full or part-time):; University College London. **M. Edwards:** A. Employment/Salary (full or part-time):; University College London. **Y. Isogai:** A. Employment/Salary (full or part-time):; University College London, Allen Institute for Neural Dynamics.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.033/LBA33

Topic: D.03. The Chemical Senses

Support: NSF CAREER 1553279

Title: Spatially organized genomic and physiological heterogeneity of the olfactory bulb mitral cell layer

Authors: *J. B. CASTRO;
Bates Col., Lewiston, ME

Abstract: Sensory inputs to the dorsal vs ventral olfactory bulb derive from distinct receptor families, and drive distinct behaviors. To address whether second-order OB neurons and circuits exhibit matching heterogeneity for input-specific readout, we used non-negative matrix factorization to cluster registered spatial expression profiles of >2,000 genes from the mitral cell layer (MCL), using publicly available ISH data from the Allen Institute. We observed clear dorsal and ventral clusters, and derived lists of candidate genes -- including several involved in cellular excitability -- that can be used as targets for physiological differentiation. Additionally, in patch clamp experiments, we observe dorsoventral differences in mitral cell physiology, with ventral cells showing higher peak firing rates (70.90±12.19Hz vs. 42.85±7.03Hz). Bulbar circuits may therefore be tuned for zone-specific computation.

Disclosures: J.B. Castro: None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.034/LBA34

Topic: D.03. The Chemical Senses

Support: other support

Title: The medial prefrontal cortical connection with the basal forebrain and its role in odor preference

Authors: *M. PATEL;
Baylor Col. of Med., Houston, TX

Abstract: The Arenkiel lab discovered a population of glutamatergic neurons residing in the basal forebrain (BF) that play a key role in appetite modulation. Specifically, selective activation of these neurons in mice results in appetite suppression leading to starvation. This phenotype, however, can be rescued if the mice are force fed. This indicates that the feeding phenotype is not linked to metabolism, but rather a dysregulation of the motivational drive to eat. This may be related to the sensory processing of the food stimuli; these glutamatergic neurons are selectively active to odor stimuli. These findings suggest that non-homeostatic pathways are likely involved. To further understand the mechanism by which the sensory stimuli interact with the BF, it is important to identify the cortical structures connected to the BF. Retrograde tracing experiments from the basal forebrain identified several cortical structures. Among these structures, the medial prefrontal cortex (mPFC) was of special interest due to its established role in cued-potentiated feeding as well as its understudied link with BF circuitry. The mPFC also plays a role in attention, motivation, and mediates addiction-related behavior. Morever, the mPFC has persistent representations of odor value. In humans, the mPFC differentially responds to food related

stimuli in hunger vs. satiety states. With this evidence, the focus of this project is investigating the hypothesis: The medial prefrontal cortex is functionally connected to the basal forebrain to influence odor preference and guide food choice. Using optogenetics, the mPFC to BF circuit was selectively activated or inhibited in mice to reveal a bi-directional real time place preference or avoidance. By pairing a neutral odor with light delivery across three days, in preliminary experiments, mice show a preference for the optogenetic activation-paired odor and avoidance to the optogenetic inhibition-paired odor. Additional experiments are underway to determine how food choice is influenced with manipulation of odor stimuli. Towards a mechanism of this phenomenon, the BF neuron activity during opto-stimulation of the mPFC to BF pathway will be assessed using GRIN lens, an in-vivo deep brain imaging method. Since the BF sends specific efferent projections with positive or negative valence, understanding how the mPFC to BF circuit may toggle these outputs can help lay the groundwork for how this circuit may underlie aberrant feeding behaviors in eating disorders.

Disclosures: M. Patel: None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.035/LBA35

Topic: D.03. The Chemical Senses

Support: ETRI/24YB1210&24ZB1330

Title: Investigating Social Interaction and Neural Response to Olfactory Stimuli in Mice Using Advanced Electrophysiological Techniques

Authors: *D. KIM[1], D. LEE[2], D. LEE[2], K. KIM[2], S. LEE[3], S. HAN[4], H.-K. LEE[1];
[1]ETRI, Daejeon, Korea, Republic of; [2]Korea Brain Res. Inst., Daegu, Korea, Republic of; [3]San Diego State Univ., San Diego, CA; [4]Korea Basic Sci. Inst., Cheongju, Korea, Republic of

Abstract: The study of social interactions in neuroscience has been primarily limited to behavioral approaches due to the constraints of traditional electrophysiological systems, which are often wired and restrict the simultaneous observation of multiple animals. This research addresses these limitations by investigating both individual and group responses to olfactory stimuli in mice using behavioral and electrophysiological methods, as well as functional magnetic resonance imaging (fMRI) to explore brain activation and connectivity.
Male C57BL/6J mice (20–25 g) served as the experimental subjects. Tungsten microelectrodes (256 μm diameter) were implanted stereotaxically into the amygdala (AMG). After a 12-day recovery period, electrophysiological signals from the AMG and behavioral changes were recorded simultaneously. Two groups of odorants were used: plant-derived α-pinene and

predator-derived 2,4,5-trimethylthiazole (TMT). A specially designed airtight test box ensured precise gas concentration, regulated by a mass flow controller. The protocol involved placing a single or grouped mice (n=4) in the test box under an air atmosphere for 10 minutes, followed by 10 minutes of exposure to either α-pinene or TMT, while monitoring electrophysiological signals and behavioral changes. We used a custom-made wireless brain signal acquisition system, a lightweight device (< 3 g) mounted on the mice's heads, which features low-computation and interest point extraction algorithms for real-time EEG analysis and LED visualization of various brain states. Mouse movements were video-recorded at 30 fps and analyzed using the Ethovision video tracking system. MATLAB programs were used to analyze local field potential (LFP) signals. The study revealed that when four experimental subjects were exposed to TMT (1 ppm) in the same test box simultaneously, the total LFP power measured in AMG was approximately 66.5% of the total LFP power observed when each subject was in the test box individually. Behavioral analyses focused on locomotor activity, spatial location, and freezing behavior according to the type of odorant. Odor-evoked fMRI acquisition was conducted on different sets of animals using a 9.4T MRI scanner to obtain structural (T2) and functional images. Group analyses were performed using a generalized linear model to compare the α -pinene and TMT groups.
Support: This work was supported by Electronics and Telecommunications Research Institute (ETRI) grant funded by the Korean government. [24YB1210, Collective Brain-Behavioral Modelling in Socially Interacting Group. 24ZB1330, Development of core technology of brain-morphic decoding and encoding]

Disclosures: D. Kim: None. **D. Lee:** None. **D. Lee:** None. **K. Kim:** None. **S. Lee:** None. **S. Han:** None. **H. Lee:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.036/Web Only

Topic: D.03. The Chemical Senses

Support: JSPS KAKENHI JP23K11297

Title: Investigating Color Associations of Odors and Comparing Fragrance Experts and Non-experts

Authors: *K. TAMURA[1], T. NISHIMURA[1], T. TORISU[2], M. SHOKO[2];
[1]Fukuoka Inst. of Technol., Fukuoka-Shi, Japan; [2]RIMO-trogen Inc., Fukuoka, Japan

Abstract: Odors can be associated with specific colors, such as a banana-like odor for yellow and a strawberry odor for pink. Previous studies have investigated the formation of odor-color

associations, but a unified interpretation is yet to be established. In this study, we hypothesized that non-experts in fragrance will form different odor-color linkages from those of experts who have background knowledge of odors.
We measured the associated colors from fragrance experts and non-experts using seven types of essential oils: lemon, lavender, geranium, eucalyptus, cedar wood, and the control (odorless mineral oil). To record the odor-color association, we developed a measurement system of colors associated with odors according to the CIEL*a*b* space. The associated colors were compared between the two groups, which had different abilities to identify odor sources. Thirteen experts and 20 non-experts participated in this study. All participants were native Japanese speakers with Japanese cultural backgrounds. The procedure was approved by the local ethics committee of the Fukuoka Institute of Technology.
First, the participants sniffed the samples and were required to respond to the lightness of the color associated with the sniffed odor using the developed system. Subsequently, the participants provided the hue values that corresponded to the lightness specified in the preceding step. After responding to the associated color, they responded to five descriptor items using the visual analog scale: strength, pleasantness, familiarity, edibility, and arousal.
Subjective ratings were compared between the experts and non-experts for each odor. The pleasantness rating of lavender was significantly higher among experts than among non-experts ($p = 0.032$). The experts showed significantly higher familiarity with eucalyptus ($p = 0.045$).
To compare the odor-color associations between the experts and non-experts, we conducted a linear discriminant analysis. The predicted variables were the color parameters according to the CIEL*a*b* (L*, a*, and b* values) of the associated colors for each odor. For eucalyptus, the independent variable color parameters of the associated colors significantly contributed to the discrimination between the experts and non-experts (Wilks' lambda, $p < 0.001$). For lavender, the discrimination model significantly predicted the presence of experts and non-experts ($p = 0.013$). The results indicated that the associated colors corresponding to some odors varied according to background knowledge.
This study was supported by the JSPS KAKENHI Grant-in-Aid for Scientific Research (C), grant number JP23K11297.

Disclosures: K. Tamura: None. **T. Nishimura:** None. **T. Torisu:** None. **M. Shoko:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.037/LBA36

Topic: D.03. The Chemical Senses

Support: KAKENHI JP JP23H02782
JST PREST JPMJPR1906

JST CREST JPMJCR1921
AMED iBrain/MINDS JP21wm0525004
AMED 21bm0704060h0001
AMED-PRIME JP23gm6510022

Title: Top-down input-induced plasticity in granule cell odor representation contributes to olfactory-associative learning in mice

Authors: *A. IDE[1], Y. SUZUKI[1,2], M. SAKAMOTO[1,2], I. IMAYOSHI[1,2];
[1]Grad. Sch. of Biostudies, Kyoto Univ., Kyoto, Japan; [2]Inst. for Life and Med. Sciences, Kyoto Univ., Kyoto, Japan

Abstract: The olfactory system mediates various odor-related behavioral responses, including associative learning between odor cues and rewards. The olfactory bulb plays an essential role in odor detection, discrimination, and interpretation of odor value as the first processing center of the mammalian brain. Granule cells in the olfactory bulb are a major class of GABAergic interneurons that provide feedback inhibition to principal neurons (i.e., mitral and tufted cells) via dendrodendritic reciprocal synapses, which contribute to odor discrimination by sharpening the signal-to-noise ratio of odor representation. Granule cells also receive corticofugal projections from higher brain regions, such as the anterior piriform cortex, and these top-down inputs are thought to contribute to the olfactory leaning-dependent plasticity of granule cells. However, it is largely unknown how the dynamic changes in odor representation of individual granule cells and their population activities contribute to different types of olfactory-associative learning. Here, we performed *in vivo* two-photon calcium imaging to record the activity of granule cells during odor-reward association tasks: the go/no-go odor discrimination task. We designed two versions of this task: one with a dissimilar odor pair (the easy task) and another with a similar odor pair (the difficult task). Our chronic *in vivo* imaging during each task revealed that the odor-induced firing activity of granule cells was elevated throughout learning, with more prominent changes observed in the difficult task. In contrast, repeated passive odor exposure led to a gradual decrease in odor representation in granule cells, suggesting increased granule cell activity in a task engagement-dependent manner may functionally contribute to olfactory learning. Additionally, when mice learned to discriminate between two odors in both tasks, the initially overlapping representations of the two odorants in granule cells became progressively distinct. We also observed that the feedback projections from the anterior piriform cortex to the olfactory bulb exhibited increased activity during learning. Furthermore, functional silencing of these top-down inputs using a pharmacogenetic approach (DREADD) led to a reduction in granule cell activity and the divergence of their odor representations, resulting in poor performance in the go/no-go odor discrimination task. Our findings indicate that learning-dependent plastic changes in functional connections between granule cells and top-down inputs and the optimized robust and selective odor representations in granule cells contribute to olfactory learning.

Disclosures: A. Ide: None. **Y. Suzuki:** None. **M. Sakamoto:** None. **I. Imayoshi:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.038/LBA37

Topic: D.03. The Chemical Senses

Title: How Are Human and Mouse Olfactory Perceptual Spaces Related?

Authors: *S. KARIMIMEHR[1,3], S. CEBALLO[2], R. PELLEGRINO[4], E. HAMEL[5], M. UREÑA[4], J. KOTLYAR[2], K. SAMOILOVA[6], A. KOULAKOV[6], J. MAINLAND[4], D. RINBERG[2];
[2]Neurosci. Inst., [1]NYU Langone Hlth., New York, NY; [3]Ctr. for Neural Sci., New York Univ., New York, NY; [4]Monell Chem. Senses Ctr., Philadelphia, PA; [5]Monell Chem. Senses Ctr., Philadelpia, PA; [6]Cold Spring Harbor Lab., Cold Spg Hbr, NY

Abstract: We are at the early stages of developing robust methods to quantify perceptual odor quality. Gaining insights into the olfactory perceptual space across different species is valuable for this endeavor. A key step in establishing a connection between species is to verify how perceptual distances of odors observed in one species correspond to those in another, and to determine how accurately we can predict the perceptual distance of odors in one species based on another. In this study, we compared the olfactory perceptual space of mice and humans across 20 different monomolecular odors. By measuring the perceptual distances of odor objects in both species through two distinct tasks, we identified a significant correlation between mouse and human odor perceptual spaces. More precise considerations revealed that this correlation is odor-dependent. Specifically, we found a negative correlation between the perceptual distances of acids in mice and humans, while non-acids showed a positive correlation. Further, we mapped the perceptual distances of both species into a human space defined by organoleptic properties such as fruity, tropical, and cheesy. This mapping revealed a strong correlation (Corr: 0.81, p-value: 3e-13) between the perceptual distances of mice and humans. Building on these findings, we developed a predictive model capable of translating the perceptual space of one species to the other with a prediction correlation of 0.61 and RMSE of 0.09. Additionally, we explored the relationship between human and mouse perceptual distances mapped to the physicochemical features of the odors. Our analysis uncovered a significant correlation (Corr: 0.78, p-value: 5e-18) between the perceptual distances of mice and humans within the physicochemical space of the odors. These results suggest that despite differences in olfactory systems, there is a substantial overlap in how mice and humans perceive odors, particularly when considering the physicochemical properties of odorants. This work contributes to our understanding of cross-species olfactory perception and opens avenues for further research into the underlying mechanisms governing olfactory similarities and differences.

Disclosures: S. Karimimehr: None. **S. Ceballo:** None. **R. Pellegrino:** None. **E. Hamel:** None. **M. Ureña:** None. **J. Kotlyar:** None. **K. Samoilova:** None. **A. Koulakov:** None. **J. Mainland:** None. **D. Rinberg:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.039/LBA38

Topic: D.03. The Chemical Senses

Support: NSF Grant #2021795

Title: Neuromodulation of odor-evoked behavioral responses in S. americana

Authors: *I. CLARK[1,2], Y. BESSONOVA[3], B. RAMAN[4];
[1]Neurosci. and Behavior, Univ. of Notre Dame, South Bend, IN; [2]Biomed. Engin., Washington Univ. of St. Louis, Saint Louis, MO; [3]Biomed. Engin., Washington Univ. in St. Louis, St. Louis, MO; [4]Biomed. Engin., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Olfaction is a critical sensory modality for food foraging, mating, and survival. Behaviorally the response to the olfactory cues in locusts, *Schistocerca americana*, can be tracked via palp-opening response (POR) assay. The opening of sensory appendages close to the mouth, known as maxillary palps, represents an appetitive reaction evoked by an odorant. Current research suggests the involvement of various neuromodulators in the regulation of olfactory-driven behaviors. In this study, we examined the regulation of olfactory responses by different neuromodulators: serotonin, dopamine, octopamine, and glutamate. These neuromodulators have been implicated in both heightened and dampened odor-evoked neural responses. We used a POR assay to study the behavioral reactions in response to a variety of displayed odorants. Six different odorants (hexanol, benzaldehyde, citral, geraniol, linalool, and paraffin oil as control) were used to examine behavioral responses in the locusts. We found that the injection of dopamine or octopamine had a very odor-dependent effect. Dopamine increased the probability of palp-opening responses whereas, we found that the injection of octopamine decreased the probability of palp-opening responses in an odor-dependent manner. In contrast, serotonin increased and decreased PORs to odorants in an odor-specific manner. Interestingly, glutamate increases the POR to most of the odorants. To further support our findings, we used the immunohistochemistry technique to locate neuromodulatory pathways in the locust brain. We used antibodies to stain for dopamine, octopamine, glutamate, and GABA. The results reveal that multiple neuromodulators are present within the antennal lobe, the very first neural circuit that receives direct olfactory sensory neuron inputs. Taken together, we reveal a concrete connection between the neuromodulators present in the antennal lobe and their effect on the olfactory-behavioral response.

Disclosures: I. Clark: None. **Y. Bessonova:** None. **B. Raman:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.040/LBA39

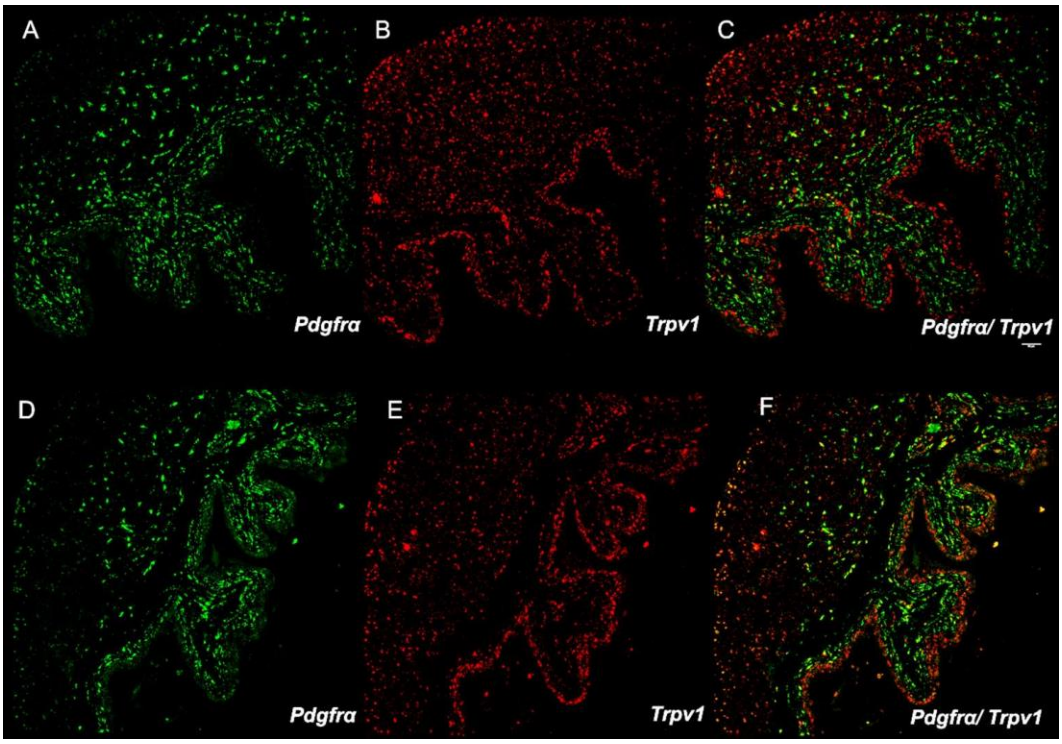
Topic: D.04. Interoception

Support: NIH Grant R01-DK135696
NIH Grant R01-DK119615
NIH Grant P01-HL152951

Title: Interstitial cell and non-interstitial cell TRPV1 channel expression in mouse urinary bladder

Authors: *M. MASINO[1], E. FLOOD[1], B. MADHU[1], O. J. VEGA RODRÍGUEZ[1], N. R. TYKOCKI[2];
[2]Pharmacol. and Toxicology, [1]Michigan State Univ., East Lansing, MI

Abstract: Transient receptor potential vanilloid type 1 (TRPV1) channels are implicated in nociception and may become sensitized during inflammation, resulting in increased release of pro-inflammatory neuropeptides. In the urinary bladder, TRPV1 channels are distributed throughout afferent nerves and vascular smooth muscle cells, but their expression in other cell types within the bladder is controversial. As such, there may be an interdependent mechanism driving interstitial cell and sensory afferent nerve sensitization. While genetically-encoded indicator mice provide evidence for TRPV1-expressing interstitial fibroblasts in the bladder wall, it is unknown if these cells continue to express TRPV1 channels after development. Additionally, sex differences in bladder TRPV1 channel expression have not been thoroughly explored. We hypothesize bladder interstitial fibroblasts express *Trpv1* mRNA after development in male and female mice. Bladders from male and female C57Bl/6 mice (ages 10 - 14 weeks) were isolated, fixed, paraffin embedded, and sectioned onto glass slides. Then, RNAscope was used to visualize urinary bladder mRNA expression patterns for Trpv1 and the fibroblast/interstitial cell marker *Pdgfrα*. While female mice appeared to have more *Pdgfrα*-expressing cells in the bladder wall, *Trpv1* and *Pdgfrα* were coexpressed throughout the bladder of both male and female mice. Surprisingly, in both sexes *Trpv1* mRNA was expressed throughout the bladder wall and epithelium in cells where *Pdgfrα* mRNA was absent. Together, these data suggest *Trpv1* mRNA is expressed in multiple bladder cell types, including interstitial fibroblasts, past development. These *Trpv1* mRNA positive cells could contribute to the feed-forward sensitization of afferent nerves in the urinary bladder. These data also reveal potential sex differences in bladder fibroblast populations that may account for differences in bladder sensation.



Disclosures: M. Masino: None. **E. Flood:** None. **B. Madhu:** None. **O.J. Vega Rodríguez:** None. **N.R. Tykocki:** F. Consulting Fees (e.g., advisory boards); Incyte Pharmaceuticals.
Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.041/LBA40

Topic: D.04. Interoception

Title: Whole-brain Mapping of Brain Regions Activated by Lipopolysaccharide-induced Peripheral Inflammation

Authors: *Z. XIE, Z[1], N. KUGA[1], T. KAYAMA[1], T. SASAKI[1,2];
[1]Dept. of Pharmacol., [2]Dept. of Neuropharm., Tohoku Univ., Sendai city, Miyagi, Japan

Abstract: Chronic and excessive inflammation in the body activates many brain regions. This study aims to gain insights into mechanisms underlying inflammation-induced brain activation. There are three main pathways to transmit signals from the peripheral organs to the brain: (1) the humoral pathway, (2) the vagal afferent pathway, and (3) the spinal neuronal pathway. After intraperitoneal injection of lipopolysaccharide (LPS) and streptozotocin (STZ), neuronal activity in the brain was evaluated by c-Fos immunostaining. The c-Fos immunostaining results showed that there were significant increases in neural activity in several brain regions including the

medial prefrontal cortex (mPFC), the anterior cingulate cortex (ACC), anterior and posterior insular cortex (IC), the hypothalamic paraventricular nucleus (PVN), the basolateral amygdala (BLA), the central amygdalar nucleus (CeA), the thalamic paraventricular nucleus (PVT), the hippocampus ventral CA1 (vCA1), the ventral tegmentum (VTA), the parabrachial nucleus (PBN), the locus coerules (LC) after LPS and STZ administration. However, only the LPS injection, but not STZ injection, induced a significant increase in neuronal activity in the nucleus tractus solitarius (NTS), the nucleus ambiguus (Amb), and the area postrema (AP). The activation of the IC, PVN, BLA, and CeA was blocked by inhibiting the humoral pathway with intracerebroventricular injection of Alloxan, a toxic material that destroys ependymal cells. On the other hand, the activation of the mPFC, ACC, vCA1, VTA, PBN, LC, Amb, NTS, and AP was blocked by vagotomy, a surgery to remove the vagal pathway. These results suggest that the IC, PVN, BLA, and CeA receive peripheral inflammatory signals via the humoral pathway, while mPFC, ACC, vCA1, VTA, PBN, LC, Amb, NTS, and AP receive peripheral inflammatory signals via the vagal afferent pathway. However, there remains an area - the PVT - that does not change even when either the humoral or vagal afferent pathway is blocked. We used silicon probes to record the firing rate in the PVT neuron. We find that the PVT may simultaneously mediate both humoral and vagal afferent pathways, which needs further study.

Disclosures: Z. Xie: None. **N. Kuga:** None. **T. Kayama:** None. **T. Sasaki:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.042/LBA41

Topic: D.05. Auditory and Vestibular Systems

Support: NSF Grant IOS1257150
NSF Grant IOS1855956
NSF Grant IOS1856237
NIH Grant R01DC010809
Paul G. Allen Frontiers Group

Title: Specific conductances in acutely dissociated hair cells from the zebrafish lateral line.

Authors: B. J. GIBBS[1,2], E. T. LUNSFORD[4,2], *Y. BOBKOV[2], J. C. LIAO[2,3];
[1]Mayo Clin. Florida, Jacksonville, FL; [2]Whitney Lab. for Marine Biosci., Univ. of Florida, Saint Augustine, FL; [3]Dept. of Biol., Univ. of Florida, Gainesville, FL; [4]Paris Brain Inst. (ICM), Paris, France

Abstract: Recent studies suggest that chloride efflux through calcium activated chloride channels might play a more significant role in the excitation of zebrafish lateral line hair cells

(HCs) than previously believed, especially in freshwater environments - defined by their low ion strength. This is a functionally disparate mechanism from the cation driven depolarizations of the homologous auditory HCs that could provide insight into signal amplification mechanisms in ionic deficient/variable contexts. To more directly implicate chloride channels in zebrafish HCs function we characterized the electrophysiological properties of these cells in primary culture. Recordings from acutely dissociated cells offer several advantages including absence of cellular crosstalk noise; extracellular environment control; more accurate pharmacological analysis; targeted functional transcriptome; perforated patch and single-channel recordings. The isolated HCs were identified based on their unique morphological characteristics: a single kinocilia; a visible stereocilia bundle; and a pear-shaped cell body. Cell identity was further confirmed functionally through calcium imaging and electrophysiological experiments. Expression of the plasma-membrane-targeted calcium indicator GCaMP6s-CAAX was exclusively associated with cells of the described phenotype, and the electrophysiological properties of those cells were consistent with zebrafish lateral line HC properties reported earlier in vivo: presence of L-type calcium channels; lack of voltage gated sodium channels; pronounced A-type potassium current with varying contribution from delayed rectifying and calcium-activated potassium channels. The HC chloride conductance was dissected using cesium based intracellular solution to suppress potassium channels and specific agonist (Eact) of calcium activated chloride channels (ANO1/2). Extracellular Eact application increased HC conductance with a reversal potential characteristic of chloride-selective conductance. The standard voltage pulse protocol revealed relatively slow activating outward currents at depolarizing voltages in the presence of Eact, consistent with the activation parameters of ANO1/2 chloride channels further confirming that Eact indeed targets calcium-activated chloride channels expressed in HCs.
We characterized electrophysiological properties of acutely isolated HCs and provide evidence, that anion efflux can drive HC activation very much like in vertebrate chemosensory neurons (olfactory, taste and pheromone receptor neurons): through calcium activated chloride channels.

Disclosures: B.J. Gibbs: None. **E.T. Lunsford:** None. **Y. Bobkov:** None. **J.C. Liao:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.043/LBA42

Topic: D.05. Auditory and Vestibular Systems

Support: German Research Foundation (DFG) Grant 1110070400

Title: Multifunctional Organization of The Computational Map of Target Distance in Bats

Authors: *A. ROUSTAZADEH;
Zoology, Tech. Univ. of Munich, Freising, Germany

Abstract: In the auditory cortex of echolocating bats, the distance to an object (target) is represented in a specialized neuronal map. Neurons in this map only fire action potentials if echoes are reflected from objects in the environment (e.g. insects or other prey items) and arrive with a specific delay after the bat has emitted a call. In contrast to structural maps, which simply reflect the topographic organization of the epithelial surface of peripheral sensors, the target-distance map is a computational map. The delay between call emission and echo arrival is computed within the neural circuitry of the bats' auditory system, and each neuron in the target distance map is tuned to a specific delay time. Our experiments investigate the representation of multiple objects in the target distance map of the bat P. discolor. Extracellular recordings are employed to reveal the minimum distance that can be resolved by single delay-tuned neurons. For this purpose, a virtual target echo is combined with two virtual masker echoes, occurring with various shorter and longer masker delays, thus simulating reflections from objects (maskers) positioned in front of and behind the virtual target. Classical delay-tuned neurons have a high facilitation ratio, meaning they only respond to favorable combinations of pulse and echoes but not to each of these stimuli alone. Surprisingly, our results show that while these neurons are specialized in detecting single targets along the distance axis, they are not well-suited to resolve multiple objects. However, the response of other neurons in the target distance map, with a significantly lower facilitation ratio, matches the behavioral performance of the bats in a similar target distance resolution task in a previous psychophysical study. Our results shed light on the different roles of neurons in the same computational cortical map, suggesting a multifunctional organization underlying this type of sensory map.

Disclosures: A. Roustazadeh: None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.044/LBA43

Topic: D.05. Auditory and Vestibular Systems

Support: NIH Grant R01 DC014950
NIH Grant R21 DC021048

Title: Local population coding of natural stimulus statistics in auditory cortex

Authors: A. D. ZHONG[1], G. R. HAMERSKY[2], *S. V. DAVID[3];
[1]Otolaryngology - Head and Neck Surgery, Oregon Hlth. & Sci. Univ., Portland, OR; [2]Neurosci. Grad. Program, OHSU, Portland, OR; [3]Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: It is generally agreed that the auditory system identifies natural sounds based on their spectro-temporal regularities, which can be linked to mechanical processes of the physical

source. However, it remains unclear how auditory cortex (AC) extracts sound statistics and represents them across its different subregions. This study aims to establish how these properties are processed and represented in AC. Specifically, it asks if neural encoding of statistical sound features is more tightly linked to a specific location in AC or to the identity of the original sound. Linear microelectrode arrays were used to record single-unit neural activity in ferret AC. Penetrations were angled normal to the cortical surface, and thus, each targeted a single cortical column. Activity was recorded from 36 sites in two awake, passive animals (10-50 units/site). During each recording, a set of 8-10 1-sec natural sound segments was presented, interleaved with model-matched synthetic versions of those sounds (Norman-Haignere & McDermott 2018). Four synthetic conditions were tested, preserving spectral correlation, temporal modulation, both, or neither. The last condition preserved only the mean power spectrum of the original stimulus. The correlation between the population response for each pair of natural and synthetic conditions defined a neural confusion matrix for a single stimulus and recording site. Weaker confusion (lower correlation) indicated that sound statistics had greater influence on responses. To determine if confusion depends on the location of the recording site or on sound identity, we performed a two-way comparison: we compared confusion matrices between stimuli at the same site and between sites for the same stimulus. If confusion patterns are determined by location, then they should be similar across stimuli within a recording site. If they are determined by the stimulus, they should be consistent within a stimulus across sites. Confusion matrices varied between both recording sites and stimuli. On average, they were more similar across stimuli within a single recording site, compared to the same stimulus across different sites. These results suggest that local neural populations are more sensitive to specific statistical features of natural sounds and less sensitive to the identity of the sound itself. In this framework, local populations tuned to distinct natural sound statistics support a code for natural sound identity distributed across the primary auditory cortex.

Disclosures: A.D. Zhong: None. **G.R. Hamersky:** None. **S.V. David:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.045/LBA44

Topic: D.05. Auditory and Vestibular Systems

Support: ADRIAN COLLEGE UNDERGRADUATE STUDENT RESEARCH SUMMER GRANT 2024

Title: Spectro-temporal receptive field of in-silico neural networks with excitation-inhibition imbalance.

Authors: *K. KURAMITSU[1], P. CHA[2];
[2]Physics Dept., [1]Adrian Col., Adrian, MI

Abstract: Previous studies highlighted intriguing connections between Autism Spectrum Disorder (ASD) and pitch-perception task performance. Existing research has investigated these connections from various perspectives including fMRI and mutational studies. A promising approach towards investigating the role of ASD on a wide array of brain functions is the Excitation-Inhibition (E/I) imbalance hypothesis, which has been shown to account for some visual perceptual characteristics of individuals with ASD. However, the implications of an E/I imbalance on auditory processing have not been investigated from a computational perspective. A recent work from Chambers et al (2019) proposed a neural network model of the auditory cortex that simulated the experimentally observed response of ferrets to auditory stimuli by reproducing the spectro-temporal receptive field (STRF). In this work, we investigate the sensitivity of auditory processing as captured by the STRF on the elevated noise associated with neural circuits with reduced inhibition. The neural network model employed in this paper is adapted from Chambers et al, and consists of a cochlear model that receives the sound signal and produces a synaptic signal to the all-to-all connected neurons representing the auditory cortex. The parameters of the neural network are initially trained to reproduce the experimentally observed ferret STRF's, and then the sensitivity of the STRF on variations of the model parameters are measured. Our results demonstrate the impact on the STRF of the excitation-inhibition ratio of the neural network.

Disclosures: K. Kuramitsu: None. **P. Cha:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

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Program #/Poster #: LBA004.046/LBA45

Topic: D.05. Auditory and Vestibular Systems

Support: Erasmus Mundus Cognitive Auditory Neuroscience Exchange Program
NIH/NICHD P50HD105328
NIH/NIMHD U54MD007597

Title: Chiropteran Neuroimaging: Structural and Functional Magnetic Resonance Imaging of the Pale Spear-Nosed Bat

Authors: *S. WASHINGTON[1], K. SHATTUCK[3], J. STECKEL[4], H. PEREMANS[5], E. JONCKERS[7], M. VAN DEN BERG[8], L. VAN RUIJSSEVELT[9], D. L. PRITCHETT[2], S. VON DEN BERG[10], S. SAVOIA[11], P. P. MITRA[12], S. LIN[1], P. WANG[1], M. VERHOYE[13], A. VAN DER LINDEN[13], K. ESSER[10], G. A. KELIRIS[6];

[2]Biol., [1]Howard Univ., Washington, DC; [3]Georgetown Univ., Washington, DC; [4]Univ. of Antwerp, Antwerp, Belgium; [5]Univ. of Antwerp, Antwerpen, Belgium; [6]Biomed. Sci., Univ. of Antwerp, Antwerp, Belgium; [7]Bio-Imaging Lab, Univ. of Antwerp, Antwerp, Belgium; [8]Bio-Imaging Lab., Bio-Imaging Lab, Univ. of Antwerp, Wilrijk, Belgium; [9]Bio-Imaging Lab. / Univ. of Antwerp, Antwerpen (wilrijk), Belgium; [10]Inst. of Zoology, Univrersity of Veterinay Med. Fndn., Hannover, Germany; [11]Cold Spring Harbor Lab., Laurel Hollow, NY; [12]Cold Spring Harbor Lab., Cold Spg Hbr, NY; [13]Bio-Imaging Lab., Wilrijk, Belgium

Abstract: Echolocating bats live huddled together in colonies comprising hundreds of individuals and use complex sounds to communicate and to navigate. These species make ideal subjects for functional magnetic resonance imaging (fMRI) studies of auditory social communication given their relatively hypertrophic limbic and auditory neural structures and their reduced ability to hear MRI gradient noise. Establishing the existence of neural networks related to social cognition (e.g., default mode-like networks or DMLNs) in order Chiroptera could pave the way towards a new frontier in the study of mammalian socialization and communication. We measured blood oxygenation level dependent (BOLD) signal at 7T from nine lightly anesthetized pale spear-nosed bats (*Phyllostomus discolor*). Specifically, we performed independent components analysis (ICA) and revealed 15 resting-state networks. We also measured neural activity elicited by noise ripples (on: 10 ms; off: 10 ms) that span the ultrasonic hearing range (20-130 kHz) of this species. Resting-state networks intersected parietal, occipital, and auditory cortices, along with auditory brainstem, basal ganglia, cerebellum, and hippocampus. We determined that two out of a possible four midline networks were the best candidates for DMLN. We also found two predominantly left and two predominantly right auditory/parietal cortical networks. Regions within all four auditory/parietal cortical networks have been demonstrated to respond to social calls. As expected by the emergence of side-band inhibition in the inferior colliculus, ultrasonic noise ripples significantly activated the auditory brainstem (cluster-level: $p=5.27 \times 10^{-5}$, FWE correction, kE=7613) yet deactivated the auditory/parietal cortex ($p=2.08 \times 10^{-9}$, FWE correction, kE=17452). Iterative ("jack knife") analyses revealed consistent, significant functional connections between left, but not right, auditory/parietal cortical networks and DMLN nodes, especially the anterior-most cingulate cortex. Thus, a resting-state network implicated in social cognition displays more distributed functional connectivity across left, relative to right, hemispheric cortical substrates of audition and communication in this echolocating bat species. The application of advanced histological methods to 12 ex-vivo *Phyllostomus discolor* brain samples that have also undergone structural imaging (i.e., T2-weighted 3D rapid spin echo and spin-echo diffusion weighted) increase the likelihood of generating detailed, 3D population-based atlases as a computerized anatomical reference for these and future chiropteran functional neuroimaging results.

Disclosures: S. Washington: None. **K. Shattuck:** None. **J. Steckel:** None. **H. Peremans:** None. **E. Jonckers:** None. **M. van den Berg:** None. **L. Van Ruijssevelt:** None. **D.L. Pritchett:** None. **S. von den Berg:** None. **S. Savoia:** None. **P.P. Mitra:** None. **S. Lin:** None. **P. Wang:** None. **M. Verhoye:** None. **A. Van Der Linden:** None. **K. Esser:** None. **G.A. Keliris:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.047/LBA46

Topic: D.05. Auditory and Vestibular Systems

Support: MSCA PROOPI340-USAL4EXCELLENCE

Title: Initiation of cortical Up states by auditory deviants: a mismatch negativity generation mechanism in unconscious states

Authors: *A. HOCKLEY[1,2], L. HERNÁNDEZ BOHÓRQUEZ[1,2], M. S. MALMIERCA[2,1]; [1]Univ. of Salamanca, Salamanca, Spain; [2]CANELAB, Inst. of Neurosci. of Castilla y León, Salamanca, Spain

Abstract: Cortical slow oscillations are the reliable changes between “Up” and “Down” states in the cortex, corresponding to high- and low activity levels. These synchronised state changes occur at a rate of 0.2-0.5 Hz and are a global event throughout the thalamus and cortex during slow-wave sleep and deep anaesthesia. Slow cortical oscillations are present in the deafferented cortex (e.g., *in vitro* or lesion studies), demonstrating that thalamocortical input is not required for generation, however intact preparations show that thalamocortical input increases slow oscillation frequency. Furthermore, thalamocortical activity precedes Up states, suggesting that thalamocortical activity is the initiator of Up states, and therefore controls Up state frequency. External somatosensory and visual stimuli have been shown to initiate cortical Up states, with the travelling wave of activity initiated from the relevant sensory cortex. Here we test initiation of cortical up states during the oddball paradigm in the urethane-anaesthetised rat. Long Evans female rats were implanted with ECoG arrays consisting of 6 silver-ball electrodes placed bilaterally over auditory cortex and medial prefrontal cortex. We recorded local field potentials and oscillatory activity from rats at 4 hours post-induction of anaesthesia with urethane. Auditory stimuli consisted of an oddball paradigm using a frequency pair of 10 and 14.142 kHz at a stimulus onset asynchrony of 250 ms. Here, we demonstrate that the urethane-anaesthetised rat exhibits strong spontaneous cortical slow oscillations, consisting of “Up” and “Down” states. Deviant stimuli of the oddball paradigm trigger cortical Up states, resulting in mismatch negativity signals across the cortex. With optimised inter-deviant timings this initiation is highly reliable. Such data provide evidence for thalamocortical initiation of cortical Up states, while suggesting a mechanism for MMN generation in unconscious states. It is tempting to speculate that these data may share some of the neural mechanisms that initiate cortical slow oscillations and mismatch negativity and/or P300.

Disclosures: A. Hockley: None. **L. Hernández Bohórquez:** None. **M.S. Malmierca:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.048/LBA47

Topic: D.05. Auditory and Vestibular Systems

Title: Variations in neural sensory encoding and prior expectation jointly account for biased auditory decision-making

Authors: *S. TUNE[1], I. BORSCHKE[1], E. GÜLGEÇ[1], N. DÜRRBECK[1], J. OBLESER[2]; [1]Univ. of Luebeck, Luebeck, Germany; [2]Univ. of Lübeck, Luebeck, Germany

Abstract: Perceptual decisions depend on integrating sensory evidence over time. Yet, the fate of incoming sensory information depends on the perceiver's current psychological and neural state, creating different sources of suboptimality: Prior expectations introduce perceptual biases; sensory evidence get weighted unequally over time; and not least sensory encoding fidelity varies in line with neural fluctuations. Here we ask how these processes jointly impact auditory decision-making and its metacognitive corollaries. In this EEG study (*N*=31, 18-33 yrs), participants listened to 1-sec trains of 20 clicks, each presented to either left or right ear (adapted from [1]). A Bernoulli process randomly presented clicks to either ear. Using a joystick, participants decided which side had more clicks. Prior expectations were manipulated via a preceding visual cue: For half of the trials, an informative (80% valid) cue indicated which ear was more likely to receive more clicks in a given trial. We here report evidence on different sources of suboptimality in perceptual performance: Psychophysical analysis showed that prior expectations from informative (vs. neutral) probabilistic cues induce a (left-right symmetric) response bias. A psychophysical kernel ("reverse correlation") analysis revealed a general upweighting of trial-initial and late-trial sensory information irrespective of prior expectations. These prior expectations, however, did bias sensory encoding at the level of auditory cortex, expressed as increased neural encoding strength contralateral to the cued ear (using EEG-based single-click encoding models). Inter-individual differences in perceptual performance were in part explained by these variations in neural sensory encoding, with overall better neural encoding accuracy resulting in increased sensitivity and more optimal decision-making. In sum, our results show how suboptimal perceptual performance arises from biases situated at different stages along the sensory processing hierarchy. [1] Keung et al. (2019). Nat Hum Behav.

Disclosures: S. Tune: None. **I. Borschke:** None. **E. Gülgeç:** None. **N. Dürrbeck:** None. **J. Obleser:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.049/LBA48

Topic: D.05. Auditory and Vestibular Systems

Title: Prior Information Modulates Communication between Prefrontal and Sensory Cortices of Monkeys Making Auditory Decisions

Authors: *C. ROACH[1], L. SURIYA-ARUNROJ[5], S. FU[2], J. I. GOLD[3], Y. E. COHEN[4]; [1]Univ. of Pennsylvania, Haddonfield, NJ; [3]Neurosci., [4]Dept. Otorhinolaryngology-Head Neck Surgery, [2]Univ. of Pennsylvania, Philadelphia, PA; [5]Chulalongkorn Univ., Bangkok, Thailand

Abstract: Perceptual decisions can be influenced strongly by learned cued expectations but exactly how and where in the brain this influence is exerted is not well understood. One possibility is that 'higher-order' brain areas like the prefrontal cortex, which encodes learned rules and expectations, applies top-down modulation to sensory areas like the primary auditory cortex (AC) to modulate perceptual decision-making. To test this idea, we trained two animals to perform an auditory discrimination task in which they reported (via joystick) whether a target tone was a 'high' or 'low' frequency. We titrated task difficulty by embedding the target in various levels of background noise. We preceded target onset by either an informative visual prior or a non-informative acoustic prior. While the monkeys performed the task, we simultaneously recorded from the ventrolateral prefrontal cortex (vlPFC) and AC using 24-channel linear arrays positioned perpendicularly across cortical layers. We analyzed the spectral properties of the local field potential (LFP) in both areas and quantified interareal communication (LFP-LFP coherence, Granger causality, and cross correlation) across different task epochs. We hypothesized that if a top-down signal from vlPFC was modulating AC responses, an evoked spectral event, likely in lower-frequency bands (theta-beta), would reliably occur between the onset of the LED and presentation of the target tone. Moreover, this event would be correlated with: a) a change in AC responsiveness to the test tone, b) an increased coherence, and c) an elevation Granger signaling in the PFC-to-AC direction. We found that correct trials in which the informative visual prior was presented were characterized by greater theta and beta coherence in the superficial and upper-middle layers of AC. Directional metrics indicate that this change in coherence was driven by information arriving from dlPFC during the presentation of priors. These preliminary findings support the idea that top-down influences on auditory perceptual decision-making involve context-dependent communication from vlPFC to AC.

Disclosures: C. Roach: None. **L. Suriya-Arunroj:** None. **S. Fu:** None. **J.I. Gold:** None. **Y.E. Cohen:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.050/LBA49

Topic: D.05. Auditory and Vestibular Systems

Support: University at Buffalo Research and Creative Activities for Undergraduates Program
University at Buffalo start-up funding

Title: Auditory neural processing and cognitive predictors of speech-in-noise understanding

Authors: I. KLOIBER, *M. DININO;
Univ. at Buffalo, Buffalo, NY

Abstract: Understanding speech in background noise requires precise neural coding of simultaneous auditory signals. It has thus been thought that young adults with difficulty perceiving speech presented with competing sound have impaired subcortical neural processing, but prior evidence is mixed. This study delved deeper into this potential relationship by using a test of speech-in-noise perception designed to be maximally sensitive to auditory subcortical processing, more precisely targeting neural mechanisms than tasks used in previous studies. Twelve normal hearing young adults attended to a sentence spoken by a target talker and ignored a simultaneously presented sentence spoken by a competing talker. Both talkers were canonically male but differed in voice pitch. Participants heard the word “and” spoken by the target talker at the beginning of each trial, cueing them to which voice pitch they should attend. However, sentences were high-pass filtered to remove fundamental frequency and the first eight harmonics, leaving only unresolved harmonics that do not produce clear cochlear excitation peaks; only pitch encoded by auditory nerve phase-locking (not cochlear place coding) remained. Participants indicated what the target talker said on each trial, representing their ability to use pitch coded by the auditory nerve to differentiate between the two talkers. Each participant also underwent recording of auditory brainstem responses to assess subcortical processing of sound and completed NIH Cognitive Toolbox tasks to assess executive function/attention and memory. Statistical analysis compared measures of auditory subcortical and cognitive function to speech perception task performance. Surprisingly, although the speech perception task was optimized to reflect neural processing, and although we observed substantial variability in subcortical wave amplitudes and latencies among participants, cognitive factors were a much stronger predictor of speech perception scores. Executive function and attention best predicted speech perception task performance. These results suggest that young adults with poorer auditory nerve function can compensate for reduced auditory perception with better executive function and attentional skills, informing the mixed results from previous studies in this area: adaptive cognitive processes may have obscured the relationship between auditory neural function and speech-in-noise perception scores. This work also provides insight into potential compensatory strategies for individuals with reduced auditory neural processing, a disorder of unspecified cause with no currently available treatment options.

Disclosures: I. Kloiber: None. **M. DiNino:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.051/LBA50

Topic: D.05. Auditory and Vestibular Systems

Support: CONACyT & DGAPA postdoctoral fellowships to YAA

Title: Neural activation of auditory cortices during rhythmic behavior in rhesus macaques

Authors: *Y. A. AYALA[1,2], J. P. MARQUEZ GUTIERREZ[1], L. PRADO[1], H. MERCHANT[1]; [1]Inst. of Neurobiology, Natl. Autonomous Univ. of Mexico, Queretaro, Mexico; [2]Dept. of Neurosurg., Univ. of Iowa Hosp. and Clinics, Iowa City, IA

Abstract: Sensory-guided rhythmic behaviors require to compare movement-related signals with the ongoing sensory flow from moment to moment. Here, we aim to understand the activation dynamics of the auditory cortices during sensorimotor synchronization in the scale of the hundreds of milliseconds (550-850 milliseconds). To do this, we trained two rhesus macaques to perceive and then synchronize their hand movements to auditory metronomes that vary in their inter-sound interval on a trial-by-trial basis. Extracellular activity was simultaneously recorded in the auditory cortices using silicon linear probes. First, macaques were able to predictively entrain to the auditory metronomes performing anticipatory movements to the ongoing sensory events. Second, we observed segregable activation profiles in both core and caudal belt cortical regions during sensation, perception, and behaving conditions. The temporal structure of the metronomes was represented as phasic and short-duration power enhancements across frequency bands (0.5-140 Hz) during the passive listening and mainly in the supra- and granular layers. This feedforward sensory-driven activation profile switched to bursts of power enhancement and suppression in the delta, theta, and betta bands during the synchronization but not perception phase. Also, these frequency bands exhibited an oscillatory and buildup enhancement mainly in the infragranular layers. Second, segregable groups of neurons exhibited shorter latencies and less variable activation to sensory or motor events in both core and belt areas. Remarkably, we identified auditory cortical neurons that were active only during the synchronization phase with a buildup activation profile across the serial order of the metronome. Finally, the unexpected omission of sounds within the metronome elicited a change in both directions, i.e., increase and decrease in the firing activity of different set of neurons. The results reveal that strong feedback behavior-related signals dynamically and differentially change LFP oscillations, set of neurons and layers as the animals entrain their movements to the regularity of the auditory sequences. Our study contributes to probe sensorimotor neural circuits that support closed-loop and continuous behaviors.

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Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.052/LBA51

Topic: D.05. Auditory and Vestibular Systems

Support: Yale University Start Up Funds

Title: Cannabis use frequency interacts with psychotic illness to predict greater perceptual prediction error signaling, perceived environmental volatility, and psychotic-like symptoms.

Authors: *M. S. GREENWALD, A. BOND, A. R. POWERS, III;
Psychiatry, Yale Univ., New Haven, CT

Abstract: Cannabis is the most used drug in the world. Despite converging evidence suggesting cannabis causally increases psychosis risk—especially for those with psychosis or clinical high risk—how it mechanicistically influences pro-psychotic processes remains unknown. Computational modeling of behavioral task data consistently suggests psychotic symptoms result from derangements in predictive processing machinery. In particular, hallucination severity consistently tracks with conditioned hallucination rate and Hierarchial Gaussian Filter (HGF)-estimated prior weighting in the Conditioned Hallucinations (CH) task. Here, we investigate how cannabis use affects psychotic-relevant parameters by studying how CH task behavior and HGF parameters vary by frequency of cannabis use. We used a large (N=516), previously analyzed, online sample of individuals with a variety of psychotic-like experiences. Participants indicated current cannabis use frequency on a 6-point forced choice scale before performing the CH task and completing self-report clinical inventories. Cannabis frequency's effect on CH and HGF parameters was tested using Bayesian Model Regression and Markov Chain Monte-Carlo (MCMC) sampling. We used monotonic priors for cannabis use frequency and performed analyses of all subjects combined and split into those with (N=84) and without (N=432) psychotic spectrum diagnoses. Parameter propriety and MCMC sampling convergence were verified via posterior predictive plots and r-hat statistics, respectively. Cannabis use predicted greater symptom burden and lower CH rates in both those with and without psychosis. However, the negative relationship between cannabis use and CH rate significantly stronger in those with diagnoses (B = -0.228, 95% CI [-0.302, -0.158]) compared to those without (B = -0.0353, 95% CI [-0.0476, -0.0236]). Additionally, only in those with psychosis did cannabis use predict greater precision-weighted prediction errors (B = 0.692, 95% CI [0.348, 1.04]) and belief in task volatility (B = 0.0371, 95% CI [0.0246, 0.0497]) but not prior weighting. Results were similar after matching cannabis-users to non-users by race, age, medication use, and hallucination

endorsement. These results suggest that cannabis's pro-psychotic effects may result from selective augmentation of volatility perception and prediction error precision—particularly in vulnerable groups. These effects are consistent with aberrant learning from noise thought to exist in prodromal psychosis. Future work should 1) study whether these effects are due to recent use vs. cumulative exposure and 2) employ cognitive tasks targeting belief updating.

Disclosures: M.S. Greenwald: None. **A. Bond:** None. **A.R. Powers:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.053/LBA52

Topic: D.05. Auditory and Vestibular Systems

Support: VA Grant IK2RX003271
NIH Grant 1R01AG073157
VA Grant I01RX003250

Title: Rapamycin reduces noise-induced vestibular loss and improves walking speed in noise exposed rats

Authors: M. ANDERSON[1], D. BAUER[2], W. M. KING[3], R. A. ALTSCHULER[4], *C. STEWART[5];
[1]Kresge Hearing Res. Inst., Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [2]Kresge Hearing Res. Inst., Univ. of Michigan, Ann Arbor, Brighton, MI; [3]Dept Otolaryngology, Univ. of Michigan, Ann Arbor, MI; [4]Dept Otolaryngology, Univ. Michigan, Ann Arbor, MI; [5]LTC Charles S Kettles VAMC, Ann Arbor, MI

Abstract: Rapamycin acts on mammalian Target of Rapamycin (mTOR) which influences multiple functional signaling pathways involved in cell protection and survival. It has been demonstrated that rapamycin, added to diet, significantly reduced hearing loss following noise exposure. Using a previously established noise exposure paradigm (free-field120 decibel sound pressure level band-limited noise, 0.5-4 kHz), we have demonstrated that in addition to causing hearing loss, this noise exposure causes changes in innervation and function of the vestibular periphery. It is unclear if rapamycin may improve vestibular evoked short-latency potentials and provide functional benefits (prevent slower walking speed) previously demonstrated in our work, in noise exposed rats. Therefore, the goal of this work was to assess benefits of rapamycin treatment in noise-exposed rats.
Rats were trained to cross a 1-meter balance beam before receiving a single 6-hour 120 dB noise exposure at 5-months of age. After noise exposure, rats were tested on the balance beam until they reached 1-year of age. A commercially prepared pelleted chow diet containing encapsulated

rapamycin or vehicle was given to rats at a dose of approximately 42 mg/kg body weight per day. Diet was started one week prior to noise exposure and continued for 8-weeks after noise exposure. Prior to starting the experimental diet and after 8-weeks on the diet, rats were given standard chow.
Rats that received the rapamycin and vehicle diets showed an initial effect of noise exposure, with an approximately 25% increase in balance beam crossing time. However, rats that received rapamycin showed improvement over the next two weeks and had only a small elevation in balance beam crossing time within 3-weeks of the noise exposure that returned to baseline within 4-weeks of noise exposure. This effect persisted after discontinuation of the diet. Furthermore, rats that received the rapamycin diet following noise exposure crossed the balance beam at a speed similar to baseline at one year of age versus vehicle treated rats which had significantly slower balance beam crossing times. Additionally, VsEP amplitude was significantly larger in rats that received the rapamycin diet versus rats that received the vehicle diet.
These results demonstrate a protective effect on the vestibular periphery and a significant improvement in walking speed, both, shortly after noise exposure and for months after discontinuation of the rapamycin diet. Taken together, these results demonstrate a measurable effect of rapamycin that may have long-term benefits for mobility and vestibular function.

Disclosures: M. Anderson: A. Employment/Salary (full or part-time):; University of Michigan. **D. Bauer:** A. Employment/Salary (full or part-time):; University of Michigan. **W.M. King:** None. **R.A. Altschuler:** A. Employment/Salary (full or part-time):; University of Michigan, Department of Veterans Affairs. 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.; VA RR&D I01 RX003250-01A2. **C. Stewart:** A. Employment/Salary (full or part-time):; Department of Veterans Affairs. 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.; VA RR&D IK2RX003271; NIA/NIDCD R01AG073157.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.054/LBA53

Topic: D.06. Vision

Support: NIH Grant EY032564

Title: Intrinsically photosensitive midget ganglion cells in primate retina

Authors: *T. GARRETT[1], J. LEFFLER[1], J. LITZ[1], B. SIVYER[2];
[1]Casey Eye Inst., Oregon Hlth. & Sci. Univ., PORTLAND, OR; [2]Casey Eye Inst., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: High acuity vision in primates is relayed to the brain by midget (MG) retinal ganglion cells (RGCs) projecting to the parvocellular region of the lateral geniculate nucleus (PMID: 3980768; PMID: 8254378; PMID: 7268423; LGN). In mice, a subtype of intrinsically photosensitive retinal ganglion cell (ipRGC), ONs-α or M4 ipRGCs, use the visual pigment protein melanopsin (encoded by the *Opn4* gene) to enhance contrast sensitivity (PMID: 30017393). However, in primate, melanopsin has not been detected in MG RGCs—which mediate high acuity vision and account for over 80% of RGCs. We combined immunohistochemistry for RGC markers (RBPMS and melanopsin) with fluorescence in situ hybridization (FISH) to identify ipRGC types in primate retina. IpRGCs expressed high levels of *Opn4* mRNA and were sparsely distributed throughout the ganglion cell and inner nuclear layers of the retina. Surprisingly, we find that *Opn4* mRNA is also expressed in high-density midget ganglion cells. Larger parasol ganglion cells did not express *Opn4*. Further, midget ganglion cells, but not parasol ganglion cells, express *Eomes* mRNA, a transcription factor which defines ipRGC identity. We used cell-attached electrophysiology recordings to confirm MG intrinsic photosensitivity. Activation of putative melanopsin protein with blue light increased MG baseline spike rate at photopic light intensities, indicating melanopsin plays a role in the visual perception of luminance. Our results: 1) support the presence of *Opn4* mRNA expression by MG in single-cell RNA sequencing studies (PMID: 30712875), 2) provide additional evidence that MGs express transcription factors associated with ipRGC lineage (PMID: 35191836), 3) demonstrate primate image forming vision is directly modulated by melanopsin phototransduction in the retina.

Disclosures: T. Garrett: None. **J. Leffler:** None. **J. Litz:** None. **B. Sivyer:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

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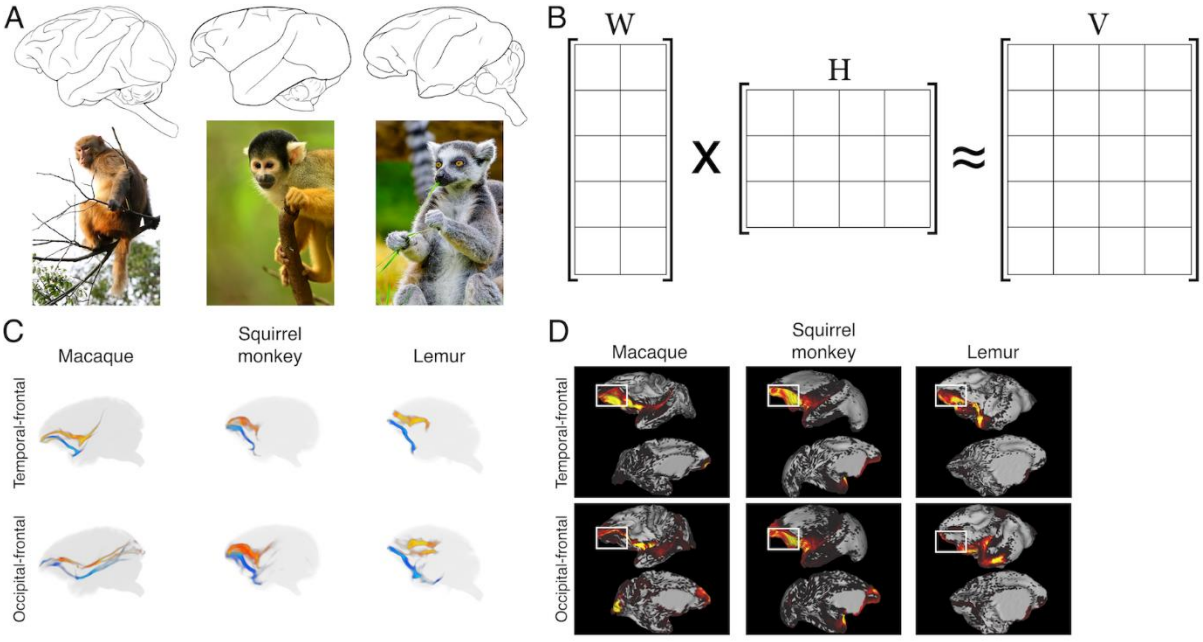
Topic: D.06. Vision

Support: Wellcome Trust (222368/Z/21/Z)
Biotechnology and Biological Sciences Research Council UK (BB/N019814/1)
Wellcome Trust (203129/Z/16/Z)
European Research Council (ERC Consolidator 101000969)

Title: An anthropoid/strepsirrhine divergence in ventral stream connectivity

Authors: *J. E. HUNT[1], S. WARRINGTON[2], L. ROUMAZEILLES[1], S. JBABDI[1], Z. MOLNÁR[1], S. SOTIROPOULOS[2], R. B. MARS[1,3];
[1]Univ. of Oxford, Oxford, United Kingdom; [2]Univ. of Nottingham, Nottingham, United Kingdom; [3]Radboud Univ. Nijmegen, Nijmegen, Netherlands

Abstract: The ventral visual stream has undergone extensive reorganisation within the primate lineage. While some work has examined restructuring of the ventral prefrontal cortical grey matter across primates, comparative studies of white matter connectivity are lacking primarily due to difficulties in data acquisition and processing. Here, we present a data-driven approach to the study of white matter connectivity using diffusion MRI data. Studying two anthropoids and one strepsirrhine — the rhesus macaque, the black-capped squirrel monkey, and the ring-tailed lemur (Panel A) — we use the unsupervised dimensionality reduction algorithm non-negative matrix factorisation (Panel B) to reconstruct temporal-frontal and ventral occipital-frontal connections in each species (Panel C). We find that the anthropoids exhibit more dorsal prefrontal innervation of these ventral visual connections (Panel D). Statistical analysis shows that these cross-species differences are far larger than any within-species differences arising from, e.g., biological sex or life history. This study supports the hypothesis that anthropoid primates underwent extensive reorganisation of both grey and white matter during their emergence as visual foragers in a complex ecological niche. The data-driven techniques presented here enable further research on white matter connectivity in previously understudied species.



Disclosures: J.E. Hunt: None. **S. Warrington:** None. **L. Roumazeilles:** None. **S. Jbabdi:** None. **Z. Molnár:** None. **S. Sotiropoulos:** None. **R.B. Mars:** None.
Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.056/LBA55

Topic: D.06. Vision

Support: NEI IRP

Title: Patterns of cholinergic innervation in the superior colliculus of the mouse

Authors: *Z. JOY, C. MEJIAS-APONTE, R. J. KRAUZLIS;
Lab. of Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

Abstract: The midbrain superior colliculus (SC) is a crucial component of the visuomotor system. The SC coordinates eye, head, and neck movements in response to environmental cues. The superficial SC (sSC) is a recipient of retinal and primary visual cortex inputs whereas the intermediate SC (iSC) receives inputs from secondary visual cortices and additional sensory information from auditory and somatosensory systems. Both the sSC and iSC also receive modulatory cholinergic inputs from the pedunculopontine nuclei and the lateral dorsal tegmental nucleus. We were interested in determining whether the expression of neurotransmitter markers can selectively demarcate SC subregions and possible functional distinctions across the SC retinotopic map. In this study, we chose cholinergic innervation (CI) as a putative target, as the expression and distribution of cholinergic axons are relatively conserved in the SC across species, making this an attractive biomarker for possible cross-species neuroanatomical comparisons. To determine CI distribution, we immunostained for vesicular acetylcholine transporter in the mouse brain. Sections were collected serially in a coronal plane and the distribution of CI was analyzed anteriorly (central visual field) to posteriorly (more peripheral). Within the sSC, a dense band of fibers was observed within the superficial gray layer (SGL) that was most dense in the anterior SC and became less dense posteriorly. Medially, (upper visual field), the band was less uniform and formed a mediolateral gradient which extended throughout the SGL and into the zonal layers. In contrast, within the iSC, CI density increased anteriorly to posteriorly. In anterior and middle portions of the iSC, CI fibers formed a thin, dorsal band and a thick, ventral band with additional dense patches between them. These bands were present medially whereas laterally, CI fiber density was uniform and less dense. Posteriorly, where the SC abuts the inferior colliculus, both bands were still present and uniformly distributed. Based on our initial assessment, CI distribution is not uniform across the posterior-anterior and medial-lateral axes of the SC. Immunostaining in the sSC is characterized by a band of fibers that is densest anteriorly and decreases posteriorly, indicating a bias in the cholinergic innervation towards the central visual field. Conversely, the iSC is characterized by an overall denser cholinergic innervation that increases in density in more posterior sections. These findings suggest that cholinergic modulation in the mouse SC has a central bias in the superficial visual layers and a peripheral bias for the deeper sensory-motor layers

Disclosures: Z. Joy: None. **C. Mejias-Aponte:** None. **R.J. Krauzlis:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.057/LBA56

Topic: D.06. Vision

Support: NIH Grant GM143545

Title: Whole Brain Atlas of ipRGC Projections and Light-induced Activity

Authors: *A. KANG, J. D. BHOI, T. M. SCHMIDT;
Neurobio., Northwestern Univ., Evanston, IL

Abstract: Light is one of the most fundamental features of an animal's environment and modulates behavior and physiology to allow animals to adapt to changes in their environment. Retinal ganglion cells (RGCs), the output cells of the retina, are a diverse class of over forty cell types, each of which sends highly processed visual information to more than 50 retinorecipient targets in the brain. The intrinsically photosensitive (ip)RGCs are a class of RGCs which express the photopigment melanopsin, endowing them with sensitivity to light independent from rod and cone input. ipRGCs project to more than 20 of the 50 retinorecipient brain regions in the mouse and play an essential role in both subconscious visual functions and conscious visual perception. While the RGC projections to the brain have been extensively mapped, the full extent of how light input from the retina functionally impacts the brain through RGCs, and how ipRGCs specifically contribute to this activation, remains an open question. The goal of the current study is to create a whole brain map of ipRGC projections and light-induced cFos expression and to identify the brain areas where cFos expression is driven by ipRGCs.
To label ipRGCs and to stimulate RGCs, male and female *Opn4*^{Cre} mice were injected intravitreally with AAV2-hSyn-FLEX-Chrimson-TdTomato virus. We then stained the ipRGC projections immunohistologically to identify the axonal projections. To stimulate RGCs, we exposed both male and female control and melanopsin null littermate mice to a 15-minute pulse of 1000 lux, broad spectrum light. Following light exposure, we used immunohistochemistry to stain brain sections for the immediate early gene cFos. We then registered individual brain sections to the Allen Mouse Brain Common Coordinate Framework and quantified ipRGC projections and cFos expression.
We find that ipRGCs project to over 20 brain regions in the mouse brain, often with intra-regional specificity. Furthermore, we find that light induces cFos expression in many brain regions, including canonical visual regions such as the lateral geniculate nucleus and non-canonical visual regions such as the medial amygdala. Interestingly, we observed cFos immunoreactivity in brain regions which do not receive direct retinal input, indicating that this technique can reveal regions downstream of retinorecipient areas. These atlases will contribute to

our current understanding of visual processing, and it will serve as a critical resource for research investigating the influence of light on a wide range of neural circuits.

Disclosures: A. Kang: None. **J.D. Bhoi:** None. **T.M. Schmidt:** None.

Late-Breaking Poster

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Program #/Poster #: LBA004.058/LBA57

Topic: D.06. Vision

Support: NIH 2R01EY027718

Title: Presynaptic cholinergic regulation of categorical selection in the optic tectum

Authors: *L. ZHANG[1], S. P. MYSORE[2];
[2]Psychological and Brain Sci., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: Categorical neural representations, which exhibit large, discrete transitions in response magnitudes at group boundaries, are found ubiquitously across brain areas and animal species. They powerfully enhance the reliability of selecting the correct category specifically when inputs are close to the boundary (or when competing stimuli of different categories are perceptually similar). In the barn owl midbrain, we recently discovered a circuit mechanism that explicitly generates categorical neural responses, namely: a donut-like inhibitory circuit motif. Specifically, we found that inhibitory neurons in the midbrain tegmentum, Imc, which receive focal input from the topographically organized sensorimotor hub, the optic tectum (OT, superior colliculus in mammals), project back to all locations of the OT space map except their inputs. This discovery, however, opened up a fundamental question. Namely, how might such an anatomically instantiated circuit mechanism be modulated dynamically to regulate the degree of categorization? This question is of significant import because cognitive functions such as spatial attention are known to dynamically improve neural representations at relevant locations, with top-down influences shown to alter the categoricalness of OTid neural responses underlying spatial selection. Here, through a biologically plausible model, we first demonstrate that excitatory input that multiplicatively enhances Imc responses can regulate the degree of categorization in OTid responses. Then, building on published anatomical reports of puzzling cholinergic inputs onto Imc, we show with Imc recordings and iontophoretic cholinergic blockade that this cholinergic input multiplicatively enhances Imc evoked responses. Next, we perform paired electrophysiological recordings in spatially aligned and misaligned OT and Imc sites, with and without iontophoretic blockade of cholinergic receptors at Imc, and test whether this cholinergic input modulates categorization in OTid. By comparing the categorization index of neural response profiles to competing stimuli in OTid across drug conditions, we show that

cholinergic input onto Imc regulates the degree of categorical signaling in OTid during competition. This powerful neuromodulatory mechanism may serve to regulate the categoricalness of neural responses during spatial decision-making.

Disclosures: L. Zhang: None. **S.P. Mysore:** None.

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Topic: D.06. Vision

Support: NSF CAREER 2047298

Title: Two spatial scales of competitive interactions in the mouse superior colliculus

Authors: *A. BANERJEE[1], N. B. KOTHARI[1], S. P. MYSORE[2];
[2]Psychological and Brain Sci., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: The midbrain superior colliculus is a major sensorimotor hub across vertebrates. It is known to be critically involved in selective spatial attention and spatial decision-making, with competitive interactions across its topographic map of space, specifically, in its intermediate and deep layers (SCid), playing a fundamental role. However, the nature of competitive stimulus interactions across the mammalian SCid space map is poorly understood. Here, with electrophysiological recordings from the SCid of head-fixed, awake mice passively viewing single and pairs of visual stimuli (N=6; 4 male, 2 female), we demonstrate that competitive interactions operate on two spatial scales following distinct rules. SCid neurons typically exhibit two inhibitory surrounds: a classical surround operating just outside the excitatory RF center, and a much larger extra-classical surround operating beyond the reaches of the classical surround. We investigated competitive interactions both within and outside the classical inhibitory surround. We found that competitive suppression due to the spatially restricted classical surround decreased as a function of distance from the RF center, whereas suppression across the extra-classical surround operated globally, staying largely constant in magnitude independently of the distance between the competing stimuli. Notably, competitive interactions within the classical surround followed a sub-additive rule relative to the responses to the stimuli presented individually, whereas those across the extra-classical surround followed a divisive rule. Together, our findings reveal two spatial regimes of functional competitive interactions across the SCid space map, and suggest the existence of separate inhibitory circuits mediating them (and the corresponding inhibitory surrounds). They also provide evidence for the space-invariant representation of long-range stimulus competition in mouse SCid.

Disclosures: A. Banerjee: None. **N.B. Kothari:** None. **S.P. Mysore:** None.

Late-Breaking Poster

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Topic: D.06. Vision

Support: Charles University PRIMUS/24/MED/007

Title: Cortical ripples in the resting state organize into large-scale events

Authors: K. STUDENICOVÁ[1], X. CHEN[2], ***K. KORVASOVÁ**[1];
[1]Fac. of Mathematics and Physics, Charles Univ., Prague 2, Czech Republic; [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Cortical ripples are short bursts of high gamma activity observed in many areas across the brain, yet their function is unknown. Unlike hippocampal sharp-wave ripples, they are typically not associated with a sharp wave in the LFP, but tend to appear in a cortical up-state. To understand under which conditions cortical ripples occur, whether they are functionally specific and how they relate to the spiking of local neurons, we investigated cortical ripples in spontaneous, as well as visually evoked neural activity in the early visual cortex of two male macaque monkeys recorded with 16 Utah arrays per animal (14 in V1, 2 in V4, data from Chen et al. 2020). The resting state activity was recorded in a dark room and the time stamps when the monkey opened or closed the eyes were extracted. During the resting state, cortical ripples appeared significantly more frequently when the monkey had the eyes closed for an extended period of time. The ripples were organized into large-scale events often spanning across the V1 and V4 areas and occasionally spreading as a traveling wave with a clear direction. With the eyes open, such strong spatio-temporal organization was missing. On the global level, events of cortical ripples temporally strongly correlate with spiking activity of neurons. However, the channel-wise correlation is variable and depends on the brain state. Particularly, the single channel cross-correlations between ripples and neuronal spikes in the V1 are higher during the resting state compared to the visually evoked condition. To assess whether channels can be assigned with orientation preference with respect to cortical ripples, we analyzed ripple responses to drifting oriented gratings. Channels exhibited a clear orientation preference, yet the orientation preference map had a smaller spatial frequency compared to the one derived from multi-unit activity. Next, we asked the question whether spontaneous ripple events exhibit any functional specificity with respect to orientation preference. To that end, we defined a set of significantly activated channels for each event (above chance compared to baseline during events), referred to as motifs. Interestingly, the motifs extracted from ripples and multi-unit activity (MUAe) envelope during a ripple event were often disjoint. We found that both MUAe and ripple motifs were indeed biased towards a consistent orientation preference, suggesting that

cortical ripples are functionally relevant. Further research is needed to mechanistically explain the relationship between cortical ripples and neural spiking activity and their exact function.

Disclosures: K. Studenicová: None. **X. Chen:** None. **K. Korvasová:** None.

Late-Breaking Poster

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Program #/Poster #: LBA004.061/LBA60

Topic: D.06. Vision

Support: NSERC Discovery Grant RGPIN-2019-06741
NSERC Discovery Grant RGPIN-2019-05690

Title: Attention differentially modulates anti-phasic BOLD responses in the human visual cortex

Authors: *R. RAFEH[1], G. NGO[3], L. E. MULLER[4], A. KHAN[5], R. S. MENON[7], M. C. MUR[6], T. W. SCHMITZ[2];
[2]Dept. of Physiol. and Pharmacol., [1]Univ. of Western Ontario, London, ON, Canada; [3]Physiol. & Pharmacol., [4]Dept. of Mathematics, [5]Robarts Res. Inst., [6]Psychology, Western Univ., London, ON, Canada; [7]Imaging Res. Labs, Robarts Res. Inst., London, ON, Canada

Abstract: Visual attention is a top-down mechanism that serves to regulate the competition between neural ensembles. On a neural level, attention acts through multiple processes: 1- attention enhances the activity of neural ensembles that represent the attended information in the visual environment, and 2- attention suppresses the activity of neural ensembles that represent information that falls outside of the locus of attention. Monkey electrophysiology research has shown that selective attention mediates the enhancement of behaviorally relevant information independently of the suppression of irrelevant information (Chen et al., 2008). Electrophysiology studies in humans suggest that the attention-driven enhancement and suppression of visual stimuli occur via distinct parallel network interactions along the visual hierarchy, where inter-areal signalling is involved in target enhancement whereas intra-areal signalling is involved in surround suppression (Yang et al., 2023). However, the poor spatial resolution of electrophysiological measurements in humans cannot directly gauge sensory processing along the visual hierarchy, limiting the interpretations of such observations. Functional magnetic resonance imaging (fMRI) can distinguish proximal visual hierarchical regions via high spatial precision measurements of blood-oxygen-level-dependent (BOLD) activity. Simultaneous fMRI and electrophysiological recordings in the monkey visual cortex have shown that the stimulus-driven enhancement and suppression of neural activity are correlated with respective increases and decreases in fMRI BOLD responses (Shmuel et al., 2006). Hence, the BOLD signal could serve as an indicator as to whether attention mediates the enhancement and suppression of

signalling along the human visual hierarchy through distinct mechanisms. In this 7T fMRI experiment, we use a frequency-tagging design to disentangle stimulus-driven increases and decreases in BOLD responses based on the phase of these responses in 7 participants. We isolated visual populations responding in-phase with the stimulus, and those responding anti-phase, and we examined how focal attention modulates these anti-phasic responses along the early visual hierarchy. We found that attention increasingly enhances in-phase but not anti-phase responses ascending the visual hierarchy, suggesting that attention-driven changes in the responses of these distinct populations are mediated by different mechanisms that are reflected in the fMRI BOLD signal.

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Topic: D.06. Vision

Support: NIH U01NS126057
EMBO ALTF 712-2021

Title: Mapping mouse visual cortex with zebra noise

Authors: *S. SKRIABINE[1], M. SHINN[2], S. A. PICARD[5], A. HAYDAROGLU[3], A. LIU[4], K. D. HARRIS[2], M. CARANDINI[2];
[1]UCL, London, United Kingdom; [3]Inst. of Neurol., [4]Inst. of Ophthalmology, [2]Univ. Col. London, London, United Kingdom; [5]Dept. of Physiology, Anat. and Genet., Univ. of Oxford, Oxford, United Kingdom

Abstract: The mouse visual cortex is widely used in studies of cortical processing. A first step in such studies is to map the basic visual preferences of the neurons: receptive field location and size, and tuning for spatial frequency, orientation, and direction of movement. To this end, we developed a dynamic stimulus called “zebra noise” and a simple analysis method based on Gabor wavelets. We generated the “zebra noise” by thresholding Perlin 3D fractal noise with a comb-like function. The resulting movie has black and white curved stripes drifting in random orientations and directions. It resembles the “trippy” stimulus of Yatsenko et al (2018) but is more efficient to synthesize and has improved visual properties, with sharp edges and with uniform statistics across space. To fit neuronal responses, we modeled each neuron as having input from spatiotemporal Gabor wavelets of multiple phases but a single position, size, spatial frequency, orientation, and direction of motion, followed by an arbitrary nonlinearity. To test the

stimulus and the model, we used two-photon imaging (with standard microscopes or with a Light Beads Microscope) to record from thousands of neurons in V1 and higher visual areas of head-fixed transgenic mice expressing GCaMP6s in all excitatory neurons or specifically in layer 5 pyramidal neurons. We assessed the repeatability of neuronal responses to different stimuli, by measuring the correlation of responses across repeats of the same stimulus sequence. The responses to zebra noise stimuli were nearly twice as repeatable as responses to sequences of black and white squares (sparse noise) which is commonly used to map receptive fields. The model based on Gabor wavelets allowed robust simultaneous mapping of preferred position, orientation, direction, and phase tuning. It explained 15-20% of the variance of the activity in visually-driven neurons, with similar performance in V1 and higher areas. Robust performance was obtained with as little as 10 minutes of zebra noise (presented 3 times), with longer durations providing only marginal improvement.Together, the zebra noise and the Gabor wavelet analysis constitute a highly effective method for characterizing the visual preferences of thousands of neurons in the mouse visual cortex. We are currently exploring its use for mapping synaptic activity (with iGluSnfr) and for comparing the selectivity of neurons across layers and areas of the visual cortex.

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Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.063/LBA62

Topic: D.06. Vision

Title: Gazo: a standalone modularized light-weighted BCI device

Authors: *C.-C. TSAO, Y.-T. WANG, Y.-L. CHU;
Res. Ctr. for Information Technol. Innovation, Academia Sinica, Taipei, Taiwan

Abstract: This study designed and 3D-printed a portable, standalone, and monocle electroencephalogram (EEG)-based brain-computer interface (BCI) system, named Gazo, to assess the feasibility of a see-through steady state visually evoked potentials (SSVEP) paradigm. Gazo consists of one sensing headset and one display module. The sensing headset can not only read 3-channels EEGs located on the occipital lobe but also, with the expansion module applied, can cover 3 additional channels spanning from the frontal lobe to the parietal lobe by a rotating joint. While traditional SSVEP provides a promising signal-to-noise ratio (SNR) among EEG-based BCI systems, the paradigm that asks users to gaze at a visual stimulus with two eyes limits its real-world applications. For instance, it may not be ideal to ask a driver to shift both eyes' attention to one visual stimulus. Therefore, we proposed the monocular display module,

equipped with a transparent screen, as a solution to provide visual stimuli to induce SSVEP and also serve as a simple graphic user interface while reducing the impact on vision. The display is connected to an ESP32 board, features wireless communication via WiFi and Bluetooth, capacitive touch, and an IMU sensor. Based on Gazo, we first assessed the SSVEP response and then focused on one prospective use case - the SSVEP-based person identification. There were 6 participants joined this study. They wore the Gazo and were asked to gaze at the 8Hz visual stimulus for 5 seconds and repeat 5 times. There was a 3-second break between each 5-second trial. The results showed a 7% SNR difference between the stimulating state and resting state, which demonstrates the feasibility of a single eyeglass-based SSVEP paradigm. In person identification, we built a machine learning pipeline with tree-based models utilizing an existing dataset (Y. Sun et al., 2024) to identify specific subjects. The average false positive rate (FPR) and false negative rate (FNR) of 5-fold cross-validation over 13 subjects were calculated, showing that both models perform well in person identification: decision tree has a FPR of 1.73% and a FNR of 16.15% while random forest has a FPR of 1.28% and a FNR of 13.85%. Gazo, as a lightweight, low cost, and wearable BCI device, is designed and 3D-printed for easy setup and mobile usage across multiple use cases. The present study demonstrates its potential in user authentication through viable visual stimulation and a reliable authentication pipeline. The adopted modular design enhances adaptability for future developments, which could lower the production and development costs and position Gazo as a product with significant room for expansion and broad applications.

Disclosures: C. Tsao: None. **Y. Wang:** None. **Y. Chu:** None.

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Title: Similar Signatures of Familiarity for Action Sequences and Image Sequences in Visual Area V4

Authors: *L. KRAMER[1], M. R. COHEN[2];
[2]Neurobio., [1]Univ. of Chicago, Chicago, IL

Abstract: Humans and other animals tend to lump sequences of actions into repeated routines, such as walking to work the same way each time. Psychology literature suggests that visual perception differs while performing novel sequences of actions as compared to familiar routines, even when the stimuli are the same—but the neural mechanisms underlying these perceptual changes remain unknown. Familiarity with an image or a sequence of images has long been known to modulate the responses of neurons throughout visual cortex, including mid-level area V4. In general, single neuron responses are lower for familiar than novel stimuli ('repetition suppression'). We tested the hypothesis that learning a sequence of actions might be associated with similar modulation of V4 responses to what is already a very familiar stimulus. To determine if the findings from a deep set of previous literature about visual learning extrapolate to a much more realistic, subject-led behavior, we developed a novel task that balances experimental control and naturalism. We taught rhesus monkeys to move a game piece one space at a time through a familiar two dimensional environment toward a goal. On each trial, we pick the starting location for the game piece and reward location. Monkeys rapidly settle on routine paths from familiar combinations of starting points and goals. Our initial results suggest that :

- V4 neurons exhibit repetition suppression during learning of new action routines, even when the visual stimuli themselves are already extremely familiar.

- Even though the magnitude of responses during familiar routines is reduced, the responses of V4 neurons are more informative about visual features like color and curvature than when the monkey performs an unfamiliar sequence of actions.

Our results suggest that similar mechanisms might underlie modulation of visual responses during learning of images and actions. More broadly, our framework enables future studies of the neural underpinnings of routine learning and its relationship to different aspects of perceptual and cognitive flexibility.
Disclosures: L. Kramer: None. **M.R. Cohen:** None.
Late-Breaking Poster

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Senior Research Fellowship from Council of Scientific and Industrial Research (to Divya Gulati)

Title: Delayed normalization elucidates temporal frequency masking interactions

Authors: *D. GULATI, S. RAY;
Ctr. for Neurosci., Indian Inst. of Sci., Bengaluru, India

Abstract: The presentation of frequency-tagged stimuli, such as a counterphase grating or an amplitude-modulated sound, generates an evoked response, referred to as steady-state visual evoked potentials (SSVEPs) and auditory steady-state responses (ASSRs) in the visual and auditory modality respectively. Such stimuli are often used in electroencephalography (EEG) based cognitive studies. When multiple stimuli are presented at once, the response to individual stimuli, depending upon the task, is modulated. Regardless of the task, having spatially overlapping stimuli leads to complex sensory interactions. Previous studies using invasive recordings from V1 have shown that the simultaneous presentation of two full-screen gratings at different temporal frequencies (TFs) leads to attenuation, especially when the TFs are nearby. This suppression is asymmetric if gratings are parallel in orientation, with lower frequencies producing more suppression. However, these studies used full-screen gratings that did not elicit a robust spiking activity, so it was unclear whether the same interactions hold for spiking activity and if the nonlinearity of the responses can be modelled. To address this, we presented smaller (~1-1.5°) gratings and plaids (two superimposed gratings) to generate robust spiking in V1 while bonnet macaques passively fixated on the monitor. We found that (i) small gratings had SSVEP peaks at lower frequencies (~4Hz) compared to the full-screen grating (~8-16Hz), (ii) although nearby TFs produced most suppression with a smaller stimulus, the asymmetry was lost, (iii) such interactions were also observed in spiking activity and (iv) a delayed divisive normalization model, where the inhibitory drive from the surround is delayed with respect from the incoming exitatory drive, can explain these results. Next, we extended our findings to the auditory domain. We recorded EEG activity from human participants in response to the simultaneous presentation of amplitude-modulated sounds at different modulation frequencies. We found a similar asymmetric response suppression of ASSRs, too. Our results shed light on how the brain processes concurrently presented stimuli and that different modalities share canonical neural computations.

Disclosures: D. Gulati: None. **S. Ray:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

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Program #/Poster #: LBA004.066/LBA65

Topic: D.06. Vision

Support: HHMI
Cullen Foundation

Title: In-vivo whole-cell recording in higher order visual areas of awake, behaving mice

Authors: *K. XIAO[1], B. SULLIVAN[2], R. A. CHITWOOD[3], J. C. MAGEE[4];
[1]HHMI, Baylor Col. of Med., Houston, TX; [3]Dept. of Neurosci., [2]Baylor Col. of Med., Houston, TX; [4]Neurosci., HHMI, Houston, TX

Abstract: Vision plays a crucial role in spatial navigation by helping animals establish an internal representation of their spatial location within a cognitive map. While the influence of vision on the hippocampus and parahippocampal circuits is well-documented, the reciprocal impact of spatial information on visual processing, particularly in mouse higher order visual areas, remains less understood. In this study, we performed in-vivo whole cell patch clamp recordings from layer 5 neurons in the lateral higher order visual areas of behaving mice engaged in a spatial navigation task with prominent visual cues. Interestingly, almost all recorded cells exhibited subthreshold responses to visual stimuli, with some generating action potentials. Furthermore, a subset of recorded cells displayed strong spatial modulation. Notably, we observed an increased incidence of dendritic plateau potentials when novel visual stimuli in the environment were introduced. These plateau potentials were hypothesized to be evoked in the distal tuft dendrites within cortical layer 1, indicating their generation by feedback inputs to higher visual areas. Our findings suggest that a subset of layer 5 neurons in higher visual areas encode spatial information in conjunction with visual cues. This study enhances our understanding of the neural mechanisms underlying spatial modulation in the visual cortex.

Disclosures: K. Xiao: None. **B. Sullivan:** None. **R.A. Chitwood:** None. **J.C. Magee:** None.

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Support: NIH Grant GM136467

Title: Insights into the Temporal Dynamics of Face Recognition: Comparing EEG Responses to Congruent and Incongruent Visual Stimuli

Authors: *B. M. AGUIRRE;
California State University, San Bernardino, San Bernardino, CA

Abstract: Insights into the Temporal Dynamics of Face Recognition: Comparing EEG Responses to Congruent and Incongruent Visual Stimuli. The face fusiform area (FFA) is essential for face recognition, but the exact timing of its activity is still debated. We used EEG to conduct three experiments examining how congruent versus incongruent visual stimuli affect processing dynamics. Participants viewed images of faces, houses, and tools (Experiment 1), celebrity faces (Experiment 2), or animal faces (Experiment 3), each preceded by a priming

question. Importantly, both conditions (congruent and incongruent) presented identical visual stimuli, ensuring that any observed differences were due to cognitive processing rather than sensory input. Our results indicate that the initial 150 ms period, critical for unconscious face detection, was unaffected by the experimental condition. However, subsequent processing showed a delay of several milliseconds for incongruent stimuli (Experiments 2 and 3), suggesting additional processing time needed for unexpected recognition. In Experiment 1, which involved less demanding tasks or generic mental imagery, no significant differences were observed between conditions. These findings highlight the crucial role of the period immediately following the first 150 ms in face identification and individuation, emphasizing the impact of top-down attention on face recognition dynamics. This study offers new insights into the temporal dynamics of face processing and the neural mechanisms underlying top-down attentional modulation.

Disclosures: B.M. Aguirre: None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

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Program #/Poster #: LBA004.068/LBA67

Topic: D.06. Vision

Title: Toward Neural Prosthetics in Higher Level Visual Areas: Effects of Single and Multi-Site Electrical Microstimulation in the Central Inferior Temporal Cortex on the Neural Population States in the Anterior Inferior Temporal Cortex

Authors: *S. ZAIDI[1,2], J. J. DICARLO[1,2,3];
[1]MIT, Cambridge, MA; [2]McGovern Inst. of Brain Res., Cambridge, MA; [3]MIT Quest for Intelligence, Cambridge, MA

Abstract: We seek to understand the neural mechanisms underlying object category recognition and to inform the development of neural prosthetics to restore those capabilities in blindness. We hypothesize that to create a coherent object category percept, it is sufficient to artificially induce specific, distinct population activity states in the anterior inferior temporal cortex (aIT) - an area implicated in category perception. To explore this, we conducted experiments in a rhesus macaque to induce specific aIT population states using single- and multi-site intracortical electrical microstimulation (ICMS) in the central inferior temporal cortex (cIT) - an area with feedforward cortico-cortical inputs to aIT. Specifically, we utilized one Utah array chronically implanted in cIT for microstimulation and one in aIT for recording the population activity states induced by cIT microstimulation during passive viewing of a blank screen. For reference, we measured the (lag-adjusted) aIT responses induced by 80 visual images presented to the retina of the passively viewing subject. We found that short microstimulation bursts (10 biphasic pulses at

250 Hz, duration 40msec) applied at most individual cIT sites (10/12 tested) were sufficient to induce significant, reproducible responses in the aIT population activity pattern (measured in the 50 msec window post-stimulation onset, after artifact removal). The population magnitude of those aIT response changes (L2 norm) increased monotonically with increasing current, and, at max, approached 67% of the magnitude of the changes produced by the best visual stimulus tested. Importantly, we found that different cIT sites produced distinct aIT changes, but with a tendency for spatially close stimulation sites to produce more similar aIT responses, consistent with known cIT spatial topography at that scale (< 1mm). Next, we investigated the simultaneous stimulation of pairs of cIT sites and observed that the maximum magnitude of the aIT population changes increased to 102% of the best visual stimulus. Additionally, simultaneous stimulation of pairs of cIT sites induced aIT population states that were unreachable by the single sites alone. Together, these results suggest that microstimulation can push the aIT population into states that, while slightly weaker, correspond to states induced by natural images, and that multi-site stimulation may allow reasonably accurate "steering" of the aIT activity to states unachievable by single-site stimulation. Future experiments involving monkeys making category judgments will test if the induced aIT effects result in perceptual changes as predicted by leading computational models.

Disclosures: S. Zaidi: None. **J.J. DiCarlo:** F. Consulting Fees (e.g., advisory boards); WuTsai Institute at Yale University, Lefler Center at Harvard University, ARNI NSF Center at Columbia University.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.069/LBA68

Topic: D.06. Vision

Support: The National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (No. RS-2024-00435727)
The National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (No. RS-2024-00349515)

Title: Coaxial bias in human perception of spatial extent, amidst radial bias in the spatial representation of the early visual cortex.

Authors: *J. RYU, S.-H. LEE;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: An accurate perception of an object's spatial extent-an enclosed region they occupy in space-is crucial for dexterous animals, including humans, to skillfully interact with objects of

various shapes. Although the topographic mapping of space in the early visual cortex (EVC, V1/2/3) has been favored as a neural correlate of spatial extent perception, its exact nature and contribution to perception remain unclear. To address this problem, we examined the topographic anisotropy of EVC's spatial representation and perceived spatial extent, as well as their relationship, in the context of natural image statistics. Our approach leveraged distinct topographic anisotropies present in the co-occurrence statistics of local orientation edges in real-world images and retinal images, respectively: the 'coaxial' bias, where edges sharing a common axis predominate in world images, and the 'radial' bias, where edges are aligned along the radiating from the fovea.Given these two biases, which are not exclusive to each other, EVC's topographic spatial representation is expected to be biased both coaxially and radially because, from a theoretical perspective, reflecting input statistics in neural representation maximizes its encoding efficiency. However, it remains unclear which of coaxiality and radiality is the dominant factor, due to the prevalence of neurons preferring radial orientation. Additionally, the impact of both factors on the anisotropy in perceived spatial extent and EVC's contribution to the anisotropy remains unexplored. Here, we created critical viewing conditions that disentangle the coaxial and radial biases and compared the cortical(fMRI) and behavioral responses under those conditions. Results showed an intriguing contrast between EVC and perception: EVC's anisotropy was mainly influenced by radiality and weakly by coaxiality, while perceptual anisotropy was mainly influenced by coaxiality and weakly by radiality. Despite this contrast, the inter-individual variabilities in the degree of anisotropy for both factors were significantly shared between EVC and perception.Our findings suggest that spatial extent perception builds on EVC's spatial representation but requires an additional mechanism to transform its topographic bias. Additionally, the predominance of the radial bias in both EVC and retinal image statistics suggests that EVC's functional role is to represent retinal images with high fidelity, rather than real-world images, transmitting these representations to downstream regions, where the real-world properties are reconstructed with the knowledge of how retinal images are generated.

Disclosures: J. Ryu: None. **S. Lee:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.070/LBA69

Topic: D.06. Vision

Title: Enhanced specificity for single eye ocular dominance column mapping using neurophysiologically informed spatial filtering in ultra-high resolution fMRI

Authors: *M. E. SCHMIDT[1], D. HAENELT[1,2], E. KIRILINA[1], N. WEISKOPF[1,3,4];
[1]Neurophysics, Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany;
[2]Athinoula A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Charlestown, MA;

[3]Fac. of Physics and Earth Syst. Sci., Felix Bloch Inst. for Solid State Physics, Leipzig Univ., Leipzig, Germany; [4]Wellcome Ctr. for Human Neuroimaging, Inst. of Neurology, Univ. Col. London, London, United Kingdom

Abstract: Advances in ultra-high-resolution functional magnetic resonance imaging (fMRI) have enabled the mapping of submillimeter-sized ocular dominance columns (ODCs) in human primary visual cortex (V1). This was achieved through differential contrasting of fMRI signals obtained during left vs. right eye stimulation to remove nonspecific signals of both conditions. However, this approach is not applicable in many clinical conditions such as monocular blindness and retinal and optic tract injuries, limiting the examination of changes in ODC activity in these cases. In this study, we developed neurophysiologically informed spatial filtering for identifying fMRI activation on the level of ODCs due to single eye stimulation in healthy controls. We quantified and evaluated the filter's effectiveness for different acquisition methods and across different cortical laminae. Five subjects (age = 28.00 ± 2.61 years (mean ± standard deviation); 2 females; Haenelt et al., 2024, in revision) received monocular stimulation using anaglyph glasses during the acquisition of three types of fMRI pulse sequences with different sensitivity and specificity: gradient echo- and spin echo-based (GE-BOLD and SE-BOLD) fMRI and Vascular-Space-Occupancy (VASO) fMRI. A General Linear Model (GLM) was used to calculate the beta values of the single-condition contrasts (left or right eye stimulation vs. baseline) on flattened V1 surfaces of ten equidistant cortical laminae. The spatial filter was designed based on the spatial frequency spectra of four digitized flattened histological ODC (Adams, Sincich & Horton, 2007) and applied to the beta maps. Specificity before and after filtering was measured as the ratio of the total variance within the difference and the sum of the single-condition maps. Specificity increased from 0.09 ± 0.02 to 0.21 ± 0.03 for GE-BOLD, from 0.12 ± 0.02 to 0.22 ± 0.02 for SE-BOLD, and from 0.18 ± 0.02 to 0.23 ± 0.02 for VASO after filtering. Only after filtering a slight peak of expected increased sensitivity in mid-cortical layers was observed for all sequence types. A repeated measures ANOVA revealed significant main effects of filtering ($F = 1825$, $p < 0.001$), sequence ($F = 25$, $p < 0.001$), and cortical depth ($F = 114$, $p < 0.001$). Before filtering, the specificity for GE-BOLD was significantly lower than for VASO ($p < 0.001$), while it was not after filtering ($p > 0.2$). These results suggest that neurophysiologically informed spatial filtering enhances the specificity of single-condition ODC mapping in fMRI. This method may expand our access to image the functional organization of ODCs in those patient groups for whom the conventional methods of ODC mapping are not applicable.

Disclosures: M.E. Schmidt: None. **D. Haenelt:** None. **E. Kirilina:** None. **N. Weiskopf:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.071/LBA70

Topic: D.06. Vision

Support: NIH 5R01EY020950
NIH R01EY026286

Title: Spatial organization of binocular disparity preference in tree shrew primary visual cortex

Authors: *L. YANG[1], S. TANABE[2], J. CANG[1,2];
[1]Biol., [2]Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: The visual cortex is organized into feature maps, whereby adjacent neurons are tuned to similar features of the stimulus. Understanding the architecture of these feature maps and their spatial relationship can provide clues on what role cortical organization plays in neural computation. A major characteristic of neurons in the primary visual cortex (V1) of many mammals, such as primates, cats, and tree shrews, is their selectivity to the orientation and the disparity of stereoscopic images. The spatial organization of binocular disparity preference and its relationship to the well-studied orientation maps are currently unknown. Here, we aim to fill this gap using tree shrews as a model system, because they live in environments requiring depth computation and their V1 neurons show exquisite tuning to binocular disparity. We presented dichoptic drifting gratings with various orientations and phase disparities between the two eyes. Standard 2-photon calcium imaging was carried out in awake tree shrews, using viral delivery of GCaMP. Consistent with previous work, we observed robust orientation columns in tree shrew V1 with characteristic pinwheel structures. For a single imaging plane at a certain depth, each orientation domain displayed a narrow range of phase disparity preferences. The phase disparity preference varied smoothly from one orientation domain to the next. Across the imaging plane, orientation preference and phase disparity preference were tightly coupled. This feature of organization was observed in both pixel- and neuron-based analyses. Notably, the pattern of tight coupling appeared to shift gradually as we moved the imaging plane to deeper depths. Unlike the organization of phase disparity preference, orientation columns remained constant throughout the depths. Together, our findings show that orientation and phase disparity are systematically mapped onto a volume of the cortex, thus revealing a spatial organization of binocular disparity preference in relation to orientation columns. The organization we found in tree shrew V1 could be a biological solution for mapping a manifold in 4D (i.e., every combination of orientation and disparity) onto a volume in 3D (i.e., cortical surface and depth).

Disclosures: L. Yang: None. **S. Tanabe:** None. **J. Cang:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.072/LBA71

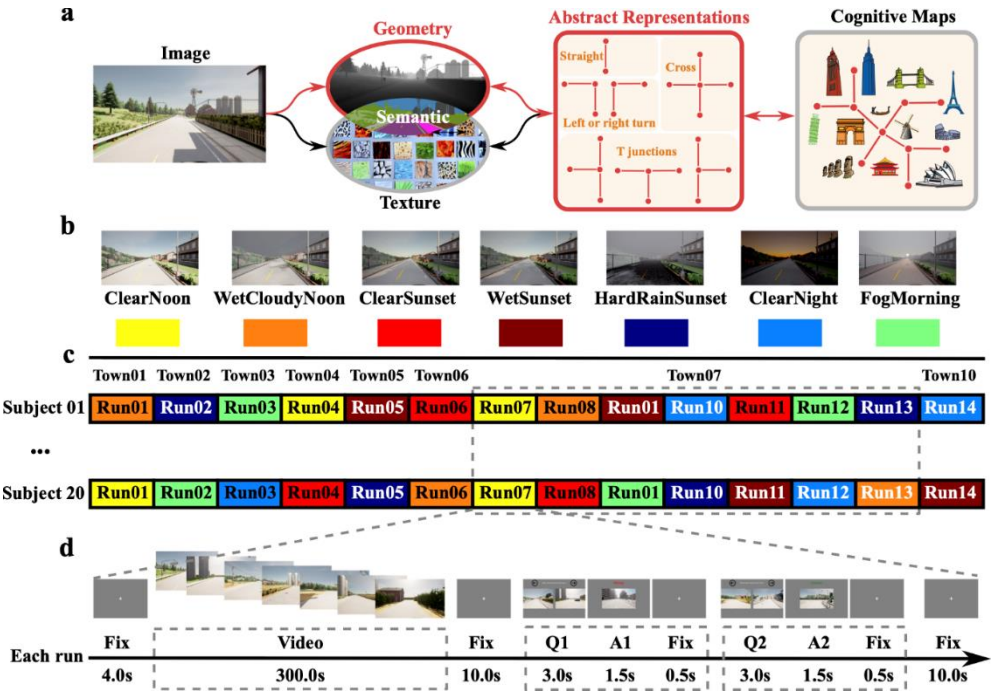
Topic: D.06. Vision

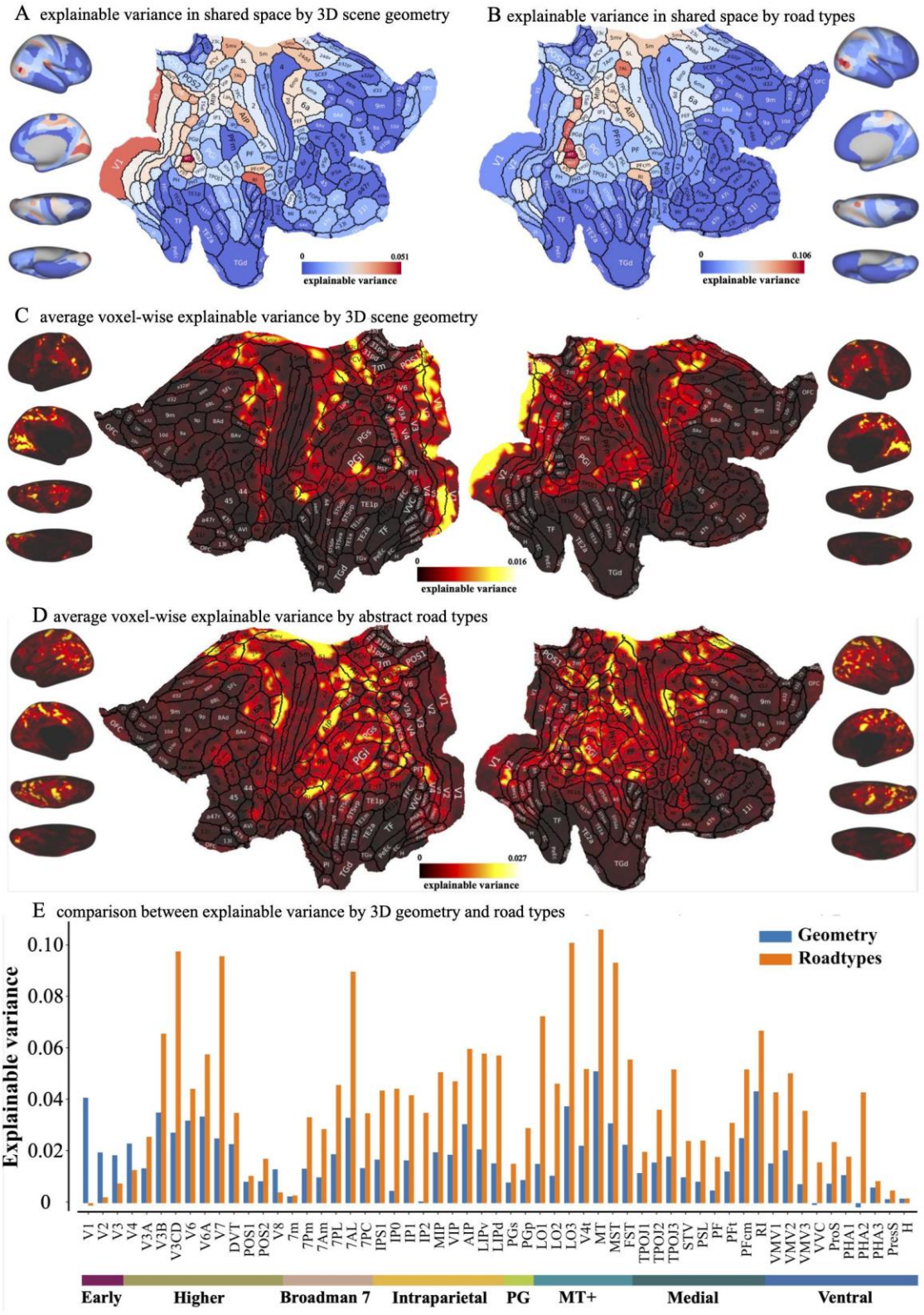
Support: WPI-IRCN startup budget (M.B. Cai and T. Zeng)
JSPS KAKENHI Grant JP21K20679 (T. Zeng)

Title: Geometry representations along visual pathways in human spatial navigation

Authors: T. ZENG[1], ***M. CAI**[2];
[1]Fudan Univ., Shanghai, China; [2]Dept. of Psychology, Univ. of Miami, Coral Gables, FL

Abstract: The representation of geometric structures in the environments is key to self-localization during human spatial navigation (Fig 1a). Its spatial organization in the visual system is not fully characterized. We scanned 20 participants with fMRI while they watched first-person-view videos taken from cars navigating through 8 virtual reality towns with identical routes (Fig 1c,d), thus eliciting identical time courses of geometric representations in the brain. Importantly, the weather and lighting conditions were randomized across participants (Fig 1b,c). Using shared response model, a functional alignment algorithm, we extracted synchronized neural signals in a low-dimensional shared latent space which capture the geometric representation invariant to low-level visual features induced by weather and lighting conditions. We built encoding models to examine the variance of the synchronized neural signals explainable by two types of geometry representations. We found that a compact representation of 3D scene geometry captured by a deep generative model is carried by a large network of brain regions forming three parallel "geometry visual pathways" starting from the primary visual cortex: the dorsal and medial pathways end in the intraparietal areas, while the ventral pathway arrives at the hippocampus via the parahippocampal gyrus (Fig 2A,C). Furthermore, road type, a more abstract geometry representation, is carried by overlapping pathways excluding early visual areas V1-V3 (Fig 2B,D,E).





Disclosures: T. Zeng: None. **M. Cai:** None.
Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.073/LBA72

Topic: D.06. Vision

Title: State dependent activation of layer 1 specific presynaptic inhibition in the visual cortex

Authors: *M. ALYAHYAY[1], A. MIROW[3], S. LIEBMAN[3], M. SOHEIB[4], A. LUGTUM[5], G. POUCHELON[3], L. A. IBRAHIM[2];
[1]KAUST, thuwal, Saudi Arabia; [2]Dept. of Neurobio., KAUST, Thuwal, Saudi Arabia; [3]Cold Spring Harbor Lab., Laurel Hollow, NY; [4]King Abdullah Univ. of Sci. and Technol., thuwal, Saudi Arabia; [5]King Abdullah Univ. of Sci. and Technol., Thuwal, Saudi Arabia

Abstract: Layer 1 (L1) of the neocortex serves as a critical integration hub where diverse neuronal inputs converge. It primarily consists of the dendrites of lower layer pyramidal neurons (from L2/3 and L5); axons from diverse brain regions, axons of local inhibitory neurons such as somatostatin (SST) neurons, as well as resident cortical inhibitory neurons (L1 cINs), primarily expressing NDNF as a marker and having their axons primarily confined within L1. Pyramidal neuron apical dendritic tufts in L1 are modulated by both excitatory and inhibitory inputs, which together shape the neuronal output. There are two main types of inhibitory inputs to the distal dendrites of pyramidal neurons: (1) Specific synaptic inhibition, which is mediated by SST neurons, known for their targeted and precise inhibitory effects, and have extensive axonal arborizations in L1. (2) Non-specific, slow, and prolonged inhibition mediated by L1 cINs, which likely affects a broader area and lasts longer. However, how these two sources of inhibition differentially impact dendritic integration and under what conditions they are specifically engaged is not well understood. In this study we show that these two sources of inhibition are able to modulate each other presynaptically. While SST neuron population is known to inhibit NDNF neurons, we also found that NDNF neurons are able to inhibit SST axons in L1 via a presynaptic mechanism. Using genetic combinatorial strategy with monosynaptic retrograde labeling, synaptic labeling and calcium imaging, we found that projections from NDNF-expressing neurons contact SST neuron terminals and that they control their inhibition upon visual stimulation and especially during locomotion, independently of the SST neuron soma inhibition. These findings reveal that inhibitory inputs onto pyramidal neuron dendrites are dynamically regulated, likely state-dependent, and that the two sources of inhibition don’t act simultaneously, but can inhibit each other depending upon whether SST or NDNF neuron is more activated.

Disclosures: M. Alyahyay: None. **A. mirow:** None. **S. Liebman:** None. **M. Soheib:** None. **A. Lugtum:** None. **G. Pouchelon:** None. **L.A. Ibrahim:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.074/LBA73

Topic: D.06. Vision

Support: NIDA Training Grant R90DA 060338
NIH NS109990

Title: Integration of Distinct Velocity Vectors by Direction and Motion Axis Selective Retinal Ganglion Cells

Authors: *Z. DENG[1], M. AHMON[1], W. WEI[2];
[1]Univ. of Chicago, Chicago, IL; [2]Neurobio., The Univ. of Chicago, Chicago, IL

Abstract: The pattern of local image velocities carry an abundance of behaviorally relevant information. Previous studies of how the visual system analyzes complex motion have largely focused on the cortical pathway, where direction-sensitive neurons are found to compute either a vector summation (VS) of velocity signals or follow an intersection of constraints (IOC) rule. And yet, the integration of local image velocities begins as early as the retina. The goal of our study is to determine how retinal ganglion cells encode complex motion patterns that contain distinct velocity vectors.

Specifically, we characterize how two types of motion-sensitive cells in the mouse retina - the direction-selective and motion axis selective cells - respond to drifting gratings and plaids composed of two component gratings moving at the same spatial frequency but varying temporal frequencies. For direction-selective ganglion cells that respond robustly to plaids, their preferred directions shift as the angle between the component gratings widens. In response to plaids with 15- and 45-degree angles, direction-selective cells' preferred directions align with the VS prediction. However, in response to plaids with 135- and 160-degree angles, the preferred directions deviate significantly from the VS prediction: they shift toward but do not align with the IOC prediction. Therefore, this shift in preferred direction for plaids with 135- and 160-degree angles is not well described by either VS or IOC, indicating that the retinal direction-selective circuit is performing a novel computation of integrating component velocity vectors.

For motion-axis selective cells, defined as cells which respond strongest to a particular motion axis while responding weakest to the orientation orthogonal to the preferred motion axis, their preferred motion axis for plaids is best aligned with the average motion axes of the two component gratings across 15-, 45-, 135- and 160-degree angles.

While numerous studies have elucidated how direction-selective and motion axis selective ganglion cells respond to stimulus such as gratings and spot, how the two cell types integrate image velocities within their receptive fields is unknown. Our study sheds light on how different types of retinal ganglion cells pool local motion signals across space and time before transmitting this information to the rest of the brain.

For how direction-selective neurons in the retinorecipient region superior colliculus respond to similar plaid stimuli, please see poster #3064 titled “Vector Summation and Bayesian Inference of Motion Direction Estimation in the Superior Colliculus” in session number PSTR344.

Disclosures: Z. Deng: None. **M. Ahmon:** None. **W. Wei:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.075/LBA74

Topic: D.06. Vision

Support: R01-EY-017366

Title: Area MT carries acceleration information in a quickly-decodable representation

Authors: *P. CHEN[1], A. HUK[2];
[1]Semel Inst., Univ. of California Los Angeles, Los Angeles, CA; [2]Fuster Lab. for Cognitive Neuroscience, Dept. of Psychiatry and Biobehavioral Sci. &, UCLA, Los Angeles, CA

Abstract: The role of primate area MT in visual motion processing has been extensively studied, but how the brain might extract motion acceleration information from MT (and the medial superior temporal area, MST) is unclear. One might expect acceleration encoding to require calculating the rate of change of velocity, itself calculated from changes in position over time. In this case,activity in visual motion sensitive neurons in area MT would encode velocity, and the brain would indirectly estimate acceleration by calculating changes in decoded velocity. An alternate mechanism, however, could operate more rapidly and directly. In this case, the brain could exploit interactions between MT’s standard motion encoding and idiosyncratic temporal dynamics of neural responses (originally posited by Lisberger & Movshon, 1999). Such“opportunistic encoding” would thus exploit nonlinearities usually ignored in studies of MT coding. We tested between these two theories by recording the time course of response from ensembles of MT (729 units) and MST (461 units) neurons while two awake, fixating rhesus macaques (male) viewed linearly accelerating dot motion stimuli. More than half of the recorded MT units exhibited stronger responses to linear acceleration over linear deceleration or no acceleration. We applied dynamic ensemble-level decoding (Poisson independent decoder) to the neural activity and quantified the information available about acceleration and velocity. Direct decoding of acceleration from MT was possible on faster timescales, and could be done with higher fidelity, than indirect decoding based on velocity encoding in MT. Hence, distinct motion acceleration information could be efficiently readout from a rich representation in the MT ensemble responses, regardless of the source of the acceleration tuning and other motion property representations. A similar analysis of MST activity did not suggest this later stage of

motion processing has a more refined acceleration representation. Together, these results suggest that the brain may learn to exploit nonlinear idiosyncrasies of neural responses to efficiently extract behaviorally relevant information on fast time scales, instead of performing explicit calculation of some variables matched to the first principles.

Disclosures: P. Chen: None. **A. Huk:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.076/LBA75

Topic: D.06. Vision

Support: NSF IIS 1817226
UC San Diego Social Sciences Research Grant
HDSI Chancellor's Endowed Chair
NSF IIS CRCNS 2208362
Hardware funding NVIDIA, Adobe, Sony

Title: An exploration of EEG Image Reconstruction

Authors: *T. FEI[1], V. R. DE SA[2];
[2]Cognitive Sci., [1]UCSD, La Jolla, CA

Abstract: This study investigates the properties of visual reconstruction from EEG, an emerging phenomenon gaining rapid attention where scientists attempt to reconstruct a viewed stimulus from EEG recorded from the observer. Using a publicly available large EEG visual perception dataset (THINGS-EEG2), we simulated reduced channel density and electrode swapping over the posterior 17 electrodes. Results show that reducing posterior channel density to 8 electrodes only mildly decreased reconstruction performance, aligning with EEG's low spatial resolution. However, swapping the signal from each electrode with its corresponding electrode across the midline at test time significantly reduced performance, highlighting the asymmetry in hemispheric roles and the importance of specific scalp locations. We also identified patterns in the main color and semantic category of stimulus images reflected in reconstructions: food images tend to have warm, reddish colors, while animal images often display a green surround with a central blob. This correlation in the stimulus space presents a challenge in dissociating low-level visual features from visual semantics in EEG data.

Disclosures: T. Fei: None. **V.R. de Sa:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.077/LBA76

Topic: D.06. Vision

Title: A triune structure of experienced consciousness

Authors: *C. TYLER;
Smith-Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: Rationale. A key issue in the science of consciousness is: How the world represented in human consciousness? This question is addressed from the established viewpoint that human consciousness (C*) is a function of the brain that receives multiple forms of sensory input from an external world consisting of a vast array of accessible energy sources from which brain then constructs a representation of this world on the basis of their contingent relationships. It has been proposed, since Brentano (1874), that such representation is the essence of C*; that it always represents something other than itself (usually something in the external world), which he termed 'intentionality'. His proposal may be critiqued by the introspective procedure of analyzing one's experience with closed eyes. Methods. A sample of 20 individuals were asked to describe their visual experiences (or 'qualia') when they closed their eyes, and to specify where in space (including inside the head) this entoptic visual imagery seemed to be located, and where, as the conscious viewer, their perceiving self seemed to be located relative to the visual imagery. Results. All observers described the closed-eye imagery as a variety of formless color experiences, intermixed with afterimages. All but one reported that this entoptic imagery was experienced as located in a space just in front of their eyes (or even as "painted on their eyelids"), not inside the brain or at the eyeballs, nor out in the space of the world. All reported that they felt that their formless self was viewing this imagery from a third location somewhere inside their head, distinct from the locations of the imagery or of objects in the outside world. The reader is encouraged to validate this observation from their own introspective viewpoint. Conclusion. This introspective analysis of the closed-eye experience shows that C* does not necessarily represent something in the external world (i.e., 'intentionality'), but can be a pure non-representational experience as such with no further reference. However, the specification of its spatial location was neither located inside the head, nor with the outside scene. These results imply that C* has a triune structure, consisting of 1) the experiencing self as a formless vantage point, 2) the inherent qualia of the experience, and 3) the projective representation of the object structures in the world giving rise to the experience. The introspectively differentiated location of each of these aspects of C*) ensures that they are not just linguistic or propositional concepts, but distinct, verifiable aspects of the structure of conscious experience.

Disclosures: C. Tyler: None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.078/LBA77

Topic: D.07. Visual Sensory-Motor Processing

Support: NSERC (Natural Sciences and Engineering Research Council of Canada)
CVR (Centre for Vision Research)

Title: Postural responses associated with continuous circular and linear vection stimuli

Authors: *K. JAKSIC, T. W. CLEWORTH;
Sch. of Kinesiology and Hlth. Sci., York Univ., Toronto, ON, Canada

Abstract: Introduction: The visual system plays a crucial role in our ability to maintain balance as it provides sensory cues that the nervous system utilizes to perceive our self-motion with respect to our environment. Vection, the illusion of self-motion when no actual movement has occurred, can be circular or linear[1]. Circular vection (CV) refers to rotations within the pitch, yaw and roll plane whereas linear vection (LV) consists of translations away or towards the individual either in the anterior-posterior (AP) or mediolateral (ML) directions[1]. This study aimed to compare the strength of continuous LV and CV stimuli on the amplitude of one's postural responses. **Methods:** Twenty young healthy adults quietly stood on a force plate while wearing a virtual reality head mounted display (HMD). The participants were exposed to a randomized sequence of nine conditions: four CV stimuli (pitch up, pitch down, counterclockwise roll and clockwise roll), four LV stimuli (ML translations left and right of the participant and AP translations towards and away from the participant), and one baseline trial. Each trial was 30 seconds long with a mandatory five-minute break between each trial. Centre of pressure displacements were calculated using the force plate and head displacement was collected using the HMD. Mean position and peak displacement were used to quantify the amplitude of postural responses. **Results:** During the 30 second trial, there was a directional effect where CV responses were greater than LV responses in both AP and ML directions. The CV responses were significantly greater than the baseline trial while LV responses showed no significant differences from the baseline. In the AP direction, there was no directional effect associated with the CV and LV responses in the first 10 seconds. In the last 10 seconds, CV responses were significantly greater than LV responses with pitch down eliciting the greatest response. In the ML direction, CV responses were greater than LV responses across all windows. **Conclusion:** Overall, CV stimuli elicited greater postural responses when compared to LV stimuli. Within the first 10 seconds, CV and LV responses were similar in the AP direction, but the CV response increased throughout the duration of the trial. CV responses were greater in the ML direction for all windows. Therefore, the strength of the postural response is dependent on the type, direction, and duration of vection stimuli. **Reference:** [1] Palmisano et al. (2015). Front Psychol 6, 193.

Disclosures: K. Jaksic: None. **T.W. Cleworth:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.079/LBA78

Topic: D.08. Multisensory Integration

Support: NIH Grant R01-EY014882
NIH Grant F31-EY031946

Title: Alterations in the spatial representation of activity across sensory cortical areas as a result of visual deprivation in adults

Authors: *Y. SONG[1,2], S. PARKINS[2,3], Y. JAOUI[2], A. GALA[1,2], C. RICHARDSON[5], H.-K. LEE[2,3,4,6];
[1]Johns Hopkins Univ. - Main Campus, Baltimore, MD; [2]Zanvyl-Krieger Mind/Brain Inst., [3]Cell Mol. Developmental Biol. and Biophysics Grad. Program, [4]Kavli Neurosci. Discovery Inst., Johns Hopkins Univ., Baltimore, MD; [5]Loma Linda Univ. Sch. of Med., Loma Linda, CA; [6]Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Loss of a sensory modality triggers global adaptations across various brain areas to allow the remaining senses to more effectively guide behaviors. These adaptions are collectively called cross-modal plasticity. While previous studies revealed diverse circuit adaptations caused by sensory loss, the spatial pattern of cortical activity changes brought by these adaptations remain largely unexplored. We aimed to fill this gap by spatially mapping the extent of activity changes in visual, auditory, somatosensory, and multisensory cortices of visually deprived mice. We applied two visual deprivation paradigms - dark exposure (DE) and enucleation (EN), each of which had a 2-day (2D) and a 7-day (7D) version - to cFos-TRAP2 mice, whose active neurons were labeled by tdTomato (tdT) fluorescence protein upon tamoxifen injection. Adult (P90 - P120) mice of both sexes were used in all experiments. We found that in the primary visual cortex (V1) both DE and EN caused a significant loss of active cells at 2D followed by a partial rebound at 7D, which occurred relatively more in superficial layers. A similar pattern was observed in the secondary visual cortex, especially in the lateral areas (V2L). These results suggest that both V1 and high-order visual cortical areas were recruited by non-visual inputs over time. The spared primary sensory cortices adapted distinctly. In the primary somatosensory barrel cortex (S1BF), there was significantly lower density in the 7DDE and the 2DEN groups compared to the 7DEN group, suggesting an opposite temporal trend in compensatory adaptations between DE and EN. Other parts of the primary somatosensory cortex showed minimal changes in activity upon visual deprivation. In the primary auditory cortex (A1), following both DE and EN, there was a relative reduction in the density of active cells in superficial depths without a significant change in the overall density, which might reflect

compensatory mechanisms such as the refinement of intracortical connectivity within layers 2/3 and layer 4 and the sparsification of sound encoding in layers 2/3. There were minimal changes in the active cell density in the secondary cortices of the spared senses and the multisensory retrosplenial cortex (RSP). Overall, our results are consistent with cross-modal recruitment of the deprived visual cortex and compensatory plasticity in the spared primary sensory cortices, both of which support enhanced processing and refinement of the spared senses. Our study also manifested the differences between the effects of DE and EN, which might suggest different prospects for patients with different types of sensory loss.

Disclosures: Y. Song: None. **S. Parkins:** None. **Y. Jaoui:** None. **A. Gala:** None. **C. Richardson:** None. **H. Lee:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.080/LBA79

Topic: D.08. Multisensory Integration

Support: NIH Grant R01HD096332

Title: Autonomic activity during a bladder distension task predicts the development of menstrual pain

Authors: E. E. GAL[1,2], N. R. OSBORNE[2], L. SINGH[2], F. F. TU[2,3], *K. HELLMAN[2,3]; [1]Northwestern Univ., Evanston, IL; [2]Ob/Gyn, Endeavor Hlth., Evanston, IL; [3]Pritzker Sch. of Med., Chicago, IL

Abstract: Dysmenorrhea (painful periods) has a prevalence of 50-80% and is the leading reason 10-20% of female high school students consistently miss class. Work from our lab suggests neural mechanisms involved in visceral sensitivity play an important role. To investigate the potential role of visceral autonomic reflexes in menstrual pain development, we conducted a prospective study on 300 adolescents. The study included visits before their first period (BL), 3-9 months after their first period (PV1) and one year after their PV1 (PV2). We measured their heart rate variability (HRV) during a non-invasive bladder filling task to assess visceral autonomic reflexes. By one year after their first period at PV1, 95 participants had low menstrual pain scores (<30 on a 0-100 scale), and 108 had high menstrual pain scores (≥30). We hypothesized that participants with a lower parasympathetic activity during the bladder-filling task at BL would be more likely to develop menstrual pain in the year after their first period. Our findings confirmed this hypothesis, showing that participants with lower parasympathetic activity at BL were more likely to experience menstrual pain at PV1 ($p=0.046$). Within 2 years after their first period (at PV2), 62 participants had low menstrual pain scores and 90 had high

menstrual pain scores. Participants with menstrual pain by year two had higher sympathetic and parasympathetic activity at BL during multiple points during the bladder task (p's<0.05). However, there was no significant correlation between resting heart rate and blood pressure and the likelihood of experiencing menstrual pain. Therefore, visceral-autonomic mechanisms, rather than baseline autonomic mechanisms, were a better predictor of menstrual pain development. The connection between autonomic reflexes in visceral organs and the development of menstrual pain suggests that preventative treatments such as HRV biofeedback could benefit at-risk adolescents.

Disclosures: E.E. Gal: None. **N.R. Osborne:** None. **L. Singh:** None. **F.F. Tu:** None. **K. Hellman:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.081/LBA80

Topic: D.08. Multisensory Integration

Title: Bayesian integration of audiovisual speech by machine-learning models is similar to human observers

Authors: *H. MA, Z. WANG, J. F. MAGNOTTI, M. S. BEAUCHAMP;
Dept. of Neurosurg., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Humans perceive speech by integrating auditory information from the voice of the talker and visual information from the face of the talker. Machine learning (ML) has made remarkable progress in reproducing human abilities, including in the domain of audiovisual speech recognition (<1% error rate for state-of-the-art models). Human audiovisual speech recognition follows principles of Bayes-optimal integration, with each modality weighted by its reliability (Ma et al., PloS One 2009). To determine whether ML models of audiovisual speech recognition follow similar Bayesian principles, we applied the standard technique used to estimate modality weights: assessing recognition of stimuli containing a mismatch between modalities (Ernst and Banks, Nature 2002). Although speech perception is predominantly auditory, some incongruent audiovisual speech shows a strong influence of the visual modality. For instance, when presented with the pairing of auditory /ba/ with visual /fa/ (AbaVfa) human observers often report a percept of /fa/. The Bayesian framework accounts for this finding by positing that the visual speech feature corresponding to /fa/ (upper teeth pressed onto the lower lip) is a highly reliable indicator of auditory /fa/, resulting in an upweighting of the visual modality (Yu et al., Frontiers in Neuroscience 2024). Eight different speech stimuli were recorded from four female talkers (Aba, Afa, Vba, Vfa, AbaVba, AfaVfa, AbaVfa, AfaVba). The stimuli were presented to AV-HuBERT (audiovisual hidden unit bidirectional encoder

representations from transformers; Shi et al., arXiv 2022), an ML model trained on hundreds of hours of audiovisual speech. For each stimulus, the relative probability of /ba/ or /fa/ was calculated by summing the probability of tokens containing either b/p or f/ph (only the top 100 tokens were considered). AV-HuBERT performance was near ceiling for Aba and Afa syllables, with a small increase in accuracy for AbaVba and AfaVfa (95% vs. 99%, p = 0.03). Adding incongruent visual information dramatically changed the observed responses. For AbaVfa, there were 97% /fa/ responses, compared with 4% /fa/ for Aba (p = 0.0001). For the opposite pairing of AfaVba, there were 64% /ba/ responses compared with 5% for Afa (p = 0.03). In human observers, a similar pattern was observed, with 88% /fa/ responses for AbaVfa and 28% /ba/ responses for AfaVba (Shahin, Neuroscience Letters 2019). The similar response of ML and human observers to incongruent audiovisual speech suggests that ML models may be a useful tool for interrogating the perceptual and neural mechanisms of human audiovisual speech perception (Yamins et al., PNAS 2014).

Disclosures: H. Ma: None. **Z. Wang:** None. **J.F. Magnotti:** None. **M.S. Beauchamp:** None.

Late-Breaking Poster

LBA004: Theme D Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA004.082/LBA81

Topic: D.08. Multisensory Integration

Support: NIH Grant P41 EB018783 (Wolpaw)
NYS Spinal Cord Injury Research Board C37714GG (Gupta)
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Title: Contralateral Parietal Low-Beta Power informs of Proprioceptive Uncertainty in Chronic Stroke

Authors: *S. RUEDA-PARRA[1], A. J. FARRENS[2], D. J. REINKENSMEYER[3,4,5,2], D. GUPTA[1,6];
[1]Natl. Ctr. for Adaptive Neurotechnologies, Albany, NY; [2]Mechanical & Aerospace Eng., [3]Biomed. Engin., [4]Anat. and Neurobio., [5]Physical Med. and Rehabil., Univ. of California Irvine, Irvine, CA; [6]Electrical and Computer Engin., Univ. at Albany, Albany, NY

Abstract: Background
Proprioception involves judging limb positions in space, which involves processing uncertainty. People with stroke can have impairment in uncertainty processing among other cognitive impairments, which affect proprioceptive judgment. Previous studies (Palmer et al., 2019; Rueda Parra et al., 2024) demonstrated an association of low-beta (Lβ, 13 - 20 Hz) power with

uncertainty processing. We study this neural correlate of uncertainty processing and its relationship to proprioceptive errors in a crisscross robotic finger proprioception task (Ingemanson et al., 2016). This is part of a randomized control trial dataset (NCT04818073).

Methods

Thirty-two people with chronic stroke participated with informed consent (IRB# 476). The THINGER robot passively moved their middle and index fingers along opposite paths intersecting at the midpoint of a 32° range of motion. Participants pressed a button with the non-paretic hand when perceiving finger overlap, with the vision of the hand occluded. Proprioceptive errors were estimated as the median angle between the fingers over 100 repetitions, dividing the participants into small ($\leq 16°$, n = 21) and large ($> 16°$, n = 11) error groups.Non-invasive electroencephalography (EEG) (DSI-24, Wearable Sensing) was acquired at 300 Hz with BCI2000, referenced to linked earlobes, and synchronized with kinematic data. EEG was filtered (0.5, 40)Hz, ICA denoised, and epoched, relative to movement offset; noisy epochs were removed. We analyzed the period of proprioception from -300 to -100 ms before button press. Lβ power was extracted with Morlet Wavelet Convolution, baseline normalized, and expressed as a percent of change relative to a pre-movement baseline (-400 to -100 ms). We evaluated the Lβ power at the parietal electrode contralateral to the paretic hand. Median Lβ power across trials was tested for correlation with proprioceptive errors using Spearman's rho(ρ).

Results

Correlation analysis showed a positive relationship for all participants ($\rho = 0.39$, $p = 0.026$). This relationship was significant and strong in the small error group ($\rho = 0.76$, $p = 0.0001$), but not in the large error group ($\rho = -0.16$, $p = 0.63$). These results suggest that Lβ power is more attenuated when people make smaller proprioceptive errors.

Conclusion

Parietal Lβ power modulation was found to be associated with proprioception in people with stroke. Given Lβ's association with uncertainty, our results suggest that its modulation here is potentially capturing the underlying proprioceptive uncertainty in the task. This could serve as a potential marker for neurophysiological assessment or intervention in sensory rehabilitation after a stroke.

Disclosures: S. Rueda-Parra: None. **A.J. Farrens:** None. **D.J. Reinkensmeyer:** None. **D. Gupta:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.001/LBA82

Topic: E.01. Eye Movements

Support: ERC Grant 755745

ISF 380/17

Title: From optimality to reality: decision making encoding in the output of the basal ganglia

Authors: *G. ZUR[1], N. LARRY[2], M. JOSHUA[3];
[1]Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]ELSC, Hebrew Univ. of Jerusalem, Ramat Hasharon, Israel; [3]The Edmond and Lily Safra Ctr. for Brain Sci., The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: The Substantia Nigra pars reticulata (SNpr), an output structure of the basal ganglia, plays a crucial role in eye movements, encoding reward expectations and eye movement directions through dynamic activity at different trial stages. However, the mechanism by which the brain uses these reward expectations to guide movement remains unclear. Possible theories are that the SNpr encodes the motor eye movement, representing the selected action, or that it encodes information about the expected reward to guide the preferred action. This study addresses this gap by examining SNpr activity dynamics in a decision-making task involving simultaneous reward presentation and action selection.We recorded SNpr activity in two monkeys performing an eye-movement task based on reward-based decision-making. The monkeys were trained to associate five different color cues with varying probabilities of reward. In each trial, two color cues appeared, and after a delay, the targets began moving. The monkeys tracked one of the two targets with their eyes, demonstrating high performance (95%) in selecting the target with the highest reward probability. We examined SNpr activity at different trial stages.We employed decoding to determine what information is carried by SNpr neurons. During the color cue presentation, the SNpr encoded both targets and their positions. The decoder better classified the target with the highest probability of reward compared to the target with the lowest probability, indicating highly accurate coding of the optimal target. This was observed even in trials where the monkeys pursued the low-probability target, suggesting SNpr initially encodes the preferable target in terms of reward probability, regardless of the monkeys' subsequent selection. During the motion stage, SNpr activity correlated tightly with the monkeys' actual behavior in both correct and error trials, rather than with the optimal target. Thus, the dynamics of SNpr activity demonstrate a transition from encoding the trial's optimal target to encoding the performed action.

Disclosures: G. Zur: None. **N. Larry:** None. **M. Joshua:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.002/LBA83

Topic: E.02. Cerebellum

Support: NIH Grant R01EY035241
NIH Grant K99EY030528
NIH Grant R01NS112917

Title: Spatial and temporal transformations in the cerebellar circuit during smooth pursuit eye movements

Authors: *D. J. HERZFELD, S. G. LISBERGER;
Duke Univ., Durham, NC

Abstract: The floccular complex of the cerebellum is crucial for smooth pursuit eye movements. We recorded 1,000+ neurons from the floccular complex of rhesus monkeys using multi-contact silicon probes. We used established methods to assign putative neuron identities to many single-units, allowing us to link the activity of identified neural populations to behavior in this exemplar sensorimotor task. Identified floccular neurons showed time-varying functional responses that clustered according to neuron type, despite functional responses not being a criterion for establishing neuron identity. The different functional properties of different neuron types highlights active computation by the cerebellar circuit. Mossy fibers (MFs), the primary input to the cerebellar cortex, showed firing rate responses strongly related to eye position, with uniformly distributed preferred pursuit directions. In contrast, the simple spikes of Purkinje cells (PCs), the sole output of the cerebellum, responded primarily to eye velocity, with little dependence on eye position, and a strong directional bias in preferred directions. We evaluated the spatial and temporal transformation from MFs to PCs by analyzing the responses of other floccular neural populations. Molecular layer interneurons (MLIs) exhibited strong eye velocity-dependent responses, with preferred pursuit directions opposite to those of simultaneously recorded Purkinje cells. As MLIs receive parallel fiber inputs, their velocity-sensitive responses suggest that the transformation from position to velocity occurs in the granule cell layer. PC complex spikes showed preferred directions that were consistently opposite those of PC simple spikes, suggesting that the spatial transformation may be mediated by the combination of complex spike induced plasticity and anisotropic MLI preferred directions. Golgi cells showed little modulation, indicating limited involvement in the granule layer dependent position-to-velocity transformation. Unipolar brush cells displayed stronger position-related responses than mossy fibers, consistent with their role in integration. These findings suggest the position-to-velocity transformation occurs between MFs and granule cells. A mathematical model reproduces the position-to-velocity transformation through short-term synaptic plasticity at the MF to granule cell synapse. Our results identify the source of two key transformations in the floccular complex: the conversion of position-to-velocity responses at the MF to granule cell synapse and a spatial transformation in the molecular cell layer due to MLI inputs and complex spike-mediated plasticity.

Disclosures: D.J. Herzfeld: None. **S.G. Lisberger:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.003/LBA84

Topic: E.02. Cerebellum

Title: Cerebellar expression of Rhomboid-3 contributes to aging-related motor decline

Authors: *E. FIELDS[1], L. MUNTER[2], A. J. WATT[3];
[2]Pharmacol. & Therapeut., [3]Biol., [1]McGill Univ., Montreal, QC, Canada

Abstract: Despite a global increase in lifespan, many individuals spend their later years plagued with poor health. Aging-related impairment in motor coordination contributes to falls in the elderly, which increases mortality and morbidity. Thus, understanding the underlying causes of aging-related motor coordination dysfunction is critical for improving health span. Rhomboid proteases are conserved intramembrane proteases that play an important role in many signalling cascades. While some Rhomboid proteases are implicated in aging-related diseases like Alzheimer's and Parkinson's diseases, little is known about the mammalian Rhomboid-3. Rhomboid-3 is expressed in the nervous system and has been identified amongst the top genes to be upregulated within the aging human brain (Kumar et al., 2013). Since Rhomboid-3 is highly expressed in cerebellar Purkinje cells, which are critically involved in motor coordination, we wondered if age-associated accumulation of Rhomboid-3 contributes to aging-associated changes in motor coordination. To understand the role of Rhomboid-3 in cerebellar aging, we tested *Rhbdl3*-knockout (R3-KO) mice on the accelerating rotarod at several ages. We found that aging (12-month old) R3-KO mice performed better on the rotarod than their wildtype (WT) littermates. Motor coordination remained elevated at later ages (18-month old) and was also visible although less dramatic in young mice (2-month old), suggesting that expression of Rhomboid-3 accumulates in age and is deleterious to motor performance. Cerebellar Purkinje cell firing is a read-out for motor function as it is impaired in cerebellar disease (Cook, Fields & Watt, 2021) and aging. To determine whether Rhomboid-3 affects Purkinje cell output, we performed loose cell-attached recordings from Purkinje cells in aged R3-KO mice and found that Purkinje cells fired at higher frequencies compared to WT littermates. To determine if Rhomboid-3 expression in cerebellar Purkinje cells is sufficient to influence motor coordination, we virally expressed *Rhbdl3* or GFP in Purkinje cells of R3-KO mice and tested motor performance before and 4 weeks after surgery. While rotarod performance of GFP-injected R3-KO mice significantly improved after surgery, there was no significant improvement in the rotarod performance of *Rhbdl3*-injected R3-KO mice. This suggests that accumulation of Rhomboid-3 in cerebellar Purkinje cells contributes to aging-related motor decline. Taken together, our data suggest that aging-related increases in cerebellar Rhomboid-3 contributes to impairments in motor coordination, thus representing a novel therapeutic target to improve motor outcomes in aging.

Disclosures: E. Fields: None. **L. Munter:** None. **A.J. Watt:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.004/LBA85

Topic: E.02. Cerebellum

Support: JSPS 22K15207

Title: Inferior olive spike modulation by cerebellar feedback and synchronicity

Authors: D. GUO[1], ***M. Y. UUSISAARI**[2];
[1]Uusisaari Unit, OIST, Kunigami-Gun, Japan; [2]Neural Rhythms in Movement Unit, Okinawa Inst. of Sci. and Technol., Onna, Japan

Abstract: Axons of the inferior olive (IO) form the sole source of the climbing fibers (CFs) that drive complex spike (CS) activity in the Purkinje neurons (PNs) of the cerebellar cortex. As the CSs are crucial for learning and executing complex behavior in all vertebrate animals, their properties and roles in (mal)function of the cerebellar system have been intensively examined in the past decades. Among the relatively recent additions to their complexity are the observations that the duration of single CSs is not invariant, and that CSs of different width can lead to distinct physiological outcomes. Despite numerous attempts to clarify the origin and significance of CS shape using recordings of PN activity, it is not clear to what extent the CS variation originates in the IO rather than from factors intrinsic to the cerebellar cortex

The extreme deep location of the IO at the ventral edge has hindered investigation of its activity modulation in living animals. In order to allow investgation of the IO network *in vivo*, we have established methodology for calcium imaging in the IO utilizing a miniature microscope coupled to a GRIN lens, placed non-invasively on the rostro-ventral surface of the nucleus in anesthetized adult male mice. This approach provides clear optical access to parts of the principal and dorsal accessory olives (PO and DAO, respectively), as well as possibility of optogenetic activation of specific afferent axons.

Here, we provide detailed comparison of the spontaneous network activity in the regions of IO in living mice, and report utilizing rigorous mixed-effects modeling that average spiking frequency in PO targeting zebrin-positive zones of cerebellar cortex is lower than in DAO region targeting zebrin-negative zones. Furthermore, even though optogenetic activation of the IO-targeting, largely GABAergic cerebellar feedback afferents led to clear decrease in sporadic spiking, no clear evidence for intrinsic post-inhibitory rebound spike generation was seen. Intriguingly, airpuff-evoked spikes were only subtly suppressed, leading to an increase in their "salience" among ongoing activity. Finally, we observed a very strong correlation between the amount of co-activation of neurons and the respective calcium event magnitude, leading to a proposition that the cerebellar complex spike width reports on the synchronicity of activity within the IO.

Disclosures: D. Guo: None. **M.Y. Uusisaari:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.005/LBA86

Topic: E.02. Cerebellum

Title: Anatomical and In-vivo study of novel superior colliculus projection to the mice inferior olive

Authors: *D. DAVID[1], M. Y. UUSISAARI[2];
[1]Okinawa Inst. of Sci. and Technol., Onna, Okinawa, Japan; [2]OIST, Okinawa, Japan

Abstract: The climbing fibers, projections of the inferior olive have been extensively studied for its role in the olivocerebellar system. However, while the function of the inferior olive has been investigated through the occurrences of complex spikes (CS) during motor learning, it remains unclear how its intrinsic properties and activity shapes CS generation upon receiving sensory stimulation.To investigate how signals from a pre-olivary structure with well-defined behavioral role, we examine the anatomical patterns of projections from the superior colliculus (SC) to the IO. We found that in addition to the previously described projection to the medial accessory olive (MAO) associated with eye movements and body orientation, the SC also sends axons into the ventral leaf of the principal olive (PO). We examine the morphology of SC-PO and SC-MAO neurons and found that they are intermingled in the intermediate and deep layers of the lateral SC with similar gross morphology; however, most neurons exclusively target either PO or MAO. Taking advantage of the ventral position of the SC-PO axons in the IO, we were able to monitor activity in the IO neurons using inscopix nVoke imaging system by accessing the IO from the ventral side and examine how optogenetic stimulation of SC-PO axons affects IO spiking in anesthetized mice. The result suggests that SC-PO pathway modulates excitability of IO network rather than directly generate spikes and highlights the need for further investigation of sensory signal integration within the IO to understand generation of CS that underlies motor learning.

Disclosures: D. David: None. **M.Y. Uusisaari:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.006/LBA87

Topic: E.02. Cerebellum

Support: Ministry of University and Research (MUR), Projects of National Interests Research - PRIN 2020
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Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN.1553 11.10.2022).

Title: Segregated projections from cerebellum to contralateral thalamus and cortical areas involved in observation and execution of grasping actions

Authors: *A. ERRANTE[1], C. RUSSO[1,2], G. CIULLO[1,3], A. PIRAS[1], E. SICURI[1], M. GERBELLA[1], L. FOGASSI[1];
[1]Univ. of Parma, Parma, Italy; [2]Univ. of Bologna, Bologna, Italy; [3]Fondazione IRCCS Neurolog. Inst. Carlo Besta, Milan, Italy

Abstract: Human and monkey studies have shown that, in addition to parietal and premotor areas, the cerebellum and subcortical structures, such as the thalamus and red nucleus, are activated during the observation of grasping actions. It has been hypothesized that the cerebellum uses the forward models to anticipate sensory outcomes of the observed actions through contralateral dentato-rubro-thalamo-cortical projections. However, it is not fully understood if the specific sectors of the dentate nucleus (DN) and thalamus involved in action observation are partially segregated from purely motor sectors. In the present study, firstly, by using an fMRI task we identified cerebellar and thalamic sectors activated during both observation and execution of grasping actions, then, we used probabilistic diffusion tractography to characterize the structural connections involving these sectors. Twenty right-handed healthy participants (11 females; mean age: 24.4 years) were instructed to observe goal-directed grasping actions or to execute the same actions. Control conditions included the observation of a static context and the execution of opening-closing hand movements, respectively. Two partially segregated sets of regions of interest were delineated: the first based on pure motor activation and the second based on conjunction analysis between observation and execution. Shared activation between observation and execution was present in the inferior parietal lobule (IPL), ventral premotor cortex (PMv), cerebellar lobules V-VI, DN, red nucleus, and thalamus. The activation of the DN and thalamus exhibited functional partial segregation with respect to purely motor sectors. The dorsal DN and ventrolateral (VL) thalamic nucleus were mostly activated during grasping execution. In contrast, the ventral DN and ventral-posterolateral (VPL) thalamic nucleus showed shared activations during both observation and execution. Moreover, the red nucleus was activated bilaterally in both motor and observation conditions. Diffusion tractography showed that tracts originating from the motor sectors of the DN project to the contralateral red nucleus and VL nucleus, in the path traveling to the contralateral rostral sector of IPL and PMv. The ventral DN was connected by partially segregated projections with the contralateral red nucleus and VPL nucleus, in the path to the contralateral caudal sector of IPL and PMv. These results provide evidence of partially segregated cerebellar outputs to thalamic and cortical regions

involved in action observation and execution. Through these circuits, the cerebellum can exploit its role in motor simulation during action observation.

Disclosures: A. Errante: None. **C. Russo:** None. **G. Ciullo:** None. **A. Piras:** None. **E. Sicuri:** None. **M. Gerbella:** None. **L. Fogassi:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.007/LBA88

Topic: E.02. Cerebellum

Support: MOST 109-2326-B-002-013-MY4
MOST 107-2321-B-002-020
MOST 108-2321-B-002-011
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MOST 110-2321-B-002-012
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National Taiwan University Hospital, grant 113-E0001

Title: Instantaneous synchrony of populational neurons in the cerebellum encodes reward events with supreme single-trial precision

Authors: L.-Y. LU[1], P. CHEN[3], ***M.-K. PAN**[4,2];
[1]Inst. of Biomed. Sci., Academia Sinica, Taipie, Taiwan; [2]Academia Sinica, Taipei, Taiwan; [3]Grad. Inst. of Pharmacology, Natl. Taiwan Univ. Col. of Medicine, Taipei, Taiwan, Taipei City, Taiwan; [4]Natl. Taiwan Univ. Col. of Med., Taipei, Taiwan

Abstract: Reward-based learning requires the brain to unambiguously detect every reward event precisely at the moment it occurs, which is the ground truth of the entire learning process. Mechanisms identified by trial-averaged or model-based approaches lack the precision needed with single-trial accuracy. Here we report a novel property of populational coding, named **Instantaneous Synchrony of Populational Neurons (ISPN)**, allowing cerebellar Purkinje cells to report reward prediction errors (RPE) to dopamine neurons in ventral tegmental area (VTA) via deep cerebellar neurons (DCNs), **with supreme detecting and temporal accuracy on a per-trial basis.** Using in vivo electrophysiology, fiber photometry, and closed-loop optogenetic manipulations in a two-choice foraging task with mice, we established that the DCN-to-VTA pathway is essential for reward-based decision making. We found that the precise encoding of a reward event does not rely on DCN neuronal firing rates, patterns, or hidden temporal features as identified by machine learning. Instead, a reward event is encoded by a synchronous resetting of the DCN neuronal population (inhibitory ISPN), occurring 50 milliseconds after reward delivery.

The synchrony is an emergent property amount neuronal interaction, not an existing property from single-cell neuronal codes. The amplitude of ISPN, indicated by the strength of synchrony, has a supreme signal-to-noise ratio for unambiguous single-trial detection and temporal recognition, and is inversely correlated with RPE. Two-photon calcium imaging in awake-behaving mice confirmed that one episode of activating ISPN of Purkinje cells precisely encoded one reward event by inducing a resetting ISPN in DCNs. Disrupting inter-neuronal synchrony, either by hyperpolarizing currents to DCN or by gap-junction blockers in the inferior olive, impaired reward recognition. Additionally, optogenetic stimulation of PC or DCN showed rewarding effect by inducing synchrony, not by increasing neuronal firing rates. For each choice, one pulse of optogenetic stimulation at PC axonal terminals, which generating one ISPN with the synchronizing temporal width of one action-potential cycle, sufficiently changed a non-rewarding choice to rewarding outcome. Our results provide evidence that real-time reward encoding is organized into the cerebellum through a novel ISPN mechanism, an emergent property of populational coding that easily achieves signal-trial accuracy. Optogenetic manipulation has a dual property in altering firing rates and causing synchrony, and optogenetic evidence explained by simple rate changes should be carefully revisited.

Disclosures: L. Lu: None. **P. Chen:** None. **M. Pan:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.008/LBA89

Topic: E.03. Basal Ganglia

Support: NIA AG065682-0
NINDS NS095253

Title: Orphan receptor GPR139 regulates cholinergic activity in the striatum

Authors: D. R. ZUELKE[1], ***N. GENTILE**[2], A. H. KOTTMANN[3];
[1]Biol., Fordham Univ., Bronx, NY; [2]City Univ. of New York, New York, NY; [3]Physiology, Pharmacol. and Neurosci., CUNY Sch. of Med. at City Col. of New York, New York, NY

Abstract: Cholinergic interneurons (CIN) are cytohistological and molecularly heterogenous, critically involved in producing smooth movement, and allow procedural and reinforcement learning. CIN integrate information streams carried by glutamate from cortex and thalamus and their activity is modulated by over 40 different signals impinging on release of acetylcholine (ACh), and likely other co-transmitters and peptidergic signaling molecules co-expressed by CIN. How the complexity of signaling modalities in which CIN engage is mapped onto molecular defined subtypes of CIN is unknown. Recently it was found that only about half of all

CIN elaborate a primary cilium, a cellular organelle known to serve as a dedicated signaling hub for the reception of extra-cellular signals that engage G protein coupled receptors (GPCRs). A paradigmatic example of cilium-dependent signaling pathway is Sonic Hedgehog (Shh) / Smoothened (Smo). We and others have found that about half of CINs are trophically dependent on Shh/Smo signaling long term and that Shh/Smo signaling impinges on CIN physiology in a graded, bidirectional manner short term. To identify effectors by which Shh/Smo signaling impinges on CIN physiology, we performed gene expression profiling using affinity purified mRNA from CIN of mice with ablation of Shh from dopamine (DA) neurons and controls. Those experiments revealed that Smo signaling is required for maintaining expression of the orphan GPCR GPR139 in CIN. GPR139 expression in the wild-type striatum reveals a prominent low (medial) to high (lateral) expression gradient suggesting that GPR139 contributes to regionally patterned CIN diversity.GPR139 is a negative modulator of endo-opioid signaling acting downstream of mu-opioid receptor (MOR) activation by morphine and fentanyl. Morphine decreases ACh release, while antagonists of MOR increase striatal ACh. We use fiber photometry with AAV GRAB sensors for DA and ACh to monitor extracellular levels of DA and ACh in the striatum of mice with loss and gain of function of Smo signaling combined with Smo and GPR139 specific pharmacology. Preliminary results indicate GPR 139 increases ACh release. Further, consistent with increased cholinergic activity we observe activation of Smo counteracts place preference formation.

Disclosures: D.R. Zuelke: None. **N. Gentile:** None. **A.H. Kottmann:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.009/LBA90

Topic: E.03. Basal Ganglia

Support: Parkinson's Foundation PF-PRF-836910
Parkinson's Foundation P0576337
NIH R01NS101354
ASAP ASAP-020529

Title: Aberrant Striatal Activity Causes Abnormal Decision-making in a Mouse Model of Impulse Control Disorder in Parkinson's Disease

Authors: *X. ZHUANG[1], J. LEMAK[2], S. SRIDHAR[3], A. B. NELSON[4];
[1]Univ. of California, San Francisco (UCSF), San Francisco, CA; [2]Neurol., Univ. of California San Francisco, San Francisco, CA; [3]Univ. of California, San Francisco, San Francisco, CA; [4]Neurol., UCSF, San Francisco, CA

Abstract: Impulsive decision-making is common across multiple neuropsychiatric disorders. One notable instance occurs in Parkinson's disease (PD), where impulsive decision-making occurs in the context of dopamine replacement therapy for motor symptoms. Impulse control disorder (ICD) can manifest as pathological gambling, compulsive shopping, binge eating, or hypersexuality, and is more common in patients treated with dopamine agonists. So far, most knowledge about ICD is from clinical studies and a few rodent behavioral studies. Convergent evidence suggests that the input nucleus of the basal ganglia, the striatum, is a critical site of circuit dysfunction in ICD. Within striatum, D2Rs are densely expressed on indirect pathway medium spiny neurons (iMSNs). In the context of decision making, excitatory prefrontal cortex (mPFC) inputs onto striatal neurons are another circuit substrate of ICD. Thus, little is known about the role of local striatal circuitry and its top-down cortical inputs in ICD. Our previous study adapted a delay discounting task to model a clinically-relevant rodent model of ICD in PD. We combined this model with optically identified single-unit recordings, optogenetics, chemogenetics in awake, behaving mice, along with ex vivo electrophysiology, to examine the role of striatal activity and mPFC-striatal synaptic connectivity in impulsive decision-making. In parkinsonian mice, we found that direct pathway medium spiny neurons (dMSNs) increased firing around reward delivery and iMSNs ramped their activity during delay periods, suggesting their involvement in encoding key aspects of delay discounting. Furthermore, PPX induced marked bidirectional changes in the firing of striatal dMSNs and iMSNs. Chemogenetic inhibition of striatal indirect pathway neurons in parkinsonian mice drove greater delay discounting, suggesting a causal role in mediating ICD-like behaviors. Additionally, cortico-striatal excitatory synaptic inputs were suppressed by chronic PPX treatment in parkinsonian mice, and this suppression was further amplified by PPX bath application. These findings suggest a potential role in driving aberrant striatal activity in vivo and contribute to abnormal decision-making. These findings shed light on the potential mechanisms of impulsive decision-making in PD patients, but also inform the use of dopamine replacement therapy with a goal of ameliorating ICD.

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LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

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Program #/Poster #: LBA005.010/LBA91

Topic: E.03. Basal Ganglia

Support: NIH NINDS T32NS041218 to BJB
NIH NINDS 2R01NS097762-06A1 to PAF
NIH NINDS R00NS112417 to RCE

Title: The superior colliculus sends divergent excitatory and inhibitory inputs to the rostral and caudal subregions of the pedunculopontine nucleus

Authors: *B. J. BERNSTEIN[1], P. A. FORCELLI[3], R. C. EVANS[2];
[1]Interdisciplinary Program in Neurosci., [2]Dept. of Neurosci., Georgetown Univ. Med. Ctr., Washington, DC; [3]Dept. of Pharmacol. & Physiol., Georgetown Univ., Washington, DC

Abstract: Sensory-motor integration in the brainstem is crucial for daily functioning and ultimately survival. Two structures involved in this process are the pedunculopontine nucleus (PPN) and the superior colliculus (SC). The PPN is a heterogeneous structure that is critical for sleep, arousal, and motor function and is implicated in both Parkinson's disease (PD) and epilepsy. Stimulation of the PPN is therapeutic in animal models of both disorders with a topography that is specific to cell type and location. The SC is important for integrating multisensory inputs to trigger motor responses, but the effect of SC projections to subregions and different cell types of the PPN is unknown. To address this gap in knowledge, we injected channelrhodopsin (ChR2) into the SC of ChAT-Cre/Ai9 (tdTomato) mice to determine functional connectivity between SC synaptic inputs to PPN cholinergic neurons using optogenetics and whole-cell patch clamp recordings in *ex vivo* brain slices. We found that all cholinergic PPN neurons recorded received excitatory synaptic input from the SC. However, the strength of the connection differed across PPN subregions. Specifically, the caudal part of the PPN (pars compacta) received excitatory postsynaptic currents (EPSCs) with larger amplitudes compared to the rostral PPN (pars dissipata). Additionally, stimulation of the SC axon terminals more strongly evoked firing in caudal PPN cholinergic neurons. We also measured inhibitory connectivity and found that inhibitory SC inputs had a higher probability of connectivity and larger amplitude currents in the caudal PPN compared to the rostral subregion. In comparing the SC excitatory and inhibitory input to the PPN, the SC excited caudal PPN cholinergic neurons more strongly than it inhibited them. Together, our data show that the SC sends both inhibitory and excitatory input to PPN cholinergic neurons and innervates the caudal PPN more strongly than the rostral PPN. Given the important role the PPN plays in regulating arousal states and motor function, uncovering how the PPN responds to different inputs from the SC is important in understanding the modulation of movement in response to sensory stimuli.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

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Program #/Poster #: LBA005.011/LBA92

Topic: E.03. Basal Ganglia

Support: NIH 5R35NS132213-02

Sutherland-Merlino Fellowship

Title: Different modulations through direct and indirect pathways in Basal Ganglia

Authors: *E. GAO[1], J. E. RUBIN[3], A. H. GITTIS[2];
[1]Neurosci. Inst., [2]Biol. Sci., Carnegie Mellon Univ., Pittsburgh, PA; [3]Mathematics, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Substantia Nigra pars reticulata is the main output nuclei of basal ganglia. The regularity in its firing pattern have been found to be one of the main pathological characters of Parkinson's Disease. The two inhibitory GABAergic inputs from globus pallidus external segment(GPe) and Striatum have distinct characters on their synaptic current and kinetics, as well as on how they are affecting SNr firing pattern. In our study, we use optogenetic tool with *in vivo* and *in vitro* electrophysiology to investigate the synaptic characters of the two projections and how they affect SNr firing. We found that when activating GPe projections, the SNr firing rate does not change as much while the synaptic current appears to be large. On the other hand, with striatal projections activated, the SNr cells will cease firing while the synaptic currents are small but slow. With one pulse stimulation of GPe projections, we found SNr neurons fire even faster than its baseline firing rate. We further dissected a hyperpolarization-activating current, Ih current to be involved in understanding this discrepancy. With ZD7288, an Ih current blocker, the inhibition from GPe becomes stronger, wile the inhibition from striatum shows less change. Based on our current data, we believe that the large synaptic current transmitted through GPe projections can activate Ih current and depolarize SNr neuron to continue firing. On the other hand, striatal projections have smaller and slower inhibitory current, which continue to hyperpolarize SNr neurons, keeping them away from regular firing. Furthermore, with mathematical modeling, we concluded that the two inhibition projections not only have different power on phase-resetting, but also may advance or delay the phase of SNr firing.

Disclosures: E. Gao: A. Employment/Salary (full or part-time):; Carnegie Mellon University, Neuroscience Institute, Carnegie Mellon University, Center for Neural Basis of Cognition. **J.E. Rubin:** A. Employment/Salary (full or part-time):; University of Pittsburgh, Mathematics Department. **A.H. Gittis:** A. Employment/Salary (full or part-time):; Carnegie Mellon University, Biology Department.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.012/LBA93

Topic: E.03. Basal Ganglia

Support: Aligning Science Across Parkinson's ASAP-020-519

Title: Mapping open and closed loop motor circuitry with ultra-high field, multi-echo resting-state fMRI

Authors: *E. RIZOR[1], I. PAPPAS[3], N. M. DUNDON[4], J. WANG[5], J. STASIAK[6], A. C. BOSTAN[7], R. C. LAPATE[2], S. T. GRAFTON[8];
[2]Psychological & Brain Sci., [1]UC Santa Barbara, Goleta, CA; [3]USC's Mark and Mary Stevens Neuroimaging and Informatics Inst., USC, Los Angeles, CA; [4]Psychological & Brain Sci., UCSB, Santa Barbara, CA; [5]UCSB, Isla Vista, CA; [6]Univ. of California, Santa Barbara, Santa Barbara, CA; [7]Neurobio., Univ. of Pittsburgh, Pittsburgh, PA; [8]Psychological & Brain Sci., Univ. of California, Santa Barbara, CA

Abstract: Human movement is partly organized and executed by cortico-basal ganglia-thalamic closed-loop circuits (CLCs), wherein motor cortical areas both send to and receive feedback from the basal ganglia, particularly the dorsal putamen (PUTd). These networks are compromised in Parkinson's disease (PD) due to neurodegeneration of dopaminergic inputs to PUTd. Yet, fluid movement in PD can still occur, particularly when induced by emotionally arousing events. Rabies virus tracing in non-human primates has identified a potential alternative motor pathway, where the ventral putamen (PUTv) receives inputs from subcortical limbic areas (amygdala and nucleus basalis of Meynert) and sends outputs to motor cortical areas. We hypothesize that this separable open loop circuit (OLC) may exist in humans and explain the preservation of movement after CLC degradation. Here, we provide evidence for the human OLC with ultra-high field (7T), multi-echo functional magnetic resonance imaging. We acquired resting-state functional connectivity (FC) scans from 21 healthy adults (avg. age=29, 12M/9F, all right-handed) and mapped left-hemisphere seed-to-voxel connectivity to assess PUTv FC with putative subcortical inputs and motor cortical outputs. When examining subcortical limbic seed to putamen voxel FC, we found that amygdala ($p<0.05$, Cohen's $d=0.32$) and nucleus basalis ($p<0.0001$, $d=0.52$) FC was greater with PUTv when compared to PUTd. On the other hand, CLC subcortical seed (ventrolateral nucleus of thalamus) FC was greater with PUTd vs. PUTv ($p<0.01$, $d=0.61$). When examining cortical motor seed to striatal limbic voxel FC, we found that cingulate ($p<0.0001$, $d=1.52$) and supplementary ($p<0.0001$, $d=1.45$) motor areas had greater FC with PUTv vs. nucleus accumbens. When examining cortical motor seed to striatal motor voxel FC, we found that SMA had greater FC with PUTd vs. PUTv ($p<0.0001$, $d=0.98$), but cingulate and primary motor areas had no significant differences ($p>0.1$). Collectively, these results suggest that PUTv is functionally connected to motor cortical areas and may be integrated into a separable motor OLC with subcortical limbic inputs.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.013/LBA94

Topic: E.03. Basal Ganglia

Support: IRP of the NIH (ZIA NS009420)

Title: An etiology and novel therapeutic opportunity: iron regulation in a mouse model of stuttering

Authors: *M. MILLWATER[1], C. BRAGG[2], D. BISHOP[4], A. ADECK[5], S. SHEIKHBAHAEI[3];
[1]Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD; [3]NINDS, [2]NIH, Bethesda, MD; [4]NIH/ NINDS, Bethesda, MD; [5]Natl. Inst. of Hlth., Bethesda, MD

Abstract: Stuttering is a neurodevelopmental motor disorder characterized by involuntary disruptions in speech fluency. Specific mutations in genes involved in lysosomal enzyme-targeting pathways (such as *GNPTAB*) are linked to developmental stuttering. Transgenic mice engineered with one of these mutations (i.e. *Gnptab*-mutant) demonstrate complex, interrupted vocal bouts, which we characterized as 'stuttering' in mice. Recently, transcranial ultrasound in adults who stutter found moderate hyperechogenicity, a parameter associated with iron deposition. Herein, we confirm, assess, and alleviate iron deposition in *Gnptab*-mutant mice, ultimately reducing the 'stuttering' phenotype in mice. After recording vocalizations, *Gnptab*-mutant (n= 12) and control littermates (n= 9) were subsequently treated with iron chelator Deferiprone (3-Hydroxy-1,2-dimethyl-4(1H)-pyridone, 0.1 g/L) for 1 month *ad libitum* via water supply. After the experiments, the brains were extracted and fixed, and iron was detected by DAB-enhanced Perl's staining. Our data demonstrate that *Gnptab*-mutant mice have ~3-folds higher iron deposition in the medial lateral striatum, dorsolateral striatum, and central striatum ($p= 0.002$, $p= 0.001$, $p= 0.011$). Successful iron chelation therapy was confirmed via Perl's staining and behavioral tests. Ultrasonic vocalization data suggest that 'stuttering' vocalization decreased following iron chelator therapy. Together, our data indicate that *Gnptab*-mutant mice have an accumulation of brain iron that is alleviated with Deferiprone, ultimately improving the 'stuttering' phenotype. Accordingly, we posit a potential novel therapeutic opportunity and etiology in a subgroup of adults who stutter.

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Late-Breaking Poster

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Program #/Poster #: LBA005.014/LBA95

Topic: E.03. Basal Ganglia

Support: Hock E. Tan and K. Lisa Yang Center for Autism Research
Simons Foundation grant to the Simons Center for the Social Brain at MIT
Saks-Kavanaugh Foundation (AMG)
NIH/NIMH P50 MH119467

Title: Regulation of stereotypic behaviors by striato-dopamine circuit disruption and manipulation in ASD model mice

Authors: *E. HUESKE, K. HIROKANE, N. MANGAL, I. LAZARIDIS, J. AZOCAR, D. HU, C. ONUORA, S. BHAGAVATULA, A. KIM, T. YOSHIDA, J. LOFTUS, A. MAHAR, A. M. GRAYBIEL;
McGovern Inst. for Brain Res. at MIT, Cambridge, MA

Abstract: Repetitive or stereotyped actions are a hallmark feature of autism spectrum disorder (ASD). We previously demonstrated that repetitive stereotyped behaviors correlate with the degree of hyperactivation of striosomes, a striatal region connecting prefrontal cortex and the midbrain dopamine system. A subset of striosomal neurons, the D1-expressing “direct” pathway neurons, are unique amongst striatal neurons in forming direct projections to midbrain dopamine-containing neurons. Importantly, it is striosomal D1 neurons that exhibit clustered striosomal c-Fos expression in correlation with stereotypic behaviors.These correlational findings led us to ask whether striosomes contribute causally to stereotypic behaviors. To directly test this hypothesis, we titrated DREADD-based chemogenetic approaches in transgenic striosomal models for inhibition of striosomal neurons. In Shank3B KO ASD model mice, we find that chemogenetic inhibition of striosomal neurons reduced excessive levels of grooming behaviors. This confirms that long-observed correlations between striosomal activity and stereotypic behaviors are reflective of a causal role for striosome neurons in stereotypic behavior.On the strength of the finding that striosomal manipulation can mitigate stereotypic behaviors, and given the neurodevelopmental nature of ASD and related phenotypes, we turned to a developmental model of ASD. Recent literature has demonstrated that stereotypic behaviors and other ASD-relevant phenotypes arise in offspring exposed to maternal immune activation (MIA). This was observed when MIA was induced at embryonic day 12, a time point in gestation centered on striosomal neuron generation and migration to the striatum. We therefore asked whether MIA disrupts striosome or striosome-dopamine circuit development, as a potential mechanism for the development of stereotypic behaviors in MIA offspring mice. We confirm that MIA offspring exhibit stereotypic behaviors and find disrupted expression of prepronociceptin (*Pnoc*), a gene we have reported to be selectively expressed in striosomes in dorsal striatum and known in development to influence developmental processes through activation of developmental regulator NF-kB. We report in an adjoining study that *Pnoc* is expressed selectively in dopamine-projecting striosomal D1 neurons, the same population that exhibits striosomal cfos clustering in correlation with stereotypies. Our findings support a model of striosomal-dopamine circuit disruption as a mechanism for the development of stereotypic behaviors, and as a potential therapeutic lever in the context of ASD.

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Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.015/LBA96

Topic: E.04. Voluntary Movements

Support: 1 R01 NS111470

Title: Fast cortical network dynamics revealed with widefield voltage imaging in a forelimb water reaching task

Authors: Y. WANG[1], S. KIM[2], H. CHOI[3], ***D. JAEGER**[1];
[1]Emory Univ., Atlanta, GA; [2]Sch. of Mathematics, [3]Mathematics, Georgia Inst. of Technol., Atlanta, GA

Abstract: To understand fast signal processing at the cortical network level, we employed the JEDI-1P voltage sensor with soma-targeted expression in excitatory neurons to perform wide-field imaging. Imaging was performed through a cleared intact skull in adult head-fixed mice at a frame rate of 200Hz (Lu, X., Y. Wang, Z. Liu, Y. Gou, D. Jaeger and F. St-Pierre (2023). Nature Communications 14: 6423.) Adult mice (N=7) were trained on a cued water-reaching task. Spontaneous inter-trial activity often exhibited periods of pronounced 4-10Hz low frequency activity. At the onset of the sensory cue predicting water reward delivery such activity was suppressed and instead task activated networks appeared. Independent component analysis (ICA) revealed a distinct low-dimensional manifold of temporal dynamics related to the task that were exhibited in specific subnetworks. Generally, an ICA with 6 components sufficed to account for 90% of cortical activity variance. Notably functional networks revealed by ICA were remarkably similar between mice. Activity was in most cases bilaterally symmetric, though specific contralateral activity in S1 barrel cortex was seen for unilateral air-puff train stimuli, and a contralateral sensorimotor network was activated aligned with the reaching movement. Prior to reaching a near-global ramp-up of voltage was observed. Narrow band-pass filtered activity showed distinct frequency components in the delta, beta and gamma ranges at specific times in the task. We trained feedforward neural networks to classify either the stimulus or behavioral outcome based on neural activity at different task periods. Stimulus side was decoded most accurately from neural activity immediately after stimulus presentation (92.6±0.9% test accuracy). The neural classifiers were also able to predict the behavioral outcome of the task (reach or no-reach) based on neural activity preceding the response period (84.0±1.1%). Analysis of model weights showed that activity in the S1 barrel cortex was the strongest predictor for

stimulus side, while the model utilized activity from M1, M2, and RSC to predict the behavioral outcome. Overall our data indicate that multiple overlapping subnetworks show specific fast task related dynamics and are predictive of trial outcomes.

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Late-Breaking Poster

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Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.016/LBA97

Topic: E.04. Voluntary Movements

Title: Implicit adaptation to online vs terminal target error

Authors: *N. W. BUTLER[1], A. SZARKA[2], G. ESCHELMULLER[2], Z. WU[2], H. E. KIM[2], R. CHUA[2];
[1]Kinesiology, Univ. of British Columbia, Chilliwack, BC, Canada; [2]Kinesiology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: As we perform movements, we use our senses to dictate how we interact with the world around us and identify movement errors as they arise. Sensory information is used to choose effective movements using past experience, an estimation of the current body location, and the task parameters. Identifying errors between a movement and the target is integral to adapting more effective future movements. These errors are obtained through the misalignment of proprioceptive information, visual information of our body, and visual information about the target. It is well known that if the visual feedback of a reaching limb is manipulated, we are able to adapt our movements to decrease the error between the visual feedback of the limb and the target. Previous work has shown that exposure to online reach error induced by unseen target jumps can lead to implicit reach adaptation, even if online control reduces the terminal hand-to-target error by the end of the movement. We studied the effects of a terminal effector perturbation that counteracted the online error from a mid-saccade change in target location. Participants looked and reached to a peripheral target with their unseen hand. A cursor representing hand position was removed during the saccade and restored at movement end for terminal feedback. In the Target condition, the target jumped forward during the saccade, requiring participants to adjust their reach. In the Target-Effector condition, both target and cursor moved, with the change in cursor position resulting in a comparable perturbation size to the target jump. Participants effectively had to reach for the initial target position and not adjust for the jump to get the cursor on target. Participants were not informed of the target or cursor perturbation. We tested whether exposure to the target jumps produced reach aftereffects when reaching to stationary targets, and if perturbed terminal feedback of the reach position affected adaptation. All participants (12) adjusted their reaches when exposed to repeated target jumps to

maintain performance. When the terminal feedback cursor was also displaced to counteract the target jump, participants completed their reaches to the original target position. In no-feedback post-tests, participants (9) unaware of the target and cursor jumps showed implicit overshoot aftereffects only in the Target condition. The results suggest an interaction between adaptive changes due to online vs. terminal error signals.

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Program #/Poster #: LBA005.017/LBA98

Topic: E.04. Voluntary Movements

Title: In competitive games, players optimize their actions to the uncertainty about their opponents

Authors: *L. BANDINI, C. DE VICARIIS, V. SANGUINETI;
Univ. of Genoa, Genova, Italy

Abstract: During any form of social interaction, people need to coordinate in space and time to bring about a change in the environment. This is important also during rehabilitation where patients are required to perform movements that are difficult for them when done alone. Competitive settings may promote engagement and motivation, but the mechanisms of sensorimotor interaction and partner adaptation in these tasks are poorly understood.To study how much players account for the sensory information about their partner in competitive settings, we designed a robot-mediated ball game. Two players, an attacker (A) and a defender (D), sit at a computer screen and grasp the handle of a robot manipulandum. Player A shoots a ball vertically to score a goal. Player D must try to intercept the ball before it crosses a horizontal line. The players cannot see their partner's position before the ball is shot, but after that, A sees D’s position and D sees the ball. To understand the effect of partner location uncertainty on joint performance, we introduced three visual display modalities: zero (partner/ball fully visible), low (partner/ball visible as Gaussian noise), and infinite (partner/ball not visible) variance. The experimental protocol was organized into 9 epochs of 30 trials each. Within each epoch, the players experienced one combination of conditions.We compared the experimental results with a probabilistic computational model of interaction, which assumes that two agents use optimal prediction of partner action (modeled as a Kalman filter) and optimal selection of their action based on the stochastic minimization of a quadratic cost function. Given the competitive nature of the game, D must minimize the distance from the ball while A must maximize the ball distance from D. In both experimental results and model predictions, we analyzed the

distribution of the actions u_A (shooting position) and u_D (interception position). We used a Gaussian mixture model to describe the joint pdf of A and D. Overall we found that u_A exhibited a bimodal distribution, while u_D was unimodal. The distributions change systematically across conditions, indicating qualitatively different behaviors. We took the inter-cluster distance to quantify u_A and the dispersion for u_D. A 2-way ANOVA showed that A had greater inter-cluster distance as their information about D became more reliable. Surprisingly, this effect occurred even when D had more reliable information. In contrast, D's dispersion only increased when A had more reliable information.These results suggest that each player represents their partner's actions and adapts their representations to the partner's changes in experimental conditions.

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Late-Breaking Poster

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Program #/Poster #: LBA005.018/LBA99

Topic: E.04. Voluntary Movements

Support: NIH grant R01NS117699

Title: Contextual inference accounts for differences in motor learning under distinct training schedules

Authors: S. SHIVKUMAR[1], J. N. INGRAM[2], M. LENGYEL[3], *D. WOLPERT[1];
[1]Columbia Univ., New York, NY; [2]Columbia Univ., New Yorlk, NY; [3]Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Training schedules have long been known to affect the learning of multiple motor tasks (Shea & Morgan 1979). Training two tasks A and B in a blocked order (AAABBB) results in faster learning of A and B, but poorer retention, than interleaved (ABABAB) or random-order training. Explanations of these effects have been largely descriptive, characterizing the benefit of interleaving as due to either (a) learning a better representation that contrasts the two memories (Kornell & Bjork 2008), or (b) improved recall due to short-term forgetting during the other task (Lee & Magill 1983). Some studies have quantitatively modeled these effects, attributing reduced performance in a blocked design to forgetting (Lu et al. 2009). Here we examined whether differences in contextual inferences underlying the learning of the two motor memories could provide a statistical account of the differences in learning. Using COIN, a recently proposed Bayesian learning framework for motor learning (Heald et al. 2021), we found that the model predicted higher retention for an interleaved schedule, as seen in previous data. We confirmed this using a dual adaptation paradigm in which participants were exposed to opposing curl-fields (the context), with each field associated with a different point on a virtual tool (the

cue). Participants were trained in either a blocked or interleaved fashion, following which feedforward adaptation was measured at the end of training using a test block of channel trials in which the cues were interleaved. We found that the average adaptation was significantly higher for interleaved training compared to blocked training ($p<0.001$, log Bayes Factor=4.6).
The COIN model predicted the memory expressed on each trial as the weighted sum of the memory learned for each context weighed by the probability associated with the context. Analyzing the internal dynamics of the model revealed that the poor retention for blocked training was not due to decay of the initial memory, but to an over-reliance on the history of field transitions as opposed to the cue to infer the context for a trial. This allowed us to make the novel prediction that interleaving null-field trials (blocked+null condition) between each field trial in the blocked condition should improve retention, despite the larger number of trials between the first training block and the final test block. We confirmed this using the same paradigm and found that adaptation was significantly higher in the blocked+null condition compared to the standard blocked condition ($p<0.001$, log Bayes Factor=1.5). Our findings suggest that the effects of training schedules on motor learning are the result of contextual inference.

Disclosures: S. Shivkumar: None. **J.N. Ingram:** None. **M. Lengyel:** None. **D. Wolpert:** F. Consulting Fees (e.g., advisory boards); D.M.W is a consultant to CTRL-Labs Inc., in the Reality Labs Division of Meta. This entity did not support or influence this work..

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.019/LBA100

Topic: E.04. Voluntary Movements

Support: Royal Society Te Apārangi Marsden Fast-Start Grant 19-UOA-220

Title: Effects of sleep deprivation and threat on primary motor cortex function during selective stopping

Authors: *A. NIEUWENHUYS[1], C. G. WADSLEY[2], J. CIRILLO[3], J. KIM[1], R. SULLIVAN[1], W. D. BYBLOW[1];
[1]Dept. of Exercise Sciences, The Univ. of Auckland, Auckland, New Zealand; [2]Human Physiol., Univ. of Oregon, Eugene, OR; [3]Discipline of Physiol., The Univ. of Adelaide, Adelaide, Australia

Abstract: Study objectives: Adaptive responding in dynamic performance environments sometimes requires individuals to selectively cancel only a part of a multicomponent motor action. Sleep deprivation may negatively impact response inhibition in such response-selective stopping contexts. Especially under high stress, with previous research indicating amplified

hyper-limbic responding after sleep deprivation. The current study investigated effects of sleep deprivation on selective stopping in threat and no-threat conditions, using behavioral testing and non-invasive brain stimulation.
Methods: 19 healthy human participants underwent one night of total sleep deprivation (SD) versus normal sleep (NS) and subsequently performed a bimanual anticipatory response inhibition task under threat and no-threat conditions. Behavioral measures of going and stopping were taken, electromyographic (EMG) recordings were collected from task effectors, and corticomotor excitability (CME) and short- and long-interval intracortical inhibition (SICI and LICI) were assessed in primary motor cortex (M1), using transcranial magnetic stimulation that was implemented before ('early') and after ('late') presentation of the stop signal.
Results: Preliminary analysis using Bayesian repeated measures ANOVA revealed impaired response- and stopping-related success rates after SD compared to NS. Speed of stopping and stopping interference were not meaningfully impacted by SD. In-task CME at the early timepoint was elevated with SD, along with an earlier onset of response-related EMG bursts. SICI and LICI were not meaningfully impacted by SD. Threat did not meaningfully impact behavioral or neurophysiological measures of response inhibition, and no evidence was observed for interactions between sleep deprivation and threat.
Conclusions: Sleep deprivation negatively affects response- and stopping-related success rates in a selective stopping context. Elevated in-task CME at the early timepoint may reflect reduced suppression during response preparation. The absence of effects on stopping speed, SICI and LICI, however, suggests that effects of sleep deprivation on stopping success are unlikely to be due to inappropriate modulation of M1 intracortical inhibition during selective stopping. Instead, reduced stopping success may be associated with increased attentional lapses after sleep deprivation, or detriments to proactive response inhibition processes. No evidence was observed for the hypothesis that sleep deprived individuals have greater difficulty exercising top-down inhibitory control over their responses, specifically under high-threat.

Disclosures: A. Nieuwenhuys: None. **C.G. Wadsley:** None. **J. Cirillo:** None. **J. Kim:** None. **R. Sullivan:** None. **W.D. Byblow:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.020/Web Only

Topic: E.04. Voluntary Movements

Support: McNair Foundation

Title: Inferring the role of the intraparietal sulcus in movement inhibition based on inter-areal communication

Authors: *J. KANG[1], L. MATTAR[1], J. VERGARA DE LA FUENTE[1], H. G. REY[2], A. WATROUS[1], S. A. SHETH[1], B. Y. HAYDEN[1], E. BARTOLI[1];
[1]Baylor Col. of Med., Houston, TX; [2]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: The intraparietal sulcus (IPS) has been proposed to be involved in various cognitive and motor processes such as attention, movement planning, perceptual decisions, and working memory. Recent studies showed that IPS may also be involved in movement inhibition, but its role is currently debated. It has been suggested that IPS is related to planning and online control of movement and that it is functionally separated from the network for inhibitory control (Hannah and Jana, 2019). In contrast, human functional magnetic resonance imaging (fMRI) studies demonstrated that IPS and the inferior frontal gyrus (IFG), a critical node in the inhibition network, are functionally connected during movement inhibition and that transcranial magnetic stimulation (TMS) over IPS prolonged stop-signal reaction time (Osada et al., 2019; 2021). Due to limited temporal resolution in fMRI, whether and how the interplay between IPS and other brain regions subserves movement inhibition remains unclear. In the present study, we aim to establish the timing and directionality of communication flow between IPS and other cortical nodes during movement inhibition. We measured functional connectivity using local field potentials (LFPs) from intracranial electrodes in a sample of 19 human participants undergoing invasive monitoring for epilepsy (F=11; age range= 24 to 68y) while they performed a stop-signal task. We quantified LFP-LFP Granger causality and pairwise-phase consistency between IPS and a set of other brain regions recruited during inhibition control: IFG, anterior cingulate, insula, and orbitofrontal cortex (Zhang et al., 2017). Granger causality analyses revealed that information flows primarily from frontal areas to IPS but not vice versa. This suggests that IPS is primarily a receiver rather than a sender of information during movement inhibition. Furthermore, LFP-LFP phase alignment between IPS and IFG was higher in stop-success than stop-fail trials. Thus, sharing of information between IPS and IFG has a critical role in successful movement inhibition. In summary, our functional connectivity measures show that IPS is not a sender but a recipient of information and that the flow of information between IPS and IFG is higher during successful movement inhibition. In light on these findings, previous evidence of disrupted inhibition performance caused by TMS over IPS could be explained by the interruption in the flow of information from frontal areas to IPS. These top-down influences from frontal areas to IPS indicate that parietal regions are recruited to *aid* inhibition control, potentially by deploying attentive resources or adjusting movement plans following errors.

Disclosures: J. Kang: None. **L. Mattar:** None. **J. Vergara de la Fuente:** None. **H.G. Rey:** None. **A. Watrous:** None. **S.A. Sheth:** F. Consulting Fees (e.g., advisory boards); Abbott, Boston Scientific, NeuroPace, Zimmer Biomet. **B.Y. Hayden:** None. **E. Bartoli:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

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Topic: E.04. Voluntary Movements

Support: Centre interdisciplinaire de recherche sur le cerveau et l'apprentissage (CIRCA)
Fonds de recherche du Québec - Santé (FRSQ)
Natural Sciences and Engineering Research Council of Canada (NSERC)
Discovery Grant

Title: Mechanisms of interhemispheric connectivity between premotor areas and primary motor cortex: a dual-site TMS study

Authors: *L. K. CHIU[1], E. ALLAHVERDLOO[2], N. HARROUM[2], A. O'FARRELL[2], N. DANCAUSE[3], J. L. NEVA[2,1];
[1]Ctr. de recherche de l'institut universitaire de gériatrie de Montréal, Montreal, QC, Canada; [2]École de kinésiologie et des sciences de l'activité physique, [3]Dept. of Neurosciences, Univ. de Montréal, Montreal, QC, Canada

Abstract: Goal-directed movement production is associated with unique neurophysiological alterations in premotor and motor cortices. Premotor cortex (dorsal, PMd; ventral, PMv) contributes to movement execution by influencing primary motor cortex (M1) output within and between hemispheres. Here, we specifically investigated the interhemispheric connectivity from PMd and PMv to M1 using dual-site transcranial magnetic stimulation. The main objectives of this study were to examine the impact of the premotor areas (PMd and PMv) on M1 in the contralateral hemisphere by systematically varying (1) the stimulation sublocations within each premotor area, and (2) the interstimulus interval (ISI) between the premotor areas and contralateral M1. 30 right-handed young adults (15F; 26.5±4.3 yrs) participated in three experimental conditions to examine interhemispheric inhibition (IHI) between the two premotor areas and M1: (1) PMd to M1, (2) PMv to M1 and (3) M1 to M1. PMd and PMv locations were determined relative to the M1 hotspot of the first dorsal interosseous muscle (PMd: 2 cm anterior, 1 cm medial; PMv: 3 cm anterior, 2.5 cm lateral), using each participant's structural MRI. First, the sublocations within PMd and PMv were systematically examined using a 3x3 grid centered over each cortical region. To assess IHI, the conditioning stimulus was applied to each of the 9 sublocations over right PMd, PMv, and M1 at 10 ms ISI before the test stimulus over left M1. Second, we investigated the time course of IHI between PMd and PMv to contralateral M1 by testing ISIs of 0, 10, and 50 ms. IHI ratio was calculated by comparing the mean peak-to-peak motor evoked potential amplitudes of the conditioned to unconditioned trials at each sublocation and ISI. Overall, both premotor areas and M1 had distinct inhibitory effects on the contralateral M1 ($p<.001$) with a significant interaction effect between cortical region and grid location ($p=.0545$). The significant main effect of sublocations ($p<.001$) within (1) M1 showing greatest inhibition at the M1 hotspot with less inhibition at the other sublocations, (2) PMd showing greatest inhibition at a single non-central location, and (3) PMv showing no significant inhibition. For the time course of IHI, we found that each ISI showed significantly different magnitude of inhibition within each premotor area ($p<.001$). Further, we found significant inhibition for PMd at all ISIs (0, 10 and 50 ms), PMv for 0 ms ISI, and M1 for 0 and 50 ms ISIs. These results reveal distinct spatial and temporal neurophysiological mechanisms of

interhemispheric connectivity between premotor cortices and contralateral M1, which may play an important role in goal-directed movement.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.022/LBA102

Topic: E.04. Voluntary Movements

Support: NSF DGE 1828993
NIH R01NS123517
NIH R01NS130789
NIH U19NS118284
Stanford Human-Centered AI Seed Research Grant
Stanford University Wu Tsai Neurosciences Institute

Title: Compression as an analytical tool for detecting changes in spiking neural data after electrolytic lesioning

Authors: *A. TOR[1,2], Y. WU[2], L. YAMADA[3,4,2], S. CLARKE[3], T. WEISSMAN[2], P. NUYUJUKIAN[3,4,2,5,6];
[2]Electrical Engin., [3]Bioengineering, [4]Neurosurg., [5]Wu Tsai Neurosciences Inst., [6]Stanford Bio-X, [1]Stanford Univ., Stanford, CA

Abstract: The complexity of neural data changes as the brain processes information during events. Compression algorithms, which are information-theoretically sound and universally consistent, identify and exploit redundancies in data in order to compress it to essentially optimal sizes, regardless of underlying statistics. These algorithms may be used to conveniently and efficiently estimate a given signal's Shannon entropy, a biologically relevant measure of the complexity of a signal. It is therefore natural to explore their effectiveness in the analysis of spiking neural data. In this study, we focus on using compression to analyze recordings (96-channel Utah arrays) taken from two male adult rhesus macaques performing reaching tasks 3 days before and 3 days after administering electrolytic lesions in M1 (Subject U: 4 lesions, H: 3). In particular, we use the inverse compression ratio (ICR), which compares the sizes of compressed and uncompressed data to estimate the amount of statistically unique information. We calculate ICR with temporally-independent lossless compression (gzip), and temporally-dependent lossy compression (H.264). Because it is lossless, ICR calculated with gzip may be thought of as a direct, consistent estimator of the upper bound of the entropy rate of the signal. On the other hand, ICR calculated with lossy H.264, originally developed for video compression,

estimates entropy rate subject to tunable quantization meant to minimize visually observable distortion. We compare the performance of compression against standard techniques, such as average firing rates and Fano factor. We also compare compression to dimensionality reduction techniques, a class of methods typically used to assess noisy data by identifying meaningful low-dimensional subspaces, such as principal component analysis (PCA) and factor analysis (FA). Mann-Whitney U-tests and Mood's Median tests on aggregate data comparing each metric before and after lesioning reveal that ICR is able to significantly detect changes in neural activity for each lesion ($p < 0.01$ for both tests), where all other metrics are unable to consistently identify the effects of electrolytic lesioning with statistical significance. This suggests that compression algorithms may be a useful tool to detect the presence of statistical and structural changes in neural data. Information-theoretic analyses may complement techniques like dimensionality reduction and firing rate tuning as a convenient and efficient tool to characterize variance in neural data.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.023/LBA103

Topic: E.04. Voluntary Movements

Support: Rhodes Scholarship

Title: Striatal encoding of context-dependent reaching

Authors: *S. TINELLI[1], A. SHAROTT[2], Y. PENG[3];
[1]MRC Brain Network Dynamics Unit, Nuffield Dept. of Clin. Neurosciences, Univ. of Oxford, Oxford, United Kingdom; [2]Brain Network Dynamics Unit, Oxford, United Kingdom; [3]Inst. of Neurophysiol., Charite Univ., Berlin, Germany

Abstract: Paradoxical kinesia, a symptom of Parkinson’s disease which describes how some patients struggle to self-initiate movements but can perform the same movement if externally cued to do so, reveals an interesting and yet unexplained redundancy in the motor system. It has been suggested that this paradoxical movement is explained by differences in the routing of task-relevant motor information through unique brain regions during performance of internally generated and externally cued actions. It is unclear whether such differences would manifest at the level of single neurons, population dynamics or both. To investigate this question, we developed a behavioural task where head-fixed mice reach for a drop of sucrose solution, with the availability of the drop triggered by the initiation of the movement. Mice were trained to

perform reaches where reward availability was cued by an auditory tone or reaches were self-initiated within the same session. This enabled us to simultaneously record neurons from multiple brain areas (including premotor cortex, motor cortex, frontal regions and medial striatum) using Neuropixels probes while animals performed trials of different movement contexts (cued and self-initiated reaches) with the same movement kinematics. Preliminary results indicate that movement context is captured by low dimensional, linear latent dynamics in all regions, with the greatest difference between tasks found in the medial striatum. At the single unit level, a small proportion of premotor and striatal units appear to encode contextual information about reach type in a near-binary fashion. Striatal representation of context is stable compared to premotor units, indicating a more persistent functional role in the storage of contextual information during task performance. Upcoming recordings will investigate whether context is represented similarly across the mediolateral striatal axis. Revealing the neural mechanism underlying context-dependent movements could inform the development of improved therapeutic strategies for movement disorders.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.024/LBA104

Topic: E.04. Voluntary Movements

Support: NIH R01NS123517
NIH R01NS130789
NIH U19NS118284
Stanford Human-Centered AI Seed Research Grant
Stanford University Wu Tsai Neurosciences Institute
Stanford Wu Tsai Human Performance Alliance Research Fellowship
NSF GRFP DGE-1656518
Stanford Neurosciences Interdepartmental Program
NSF DGE-1828993
Fulbright Canada Student Award
Stanford Bioengineering Department Fellowship

Title: Impact of behavioral context on low-dimensional motor cortical state during unconstrained behavior using a wireless, fully-implanted, 1024-channel system

Authors: *M. SILVERNAGEL[1], A. Y. TOR[1], S. E. CLARKE[2], E. J. JUN[3], K. MARSHALL[2], R. SUTHERLAND[7], N. EVEN-CHEN[7], P. NUYUJUKIAN[2,4,1,5,6];
[1]Electrical Engin., [2]Bioengineering, [3]Neurosci., [4]Neurosurg., [5]Wu Tsai Neurosciences Inst., [6]Bio-X, Stanford Univ., Stanford, CA; [7]Neuralink, Fremont, CA

Abstract: A rich literature details how coordinated neuronal firing during the execution and planning of movement results in repeatedly observed dynamics (Svoboda 2018). Recently, there have been calls to evaluate whether classical findings -- which often constrain motion to reduce confounds -- persist during more complex movement (Gao 2015). Here, we show how similar movements performed in varying behavioral contexts (requiring seemingly different levels of movement complexity) result in low-dimensional state space offsets of the neuronal activity. In a rhesus macaque with a wireless 1024-channel system (N1, Neuralink, Fremont, CA) implanted in arm-related areas of motor and premotor cortex, we compared periods of unconstrained, seated arm movements to unstructured foraging for treats. All data were recorded on the same day. Seated arm movements were collected during a mouse-controlled grid task, where the animal moved a computer mouse to select highlighted squares on a 35x35 grid. This generated 1155, 500-ms reaching segments, which we combined with 1155, 500-ms segments from foraging. Using this joint dataset, we performed PCA and projected all data onto the top three PCs. This generated two distinct clusters of neuronal activity. After normalization, the distance between the centroids of these clusters was 0.3 ($p < 0.005$, permutation test; compare to 0.002 under the null hypothesis), and the angle separating the axis of maximum variance in each cluster was 70 degrees ($p < 0.005$, permutation test; compare to 1 degree under the null hypothesis). Notably, the computed dimensionality during the grid task and unconstrained foraging was nearly identical; to explain 75 percent of the cumulative variance, 137 dimensions were needed for the mouse task compared to 138 during foraging. In a separate laboratory, we compared similar activity in a rhesus with a 96-channel multielectrode array (Utah array, Blackrock Neurotech, Salt Lake City, UT) implanted in arm regions of motor cortex. Here, the animal performed a head-fixed, center-out reaching task followed by reaches for treats in our unconstrained observation enclosure (Silvernagel and Ling, 2021), with all data collected on the same day. Preliminary analysis supports the aforementioned results, though the N1's higher channel count yields clearer low-dimensional state trajectories, particularly at the single-trial level. Together, these results suggest that behavioral context has a sizeable impact on the low-dimensional neuronal state. Additionally, the preserved dimensionality across behavioral contexts warrants further study into whether similar neuronal dynamics can generate varied motor outputs.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.025/LBA105

Topic: E.04. Voluntary Movements

Support: Fulbright Canada Student Award
Stanford Bioengineering Department Fellowship
NIH R01NS123517
NIH R01NS130789
NIH U19NS118284
Stanford Human-Centered AI Seed Research Grant
Stanford University Wu Tsai Neurosciences Institute

Title: Tensor decomposition of local field potential dynamics in motor cortex permits robust prediction of behavioral setpoints and fluctuations in a multi-month arm reaching dataset

Authors: *K. MARSHALL[1], S. E. CLARKE[1], P. NUYUJUKIAN[1,2,3,4,5];
[1]Bioengineering, [2]Neurosurg., [3]Electrical Engin., [4]Wu Tsai Neurosciences Inst., [5]Stanford Bio-X, Stanford Univ., Stanford, CA

Abstract: While acute relationships between local field potential (LFP) spectrum features (i.e. bandpower, aperiodic exponent) and arm movement (i.e. reaction time, speed, angular error) exist in the motor cortex, it is unclear if similar structures exist over longer timescales. Finding such multiscale behavioral correlates could clarify how LFP oscillations shape movement. In spiking data, population factors are more stable than individual neurons. By analogy, LFP representations using correlated time-frequency activity may be more informative than single bands, motivating tensor decomposition.

Two adult male rhesus macaques performed a reaching task over months (H: n=87 days, U: n=105). Correlations were found between daily medians of reaction time and beta/gamma (Pearson's correlation, $p < 0.05$), as well as between speed and delta/aperiodic exponent ($p < 0.05$). A regression model (selected with Akaike information criterion, evaluated with a cross-validated coefficient of determination) decoded reaction time and reach speed on random heldout days (one-tailed bootstrap, $p < 0.05$). By contrast, a principal component (PC) model using median firing rates could not predict any behavioral metrics. Electrolytic lesions (H: n=8, U: n=4) were also performed in this period, and this data was used to test model robustness. Lesions produced atypical next-day changes in gamma power and aperiodic exponent (two-tailed bootstrap, $p < 0.05$); relatedly, this regression procedure could not predict behavior on heldout post-lesion days. But, when peri-movement time-frequency dynamics were arranged in a tensor (frequency x milliseconds x days), Tucker decomposition features produced similar speed and better reaction time predictions (paired one-tailed bootstrap, $p < 0.05$). The reaction time model was robust to lesions (one-tailed bootstrap, $p < 0.05$). Single-trial fluctuations around daily medians (H: n=57173 trials, U: n=68303) were then explored. Interestingly, all correlations were preserved ($p < 0.05$) except for between beta and reaction time. Finally, a tensor decomposition (over trials) produced better reaction time, speed, and angular error predictions ($p < 0.05$) than spectrum features, and was similar to a firing rate PC model. Tensor features were superior to both techniques when predicting post-lesion fluctuations ($p < 0.05$).

Overall, this work suggests LFP tensor decomposition features produce better predictions of movement performance at multiple temporal resolutions when compared to single bands and firing rates. It also hints at diverse roles played by individual oscillations in shaping movement at distinct timescales and in response to injury.

Disclosures: K. Marshall: None. **S.E. Clarke:** None. **P. Nuyujukian:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.026/LBA106

Topic: E.04. Voluntary Movements

Title: A subcortical pathway for mediating innate forelimb behaviors in mice

Authors: *S. A. LAVRENTYEVA[1], Z. WANG[2], M. BJORNI[3], A. YEH[4], E. H. FEINBERG[2]; [1]Anat., UCSF, San Francisco, CA; [2]Anat., [3]Univ. of California, San Francisco, San Francisco, CA; [4]Univ. of California Santa Barbara Neurosci., Cupertino, CA

Abstract: Many daily behaviors, such as picking up a cup of coffee, catching a ball, or swatting a bug, involve the forelimb. These movements range from reflexive to highly practiced, and previous work has largely examined circuitry that controls skilled forelimb movements. However, less is known about the circuitry for innate forelimb movements. Here we reveal that the midbrain structure superior colliculus (SC) drives touch-evoked innate reaches via projections to the premotor area lateral rostral medulla (latRM). We identified a novel behavioral paradigm in which head-fixed mice innately reach to repel somatosensory input to the whisker pad. Muscimol inactivation of SC disrupted animals' performance of touch-evoked reaches. Tracing showed that SC neurons project to latRM, which has been implicated in generating skilled forelimb behaviors (such as reach-to-grasp and lever-pressing). From electrophysiological recordings, we found that latRM neurons are active during innate reach onsets, thus positioning it as a potential site of convergence for various forelimb motor commands. In accordance with this, tracing revealed that latRM cells receiving input from motor cortex and the SC are commingled. Furthermore, we show that SC inactivation reduced reach-related activity in latRM neurons, suggesting a functional importance of the SC-latRM pathway for touch-evoked reaching. These findings not only define a subcortical pathway for forelimb behaviors, but also propose latRM as a site of convergence for movement commands from multiple different higher centers.

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Late-Breaking Poster

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Program #/Poster #: LBA005.027/LBA107

Topic: E.04. Voluntary Movements

Support: National Institute on Aging R01AG069227
National Institute of Dental & Craniofacial Research R01DE027236

Title: Impact of nerve block on the cortical decoding of tongue movements across axes of motion and marker regions

Authors: *C. HAHN[1,2], F. I. ARCE-MCSHANE[2,3,4];
[1]Paul G. Allen Sch. of Computer Sci. and Engin., [2]Dept. of Oral Hlth. Sciences, Sch. of Dent., [3]Div. of Neuroscience, Washington Natl. Primate Res. Ctr., [4]Grad. Program in Neurosci., Univ. of Washington, Seattle, WA

Abstract: The orofacial sensorimotor cortex plays an important role in controlling tongue and jaw movements in complex behaviors such as speaking and eating. Being able to reliably perform these movements has critical implications for people suffering from neurological diseases such as stroke, Alzheimer's disease, or Parkinson's disease, which are known to affect orofacial functions. Which features of the complex lingual function drive motor cortical activity is still poorly understood. Here we investigate how information in the orofacial primary motor cortex (MIo) varies based on factors such as absence of tactile sensation, axis of motion, and specific regions of the tongue. To answer this question, we tracked marker-based movements of the tongue and jaw while recording neural activity from implanted microelectrode arrays in MIo of two rhesus macaques (*Macaca mulatta*) engaged in feeding. We tested various machine learning models to predict tongue and jaw positions and found that long short-term memory neural networks had the best performance. Decoding accuracies of models based on (*i*) axis of motion, i.e., antero-posterior (x-axis), supero-inferior (y-axis), and medio-lateral (z-axis), (*ii*) tongue marker region (superficial or deep, anterior vs. intermediate vs. posterior), and (*iii*) local anesthesia applied to sensory branches of the trigeminal nerve, were then compared to evaluate the ability to predict MIo activity. Generally, decoding performance was best when using the supero-inferior tongue position and worst with medio-lateral position (Kruskal Wallis, $p<0.05$). The effect of tongue marker region was also apparent, as using tongue markers located in the posterior region for movements in the x-axis led to superior model performance (Kruskal Wallis, $p<0.05$). Model performance did not differ based on the depth of the tongue marker location (Mann-Whitney, $p>0.10$). Lastly, we found significant differences in model performance between control and nerve block conditions across all motion axes (Mann-Whitney, $p<0.05$), with the antero-posterior tongue movements showing the largest decrease in performance post-nerve block ($p<0.0001$). Overall, these findings indicate that information carried by MIo neurons differ as a function of the tongue's motion axis, region, available tactile information, and varying combinations of these factors. These have important implications for the development of evaluation tools, rehabilitation strategies, and neural prosthesis to restore orolingual function in particular and limb sensorimotor function in general.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

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Topic: E.04. Voluntary Movements

Support: NIH Grant U01 DC018671-01A1
NIDCD Grant K99 DC020235
NCATS Grant 5TL1TR001871-05

Title: The causal role of the middle precentral gyrus in speech-motor sequencing

Authors: *J. R. LIU, L. ZHAO, P. HULLETT, E. F. CHANG;
Univ. of California San Francisco, San Francisco, CA

Abstract: Fluent speech production requires the planning and articulation of accurately sequenced speech sounds. Though Broca's area has traditionally been thought to facilitate speech sequencing, recent studies have shown that damage to Broca's area does not often cause chronic speech production deficits. This has left the question of what neural populations causally control speech-motor sequencing unresolved. To address this, we used high-density direct cortical recordings while participants spoke utterances with varying syllabic sequence complexity. We identified a distributed cortical network with sustained activity modulated by the complexity of the sequences, across multiple speech areas including Broca's area and the posterior superior temporal gyrus, but strongest in the middle precentral gyrus (mPrCG). Only neural activity in the mPrCG both scaled with sequence complexity and predicted reaction time, suggesting that while other areas may be involved in higher level speech processing, the mPrCG may play a role in the motoric aspect of speech sequencing. To test whether the mPrCG is causally involved in speech-motor sequencing, we applied direct electrocortical stimulation to several areas whose neural activity was modulated by sequence complexity, while participants spoke a variety of speech sequences. We found that only stimulation in the mPrCG, and not Broca's area, caused speech disfluencies only when participants spoke complex speech sequences (like "catastrophe"), but not during simple sequences (like "papapa"). Disfluencies included increased syllable durations, increased syllable segmentation, distortions, and stuttering. Control trials ruled out other stimulation effects, such as anomia or speech arrest, as drivers of these errors. Together, these results show that stimulation of the mPrCG results in speech disfluencies resembling those of apraxia of speech, a clinical speech disorder of speech-motor sequencing and programming. In summary, we demonstrate the critical role of the mPrCG in speech-motor sequence planning and establish a neurophysiological link between speech sequencing, the mPrCG, and apraxia of speech. These results further our understanding of speech-motor sequencing and stress the necessity of accounting for the mPrCG in models of speech production.

Disclosures: J.R. Liu: None. **L. Zhao:** None. **P. Hullett:** None. **E.F. Chang:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.029/Web Only

Topic: E.05. Brain-Machine Interface

Support: National Sciences and Engineering Research Council of Canada
Canadian Foundation for Innovation
Ontario Research Fund
Canadian Institutes of Health Research

Title: On the importance of the type of imagined movement in EEG-based BCI systems

Authors: *A. MOSTOFINEJAD[1], G. MANSON[2], L. TREMBLAY[1];
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Queen's Univ., Kingston, ON, Canada

Abstract: Many EEG- and imagery-based BCI systems may have yielded limited functionality because the type of movements being imagined are too similar and/ or too vaguely characterized. To explore the relevance of distinctive imagined movements in EEG-based BCI systems, the current study employed two tasks that varied across five parameters including the somatotopic representation, side of the body, movement direction, transitiveness, and emotional valence. These two movements were: 1) signing one's name on a $10-million lottery ticket, and 2) raising one's left leg. Both movements were also contrasted with a no-movement, resting task. Participants (n = 28) first completed 120 trials of imagery followed by 120 trials of overt execution. Temporal and frequency-based EEG measures were assessed using a 32-electrode actiCAP system, with the main interest being to compare the tasks during the imagination. While the late positive component (LPC) over electrode P3 did not differ during imagination of the two experimental tasks, LPC associated with both tasks was different from rest. Also, there was a larger, negative motor-related component during the imagination of the leg-raise task at electrode Cz as compared to the sign and rest tasks. More importantly, differences were also found in the frequency domain. Imagination of the signing movement was associated with a significantly stronger pre-movement ERD at electrode C3 as compared to the leg raise and rest tasks. Also, imagination of the leg raise task was associated with a significantly stronger post-movement ERS at electrode Cz as compared to the rest and sign tasks. Critically, no single EEG measure could distinguish between all three conditions (e.g., both movements and rest) during action imagination. Also, the significant frequency measures were most likely associated with the somatotopic representation, side of the body, and transitiveness parameters. In sum, even if frequency-related measures were the most distinguishing features during action imagination, we

suggest that vastly different imagined movements should be selected for the design of BCI classifiers.

Disclosures: A. Mostofinejad: None. **G. Manson:** None. **L. Tremblay:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.030/LBA109

Topic: E.05. Brain-Machine Interface

Johns Hopkins University Whiting School of Engineering Student Initiatives Fund
The Undergraduate Catalyst Award by the Hopkins Office of Undergraduate Research

Title: An Intuitive and High Accuracy EEG-EMG Hybrid Brain Machine Interface for Telepresence Robot Control

Authors: *B. ZHOU, D. WANG, A. TINANA, K. HONG, M. KROLICK, Z. SAYYAH, B. BOCK, E. STEINBERG, S. PAVULURI;
Johns Hopkins Univ., Baltimore, MD

Abstract: Brain-machine interfaces (BMIs) have the potential to improve quality of life for those with severe motor impairments by enabling neural control of assistive devices. However, traditional non-invasive BMI based on electroencephalography (EEG) or electromyography (EMG) induce fatigue during prolonged use, reducing neural signal quality and compromising BMI performance. Additionally, traditional BMIs with numerous control options often require weeks of user training to achieve satisfactory accuracy, making them hard to learn and use. We propose a novel hybrid BMI that combines EEG Steady-State Visually Evoked Potentials (SSVEPs) and EMG signals from cheek and neck muscles to control a telepresence robot's locomotion as well as camera position. Maintaining compatibility with common severe motor impairments, measurements are limited to neural signals from the head and neck. This hybrid BMI features high decoding accuracy, minimal need for user training, and the potential to maintain multiple control options while mitigating fatigue through the alternation between EMG and EEG inputs.
Our hybrid BMI employs a Canonical Correlation Analysis (CCA) model to decode SSVEP signals and two logistic regression models for EMG signals from the zygomaticus (cheek) and the sternocleidomastoid (neck) muscles. We designed a non-simultaneous and a simultaneous experiment to collect data for the decoding algorithms. The non-simultaneous experiment provides independent EMG and EEG data for training, whereas the simultaneous experiment

provides intermixed EMG and EEG data more representative of the intended use case. Data from healthy subjects demonstrates that in non-simultaneous experiments the system achieves decoding accuracy of up to 87% for EMG and up to 100% for SSVEP in an experienced user. Notably, it also attains decoding accuracy of over 90% for EMG and over 80% for SSVEP in first-time users, showcasing usability without user training. In the simultaneous experiment, the system achieves over 76% accuracy in EMG decoding and 98% in SSVEP decoding for the experienced user, validating its performance for its intended use case. Our findings indicate the hybrid BMI's capacity for highly intuitive and accurate control, showing significant promise for improving the lives of individuals with severe motor disabilities. Future research will extend experiments to a larger and more diverse group of subjects, with and without motor disability, to enhance the scope of our data. We will also comprehensively characterize the hybrid BMI's performance (accuracy, latency, and information transfer rate) and quantify its impact on fatigue with the NASA Task Load Index (TLX).

Disclosures: B. Zhou: None. **D. Wang:** None. **A. Tinana:** None. **K. Hong:** None. **M. Krolick:** None. **Z. Sayyah:** None. **B. Bock:** None. **E. Steinberg:** None. **S. Pavuluri:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.031/LBA110

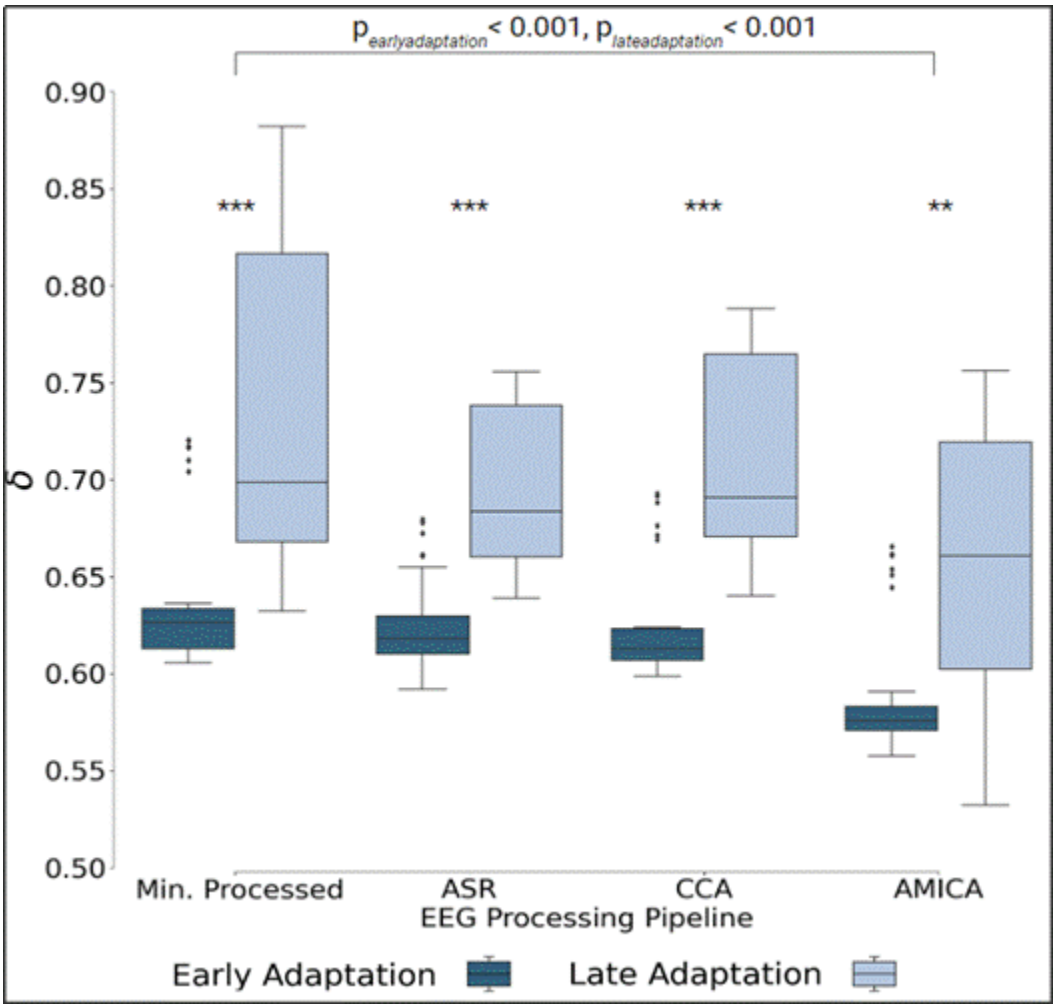
Topic: E.05. Brain-Machine Interface

Title: Evaluating the feasibility of EEG based complexity metrics to track human-robot interactions when walking with an active ankle exoskeleton

Authors: S. SULLIVAN[1], S. KERICK[1], K. MAHMOODI[1], *J. BRADFORD[2];
[1]US Army DEVCOM, US Army Res. Lab., APG, MD; [2]US DEVCOM US Army Res. Lab., Aberdeen Proving Ground, MD

Abstract: Many wearable robotics have been developed to augment human locomotion. Human-in-the-loop (HIL) optimization has been used to identify subject-specific assistive strategies to improve human-exoskeleton interactions, typically relying on biomechanics or metabolic energy cost functions. Electroencephalogram (EEG) is rarely used due to a lack of research characterizing neural features related to human-exoskeleton interactions. Wireless EEG devices have improved portability but suffer from poor signal-to-noise ratio during movement. We investigated whether EEG-derived complexity metrics, computed using Modified Diffusion Entropy Analysis (MDEA), could track human-exoskeleton interactions in noisy EEG. We applied MDEA to 128-channel wireless EEG collected while novice users walked with bilateral ankle exoskeleton assistance during early and late adaptation. We hypothesized that EEG complexity would change between early and late adaptation as subjects adapted to the

exoskeleton and that noise in the EEG signal would distort the difference between conditions. We found a significant decrease in mean complexity after removing noise from the EEG signal, but the relationship between complexity during early and late adaptation was not altered by the EEG noise removal pipeline. Significant correlations of mean complexities for all cleaning steps imply preserved temporal fluctuations. Our results suggest that MDEA may track changes in neural complexity related to human-exoskeleton interactions even in noisy EEG with minimal cleaning. Thus, EEG complexity metrics show potential for incorporation in HILO schemes for exoskeletons, enhancing the adaptability and performance of these assistive devices. **Figure 1. Mean complexities across EEG processing pipeline.** Statistical significance denoted as: ***p<0.001, **p<0.01, comparing early and late adaptation.



Disclosures: S. Sullivan: None. **S. Kerick:** None. **K. Mahmoodi:** None. **J. Bradford:** None.
Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

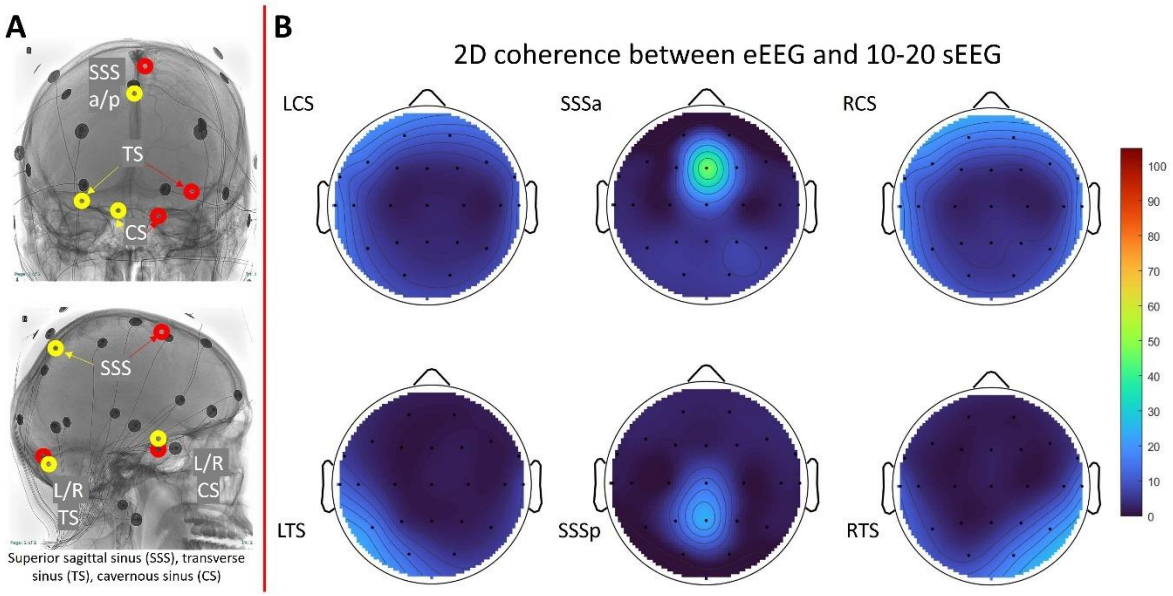
Program #/Poster #: LBA005.032/LBA111

Topic: E.05. Brain-Machine Interface

Title: Neural decoding using endovascular implanted electrodes: a coherence analysis.

Authors: *L. D. TORRES[1], K. SUZUKI[2], Y. MATSUMARU[2], K. ARAKI[2], Y. MASUDA[3], A. MARUSHIMA[2], H. HOSOO[2], M. HASSAN[2];
[1]Grad. Sch. of Sci. and Technol., Univ. of Tsukuba, Tsukuba, Ibaraki, Japan; [2]Univ. of Tsukuba, Tsukuba, Japan; [3]Univ. of Tsukuba, Tsukuba/ Ibaraki, Japan

Abstract: Introduction Brain-Machine Interface (BMI) systems have demonstrated potential in neural decoding applications. However, conventional electroencephalogram (EEG) systems face limitations in signal attenuation and invasiveness risks. To address these challenges, this study investigates a novel minimally invasive endovascular electroencephalogram (eEEG) approach. The objective is to evaluate the coherence and topological relevance of eEEG by comparing it to a standard EEG system. We aim to use endovascular electrodes to capture relevant and high-quality signals.Methods Neurological signals were recorded from an epileptic patient using a 10-20 EEG setup with 23 electrodes and 6 endovascular electrodes. Data was collected during a Wada test designed to elicit distinct neural responses.ExperimentsThe endovascular electrodes were placed in 6 locations as depicted in Figure 1A, the superior sagittal sinus (SSS anterior and posterior), cavernous sinus, and transverse sinus (left and right). The protocol was approved by the institutional board and registered on the Japan Registry of Clinical Trials, and written consent was obtained.ResultsAnalysis revealed strong topological patterns indicating coherence between the two EEG systems. The results for the entire recording (~50 minutes), illustrated in Figure 1B, show endovascular SSS electrodes (near to surface) to have the highest coherence of 47.605% for SSSp-Fz and 24.39% for SSSa-Pz. Coherence of the transverse sinus electrodes was less pronounced, and the cavernous sinus was the least due to their deep topological location compared to surface cortical areas. Further, activity-related analysis showed similar trends but with more pronounced coherence.Discussion & Conclusion The results underscore the proposed eEEG system's potential in neural decoding. Endovascular electrodes provide a minimally invasive alternative with enhanced signal quality. Future works will focus on refining the analysis methods to further
investigate the contents of eEEG, and their decomposition into sEEG to develop novel BMIs.



Disclosures: L.D. torres: None. **K. Suzuki:** None. **Y. Matsumaru:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual Property Rights. **K. Araki:** None. **Y. Masuda:** None. **A. Marushima:** None. **H. Hosoo:** None. **M. Hassan:** None.
Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.033/LBA112

Topic: E.05. Brain-Machine Interface

Support: NSF Graduate Research Fellowship Program
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Stanford University Wu Tsai Neurosciences Institute

Title: Latent subspaces, axis alignment, and labeled features for brain machine interfaces, an offline analysis

Authors: *M. U. ABDULLA[1], P. NUYUJUKIAN[1,2,3,4,5];
[1]Electrical Engin., [2]Bioengineering, [3]Neurosurg., [4]Wu Tsai Neurosciences Inst., [5]Stanford Bio-X, Stanford Univ., Stanford, CA

Abstract: Neural population activity is often modeled as a random process generated by underlying dynamic latent variables, which can be used to infer motor behaviors and control brain-machine interfaces (BMIs). In this work, we explore a linear discriminant (LDA) approach for extracting labeled features for constructing BMIs. We use retrospective data from one male rhesus macaque performing a center-out cursor control task over 16 experimental sessions (spanning 3 months). Firing activity in motor cortex was recorded using a 96-channel multi-electrode array.

First, we show that the subspace identified by multi-class orthogonal LDA performs significantly ($p < 0.0001$) better at isolating condition-dependent variance than demixed PCA (dPCA). Intended reach direction can be inferred more accurately using a Naive-Bayes decoder from instantaneous samples of LDA features (62% +/- 3%) than dPCA features (55% +/- 3%.) We also demonstrate that orthogonal LDA can be formulated as a generalization of dPCA with additional regularization reducing bias towards the first principal component.

Next, we show that the identified condition-dependent subspace has consistent structure (up to a rotation). Subspace methods like orthogonal LDA are rotation invariant, i.e. their objective functions depend on a subspace, not a particular choice of basis. Hence, an "optimal rotation matrix" was computed using an SVD-based method to align subspaces across sessions. A Naive-Bayes decoder trained on one session was found to maintain similar decoding accuracy (60% +/- 4%) on different days (after applying the optimal rotation.)

Finally, we extract labeled features from the condition-dependent subspace by mapping into a "decoding space," where each axis represents the probability the Naive-Bayes model assigns to a corresponding reach direction. Labeled features have important implications in the design of BMIs, as they allow the mapping between latent variables and control signals to be defined with a consistent, meaningful structure. As a proof of concept, we compare the short (< 1 week) and long-term (1 week - 3 months) performance of offline, linear, velocity-based BMI trained on one session in recreating cursor kinematics in different sessions. When trained on all collected neural data, an offline BMI performs 23% worse than an optimal linear model over short-term, and 82% worse long-term. When trained on labeled features, the offline BMI performs only 2% worse short-term and 7% worse long-term.

To summarize, we present a framework for extracting consistent, labeled features from neural data that may permit the design of BMIs with greater robustness to drift in the encoding of motor control.

Disclosures: M.U. Abdulla: None. **P. Nuyujukian:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.034/LBA113

Topic: E.05. Brain-Machine Interface

Support: NIH GRANT K00NS118719

Title: At-home cortical finely-tuned gamma tracking using subgaleal leads during deep brain stimulation for Parkinson's disease

Authors: A. CARRILLO SOLIS[1], **G.-P. OSBORNE**[1], R. FERNANDEZ-GAJARDO[1], S. CERNERA[1], S. S. WANG[2], D. D. WANG[1], S. LITTLE[2], P. A. STARR[1], *S. S. SANDOVAL-PISTORIUS[1];
[1]Neurolog. Surgery, [2]Neurol., Univ. of California San Francisco, San Francisco, CA

Abstract: Motor symptoms and therapeutic response in Parkinson's disease (PD) are linked to pathological oscillatory activity in cortico-basal ganglia circuits. Advances in deep brain stimulation have led to paradigms that adjust stimulation parameters based on neural signals (adaptive DBS), highlighting the need to identify physiomarkers that correlate with various brain states. Cortical physiomarkers are promising feedback signals for adaptive DBS but the lack of minimally invasive tools for long-term studies have made them difficult to explore. Studies of long-term cortical sensing use invasive subdural leads. this study aims to establish the feasibility of using permanent leads placed under the scalp, but above the skull (e.g., subgaleal) for at-home cortical sensing.
Three individuals with PD were implanted with bilateral sensing-enabled DBS devices (Percept PC), each connected to a directional lead targeting the subthalamic nucleus (STN) and a cortical lead placed in the subgaleal space over sensorimotor cortex. For cortical sensing, an octopolar 10.5 mm cylindrical segmented DBS lead was implanted over one side and an octopolar 57 mm paddle type lead, normally used for spinal cord stimulation, was implanted over the other side. We chronically tracked 60-65 Hz gamma local field potential (LFP) power using the Percept's "Timeline" function. Patients triggered the Percept's "Events" function at home when experiencing symptoms registered in their device (tremor, dyskinesia, rigidity, etc.) and at the time of levopdopa doses. When events are triggered, a 30 s snapshot of LFP power from 0-96.68 Hz is taken and stored.
We found that both subgaleal leads were able to detect a peak at 60-65 Hz activity and detect changes throughout the day that follow a circadian rhythm. Both subgaleal leads were also able to detect oscillatory activity within physiologically relevant frequency bands from Events LFP snapshots.
These findings suggest that subgaleal cortical sensing can be used with the Percept PCs at-home recording functions to detect brain-state specific changes in sensorimotor cortical activity, suggesting that subgaleal sensing may be used in adaptive DBS. On going studies will combine Events and Timeline data to assess medication-state specific fluctuations in 60-65 Hz gamma activity.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.035/LBA114

Topic: E.05. Brain-Machine Interface

Title: Neural Embedding Ranks: Aligning 3D latent dynamics with movement for long-term and cross-area decoding

Authors: *C. CHEN;
Johns Hopkins Med. Institutions, Baltimore, MD

Abstract: Introduction
It has long been thought that individual neurons in the motor cortex are tuned to specific movement parameters. Recent studies have found that the time-dependent activities of multiple simultaneously recorded neurons encode movements. In neuroscience and brain-machine interfaces, there is a strong motivation to reduce high-dimensional neural activities to lower-dimensional latent dynamics.
Related work
There are at least five categories of dimensionality reduction methods: 1) Linear methods such as PCA, jPCA, demixed PCA, and PSID. 2) Nonlinear methods like UMAP and tSNE. 3) Generative methods using recurrent neural networks or Transformers, such as LFADS, AutoLFADS, and NDT. 4) Label-guided generative methods using VAE, such as piVAE, SwapVAE, and TNDM. 5) Most recently, supervised contrastive learning methods such as CEBRA and MYOW.
Method
SoTA methods trained latent dynamics to classify different movement directions or positions using label-guided VAE or supervised contrastive learning. We are inspired by the fact that many features, including movements, are *continuous*, and a major task of many neurons is not classification but regression. For example, neurons display monotonic tunings to light intensity and sound levels. Even for discrete features like faces, neurons in the inferotemporal cortex encode *continuous* feature dimensions and can decode face identities using linear regression. We propose Neural Embedding Ranks (NER), which embed neural activities into a 3D latent space and contrast the embeddings based on movement ranks. Essentially, NER learns to regress *continuous* representations of neural activities (i.e., embeddings) on *continuous* movement.
Results
We apply NER and six other dimensionality reduction techniques to neurons in the primary motor cortex (M1), dorsal premotor cortex (PMd), and primary somatosensory cortex (S1) as monkeys perform reaching tasks. Only NER aligns latent dynamics with both hand position and direction, visualizable in 3D. NER reveals consistent latent dynamics in M1 and PMd across sixteen sessions over one year. A linear regression decoder with NER explains 86% and 97% of the variance in velocity and position, respectively. Linear models trained on data from one session can decode velocity, position, and direction in held-out test data from different dates and areas (64%, 88%, and 90%). NER also reveals distinct latent dynamics in S1 during consistent

movements and in M1 when the monkey performs curved reaching tasks.

Conclusion

NER is a neurally-inspired contrastive learning method designed to reduce high-dimensional neural activities to highly informative 3D latent dynamics.

Disclosures: C. Chen: None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.036/LBA115

Topic: E.05. Brain-Machine Interface

Support: Kootstra Talent Fellowship

Title: Decoding continuous goal-directed movement from human brain-wide intracranial recordings

Authors: *M. OTTENHOFF[1], M. VERWOERT[2], S. GOULIS[3], S. TOUSSEYN[5], M. M. SHANECHI[6], O. G. SANI[7], P. KUBBEN[1], C. HERFF[4];
[2]Neurosurg., [3]Cognitive Neurosci., [4]Fac. of Health, Med. and Life Sci., [1]Maastricht Univ., Maastricht, Netherlands; [5]Academic Ctr. of Epileptology Kempenhaeghe, Heeze, Netherlands; [6]Electrical and Computer Engin., Univ. of Southern California, Los Angeles, CA; [7]Electrical and Computer Engin., USC, Los Angeles, CA

Abstract: Neural correlates of movement have been reported from nearly anywhere in the human brain, yet the content of these correlates remains unknown. Previous work and related studies have demonstrated that these brain-wide neural correlates can be decoded into numerous, mostly discrete movement parameters (including grasping types, movement direction or force) from many cortical and subcortical brain areas. In this work, we provide a comprehensive overview by decoding 12 movement kinematics continuously, reflecting essential components of the behavioral complexities of goal-directed movement in daily life. We designed a gamified movement task that captured 3D hand movement trajectories using a motion tracker. In total, we recorded 3 hours and 19 minutes of three dimensional goal-directed hand movement from 18 participants implanted with stereotactic-electroencephalography electrodes, capturing neural data from 122 unique brain areas with 1903 individual recording sites. Using preferential subspace identification (PSID), we demonstrate that hand movement speed can be decoded significantly above chance for any electrode configuration or frequency information included in this work. Specifically, using delta activity (i.e. a low-pass filter at <5 Hz) the decoder reached the highest average reconstruction correlation of 0.39 ± 0.21 (mean, standard deviation) and a maximum of 0.72 ± 0.02, whereas broad-band high-gamma power and alpha-beta power reached 0.26 ± 0.14

and 0.37 ± 0.15, respectively. Additionally, we show that velocity (i.e. directional speed) can be decoded significantly above chance using delta activity (V_x =0.16 ± 0.12, V_y=0.13 ± 0.11 and V_z=0.19 ± 0.16). Finally, we demonstrate that significant neural correlates of hand movement speed are present throughout the brain, including deeper structures such as the hippocampus, basal ganglia and insula. These results corroborate that nearly the whole brain is involved during online motor behavior, where neural information is particularly present in the low frequency phase information and high frequency power. The ability to decode these pervasive neural correlates of online motor control shows that current motor brain-computer interfaces may not be capturing the full potential of the motor system. Moreover, these signals may open up new opportunities for new control signals for adaptive systems, for example adaptive deep brain stimulation.

Disclosures: M. Ottenhoff: None. **M. Verwoert:** None. **S. Goulis:** None. **S. Tousseyn:** None. **M.M. Shanechi:** None. **O.G. Sani:** None. **P. Kubben:** None. **C. Herff:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.037/LBA116

Topic: E.05. Brain-Machine Interface

Support: NSF 2011595
BMBF 01GQ1602

Title: Spatio-temporal Differences in Neural Activity between Prompted and Spontaneous Speaking Tasks

Authors: D. IVUCIC[1], M. DEXHEIMER[2], S. RIES-CORNOU[3], J. SHIH[4], ***D. KRUSIENSKI**[2], T. SCHULTZ[1];
[1]Univ. of Bremen, Bremen, Germany; [2]Virginia Commonwealth Univ., Richmond, VA; [3]Sch. of Speech, Language, and Hearing Sci., San Diego State Univ., San Diego, CA; [4]UCSD, San Diego, CA

Abstract: Intracranial Brain-Computer Interfaces (BCIs) that decode and synthesize speech have demonstrated significant advances toward restoring speech to individuals with severe neuromuscular disabilities. Despite this progress, data are often collected in controlled experiments relying on prompted speech. Brain processes associated with such speech can substantially differ from those of spontaneous speech, which is the desired mode of operation for a practical speech BCI. Thus, decoding models trained on prompted speech are suboptimal for decoding spontaneous speech.To examine the distinct brain processes associated with prompted and spontaneous speech, data were collected from 10 patients implanted with stereotactic EEG

(sEEG) for epileptic seizure localization. Patients performed three speaking tasks while their sEEG and voice were recorded: (1) prompted recitation (PR); (2) scene description (SD); and (3) free-response (FR) questions. The SD and FR tasks are open-ended and elicit natural, spontaneous verbal responses.The voice signals were labeled as either containing speech or silence. Broadband-gamma features were extracted from each sEEG channel and correlated with the associated audio labels across temporal lags from -200 ms to +200 ms. Statistical significance was established via permutation tests. Electrodes were grouped by spatial regions of interest, with the majority of electrodes residing in left and right temporal and right frontal areas.The results show significant correlations of left and right temporal activity to speech with positive time lag for all tasks, reflecting auditory monitoring of self-speech production. PR produced higher temporal activation than spontaneous speech across all participants. Diverse activations were observed in frontal areas across tasks, possibly related to semantic planning. PR showed significant frontal activation between cue and speech-onset. For the spontaneous speech tasks, frontal activation remained increased during task execution; unaffected activity by speech production for SD, and slightly increased activation during periods of silence for FR. These results suggest that spontaneous speech production, in contrast to prompted recitation, shows significant differences in neural activations and thus warrants a different basis for speech decoding. While future work is needed to assess differences in other important speech-related regions not sufficiently sampled in this study, such as motor cortex, and implications for speech decoding performance, this study highlights the importance of more naturalistic speech data in the development of speech BCIs.

Disclosures: D. Ivucic: None. **M. Dexheimer:** None. **S. Ries-cornou:** None. **J. Shih:** None. **D. Krusienski:** None. **T. Schultz:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.038/LBA117

Topic: E.05. Brain-Machine Interface

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Milton Safenowitz ALS Fellowship
IDE Caution Statement: CAUTION: Investigational Device. Limited by Federal Law to Investigational Use

Title: Surface muscle activity recordings improve offline motor decoding with intracortical brain-computer interfaces

Authors: N. HAHN, *[1], ***N. SHAH**[2], A. SINGH, *[3], C. FAN[4], A. D. LEVIN[3], D. AVANSINO[5], F. KAMDAR[6], S. NAUFEL[9], L. R. HOCHBERG[10], F. R. WILLETT[11], D. SUSSILLO[7], J. M. HENDERSON[8];
[1]Neurosurg., Stanford Univ., Mountain View, CA; [2]Stanford Univ., Palo Alto, CA; [3]Stanford Univ., Stanford, CA; [4]Stanford Univ., Sunnyvale, CA; [5]Electrical Engineering, Neurosurg., Stanford Univ., San Mateo, CA; [6]Stanford Univ., Moutnain View, CA; [7]Stanford Univ., Portola Valley, CA; [8]Dept Neurosurgy, R 227, Stanford Univ., Stanford, CA; [9]Reality Labs, San Mateo, CA; [10]Brown Univ., Providence, RI; [11]Neurosurg., Stanford Univ. / HHMI, Stanford, CA

Abstract: Intracortical brain-computer interfaces (iBCI) have restored communication for people with paralysis using cursor-based typing (Pandarinath et al. 2017) and handwriting (Willett et al. 2021). Here, we tested whether surface electromyography signals at the wrist could improve iBCI performance in two separate applications: (1) as a method to boost decoding performance for iBCI participants who may retain some residual muscle activity, and (2) as a way for obtaining large datasets from able-bodied people which could be used to initialize a deep learning decoder for later iBCI transfer.
Cortical signals were recorded from a BrainGate2 participant (T12) with dysarthria and impaired hand/finger movements resulting from ALS. Two 64-channel Utah arrays placed in the ventral left precentral gyrus exhibited neural signals related to the whole body, but with superior signal quality for orofacial and speech movements. Muscle activity was recorded using a 16-channel surface electromyography research wrist-based prototype (CTRL-labs at Reality Labs. 2024) placed on the right wrist of participant T12 and three able-bodied participants.
For classifying attempted finger movements (thumb flexion, extension, abduction & adduction, and all other finger extension & flexion) in T12, combining features from sEMG (RMS power) and cortical activity (threshold crossings as well as spike power) improved the offline classification accuracy from 75% (wrist-based sEMG only) & 79% (neural only) to 90% (both features). Similarly, for handwriting decoding with 25 training sentences, the character error rate (CER) improved from 38% (wrist-based sEMG-only) & 48% (Cortex-only) to 11% (both features).
To evaluate the transfer learning approach, a deep learning decoder for handwriting was first pre-trained using 294 sentences of sEMG data from 3 able-bodied participants (who were also the authors of the abstract), which resulted in 10% CER. Fine-tuning this decoder with cortical activity for 60 sentences from T12 resulted in 6% CER, a significant decrease compared to 15% CER when the decoder was trained from random initialization.
The advantages of using sEMG recordings for improving cortical decoding may translate to different tasks (ex. cursor control & speech decoding) and iBCI participants (if they have residual sEMG). This improvement may be due to a combination of statistical (ex. more channels for the same underlying phenomenon), biological (ex. sEMG and neural activity represent different aspects of movements) or behavioral factors (ex. wrist-based sEMG captures the handwriting style and sentence structure that transfers to cortical decoding).

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.039/LBA118

Topic: E.05. Brain-Machine Interface

Support: R01NS121079

Title: Exploring threshold crossing inter-electrode correlation as a method of common-noise artifact detection in Utah arrays

Authors: *T. SCHOENHERR[1,3], W. HOCKEIMER[3,4], N. G. KUNIGK[5,6,3], J. L. COLLINGER[3,5,4,6,1], S. M. CHASE[2,1,6];
[1]Biomed. Engin., [2]Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA; [3]Rehab Neural Engin. Labs, [4]Physical Med. and Rehabil., [5]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA; [6]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA

Abstract: Intracortical brain computer interfaces (iBCI) are a promising technology to restore motor function, but factors including signal disruptions will likely limit widespread adoption.

iBCIs record neural activity from hundreds of electrodes, and some disruptions, referred to as common-noise artifacts, can be identified by simultaneous voltage changes across many electrodes[1]. Here we apply a previously proposed method, inter-electrode correlation (IEC)[2], in humans implanted with Utah arrays to evaluate whether IEC can reliably identify sessions with variable signal quality or noise.

Two participants with cervical spinal cord injury each had four Utah arrays implanted in their sensorimotor cortex for an ongoing clinical trial of an iBCI conducted under an Investigational Device Exemption (NCT 01894802). Each session, one minute of full bandwidth voltage data was recorded at 30 kHz while participants were instructed to remain still. They then completed an iBCI cursor control task, which was categorized as "good" or "bad" based on task performance. For every threshold crossing (TC) recorded on each channel during the rest session, we calculated the Pearson correlation between the TC waveform and concurrent segments on all other channels. From this, we constructed a distribution of IEC values. In sessions with good iBCI performance (n = 12), the distribution of IEC values had a Gaussian distribution, with only 2.0% (IQR 1.2%-13.3%) of TCs falling outside of the Gaussian distribution (one-sample KS Test, $p < 0.05$). In sessions with poor performance (n = 18), 8.6% (IQR 4.7%-37.6%) of TCs fell outside of a Gaussian distribution (one-sample KS test, $p < 0.05$). These data suggest that sessions with more signal disruptions during the baseline period were less likely to have good iBCI control, possibly due to ongoing challenges with noise or artifact.

We next collected data with deliberate motion artifact to test whether movement caused a similar change in the IEC distribution. Neural data was recorded while a participant performed overt head movements or remained still while the iBCI connection cable was manipulated. The percentage of TCs outside of the Gaussian distribution (one-sample KS test, $p < 0.05$) went from 4.4% while the participant was at rest to 10.6% in a recording with overt head movement to 40.6% in a recording with a manipulated cable.

These results provide the framework for a statistical method to determine whether a threshold crossing is likely noise. This may be leveraged to correct for the presence of common-noise artifact online during closed-loop iBCI control as well as label artifact offline to train more robust machine learning models[1].

Disclosures: T. Schoenherr: None. **W. Hockeimer:** None. **N.G. Kunigk:** None. **J.L. Collinger:** 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.; Blackrock Microsystems. **S.M. Chase:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.040/LBA119

Topic: E.06. Posture and Gait

Title: Whole-body simulation of realistic fruit fly locomotion with deep reinforcement learning

Authors: R. VAXENBURG[1], I. SIWANOWICZ[1], J. MEREL[2], A. A. ROBIE[1], C. MORROW[1], G. NOVATI[3], ***G.-J. BOTH**[5], Z. STEFANIDI[6,1], G. M. CARD[7,1], M. B. REISER[1], M. M. BOTVINICK[8,9], K. M. BRANSON[1], Y. TASSA[4], S. C. TURAGA[1];
[1]HHMI Janelia Res. Campus, Ashburn, VA; [2]Fauna Robotics, New York, NY; [4]Robotics, [3]Google DeepMind, London, United Kingdom; [5]Janelia / HHMI, Ashburn, VA; [6]Tubingen Univ., Tubingen, Germany; [7]Neurosci., Columbia Univ., New York, NY; [8]Gatsby Computat. Neurosci. Unit, Univ. Col. London, London, United Kingdom; [9]Google Deepmind, London, United Kingdom

Abstract: The body of an animal determines how the nervous system produces behavior. Therefore, detailed modeling of the neural control of sensorimotor behavior requires a detailed model of the body. Here we contribute an anatomically-detailed biomechanical whole-body model of the fruit fly Drosophila melanogaster in the MuJoCo physics engine. Our model is general-purpose, enabling the simulation of diverse fly behaviors, both on land and in the air. We demonstrate the generality of our model by simulating realistic locomotion, both flight and walking. To support these behaviors, we have extended MuJoCo with phenomenological models of fluid forces and adhesion forces. Through data-driven end-to-end reinforcement learning, we demonstrate that these advances enable the training of neural network controllers capable of realistic locomotion along complex trajectories based on high-level steering control signals. With a visually guided flight task, we demonstrate a neural controller that can use the vision sensors of the body model to control and steer flight. Our project is an open-source platform for modeling neural control of sensorimotor behavior in an embodied context.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.041/LBA120

Topic: E.06. Posture and Gait

Support: NSF 2137255

Title: Neural Correlates and Gait Decoding for Treadmill Walking in Neurotypical Children

Authors: *M. PATRICK KRUEGER[1], J. L. CONTRERAS-VIDAL[2];
[2]Electrical and Computer Engin., [1]Univ. of Houston, Houston, TX

Abstract: Researchers in rehabilitative medicine are currently developing brain-computer interface (BCI) systems to connect the intent-to-move with physical movement to restore functionality. While BCI has shown promising results for adult neuromotor rehabilitation, research in the pediatric population has lagged. Children in various neuromechanical developmental phases have instinctive drive to ambulate and innate desire to 'play', giving the potential for greatest efficacy from these therapies, even with limited device availability. To address the knowledge gaps in the understanding of brain signals in developing children while walking and to investigate changes that occur during pediatric neuromotor development, a virtual reality avatar was used to engage 23 (13F/10M) neurotypical children aged 6-12 years while they walked on a treadmill with for 20 minutes. Multimodal data was collected for use in evaluating the neural correlates of treadmill walking as a precursor toward developing BCI controls of pediatric lower-limb exoskeletons. Multiple preprocessing pipelines were applied to the collected data with the results of each pipeline evaluated using each EEG frequency band, delta (0.1-4Hz), theta (4-7Hz), mu (7-12Hz), beta (12-30Hz), and gamma (30-49Hz), along with the combined frequency of 0.1-49Hz, with the resulting data z-score batch normalized and used as input to assess the accuracy of using Long Short-Term Memory (LSTM) and Gated Recurrent Unit (GRU) regressive deep learning algorithms with ten-fold cross validation. Pediatric gait decoding accuracy was determined using the RMSE between the predicted and measured lower-limb joint movements. It was determined that the neural activity during pediatric gait is similar to that of adults, with activation in the premotor cortex, somatosensory cortex, prefrontal cortex, and visual cortex. The gait can be predicted using EEG signals by using the LSTM algorithm. The LSTM output of all participants yielded a mean RMSE of 1.29 with SD 0.42 of z-scored data. Additionally, it was determined that using only the delta band yielded the most accurate results, where the mean RMSE of all participants was 1.1 with a SD of 0.38 of z-scored results.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.042/LBA121

Topic: E.06. Posture and Gait

Support: NIH Grant R01AG054621

Title: Group-level corticomuscular connectivity during seated locomotor perturbations for young and older adults

Authors: *S. TASIN[1], S. SHIRAZI[3], H. J. HUANG[2];
[2]Mechanical and Aerospace Engin. Dept., [1]Univ. of Central Florida, Orlando, FL; [3]Swartz Ctr. for Computat. Neurosci., Univ. of California San Diego, San Diego, CA

Abstract: Locomotor perturbations elicit electrocortical and muscular activities to monitor and potentially reduce motor errors. Perturbations may also increase muscular activation as well as increase corticomuscular connectivity (CMC). A variation of CMC in response to locomotor perturbations has not been examined. The purpose of this study was to quantify CMC patterns of young and older adults in response to brief perturbations during recumbent stepping. We hypothesized that CMC would increase around the perturbation timing, especially for efferent pathways, from the motor cortex to the driving muscles, namely, Posterior Deltoids and Rectus Femoris. We also hypothesized that the Anterior Cingulate Cortex (ACC) would have increased direct causal connectivity for afferent pathways from a subset of muscles around the perturbation timing. We recruited 17 young adults (11 females, age 25±4.9 years) and 11 older adults (4 females, age 68±3.6 years) and recorded their electrocortical and muscular activities during a repeated stepping task (four trials of 10 minutes each) on a recumbent stepper. The perturbations were brief 200 ms increases in the stepping resistance at leg extension-onset or leg mid-extension. We used a 128-channel electroencephalography (EEG) system to record electrocortical activity and 12 electromyography (EMG) sensors to record muscular activities. We used the direct Directed transfer function (dDTF) method to estimate directional connectivity between the estimated cortical source clusters from EEG and EMG of twelve muscles from the upper and lower limbs. Older adults had greater baseline connectivity in both efferent and afferent pathways (mixed ANOVA, $F(1,944)=14.1$, $p<0.0005$) with the afferent connectivity being weaker than the efferent connectivity. We found afferent connectivity during the extension onset perturbations where the Tibialis Anterior, Soleus, and Rectus Femoris muscles elicited ACC activity and during the mid-extension perturbations where the Rectus Femoris elicited ACC activity in young adults. Older adults did not have an ACC cluster and thus, no ACC-related CMC to observe. We also observed efferent connectivity from the left Posterior Parietal Cortex (PPC) to all muscles in older adults but not in young adults. Almost all left-side muscles showed bi-directional (afferent and efferent) connectivity with the motor cortex in older adults. The results provide evidence that modifying perturbation timing can change CMC and enhance specific corticomuscular pathways.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.043/LBA122

Topic: E.06. Posture and Gait

Support: NSF Career 1847891

Title: Practice improves performance and reduces attentional demands in locomotor adaptation

Authors: *S. LIU[1], N. W. BRANTLY[1], T. HUPPERT[2], D. J. WEBER[3], H. GEYER[3], G. TORRES-OVIEDO[1];
[1]Bioengineering, [2]Electrical and Computer Engin., Univ. of Pittsburgh, Pittsburgh, PA;
[3]Mechanical Engin., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Locomotor adaptation is the process of learning a new walking pattern when interacting with a novel environment and is important for mobility. Practice within even one day can improve locomotor adaptation, but the effect of practice on the neural control of locomotor adaptation is unknown. Prior work suggests that attentional control areas, such as the prefrontal cortex (PFC), are recruited in addition to task-specific areas, such as the motor cortex, to support the motor control of a new task, and, with practice, the task will be performed more automatically, freeing up the attentional resources. We hypothesize that learning a new walking pattern will initially be attentionally demanding and that practice will facilitate automaticity, resulting in better performance with decreased attentional control. To test this, 13 healthy young adult participants practiced a new walking pattern on a split-belt treadmill, where each leg was driven at a different speed. The attentional demand of split-belt walking (SBW) was measured by PFC activation assessed via functional near-infrared spectroscopy before and after five practice repetitions of alternating split- and tied-belt walking. We found that when participants first experienced SBW, PFC activation was significantly higher during SBW compared to standing rest ($t = 2.74$, $p = 0.02$) and tied-belt walking ($t = 3.47$, $p = 0.005$), suggesting that SBW is a novel task that requires attentional resources. After practice, participants improved their performance, as shown by a reduction in step length asymmetry during SBW ($t = -5.26$, $p < 0.001$). Additionally, a paired analysis comparing PFC activity before and after practice revealed that 9 out of 13 participants decreased their PFC activation relative to standing rest. At the group level, this reduction is trending but not significant yet ($t = -1.48$, $p = 0.17$). To confirm that the decrease in PFC activation indicates a transition from attentional to automatic control, rather than merely from treadmill familiarity, we also compared PFC activation during SBW before and after practice relative to tied-belt walking. We found that PFC activation decreased in 9 out of 13 participants. As a group, PFC activation decreased but not significantly ($t = -0.60$, $p = 0.56$). While these results are preliminary, they align with our hypothesis. With ongoing data collection, we expect to clarify if locomotor adaptation, such as learning a new walking pattern on the split-belt treadmill, requires attentional resources initially and becomes more automatic with practice. This study will elucidate the neural circuitry underlying locomotor adaptation and the development of expertise through practice.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.044/LBA123

Topic: E.06. Posture and Gait

Support: NIH R01 AG072756-01

Title: Transcranial magnetic stimulation (TMS) disruption of supplementary motor area (SMA) cortical activity reduces long-latency response in leg muscles during balance control

Authors: *E. ZHU[1], J. L. MIRDAMADI[2], K. KERR[3], S. BOEBINGER[5], R. RASTOGI[6], K. JAKUBOWSKI[7], R. RAJASHREE[4], N. A. BAUNE[2], M. R. BORICH[3], L. H. TING[8];
[1]Neurosci. Grad. Program, Emory Univ., Decatur, GA; [2]Rehabil. Med., [3]Emory Univ., Atlanta, GA; [4]Emory Univ., Decatur, GA; [5]Georgia Inst. of Technol., Atlanta, GA; [6]Northeastern Univ., Boston, MA; [7]Biomed. Engin., Northwestern Univ., Chicago, IL; [8]Biomed. Engin., Emory Univ. and Georgia Tech., Atlanta, GA

Abstract: Falls are a leading cause of injuries for older adults and people with neurological movement disorders. Understanding balance mechanisms is important for developing effective rehabilitation interventions to improve their movement and everyday well-being. Human cortical areas are involved in maintaining balance, especially in individuals with balance impairment. One previous study with TMS interference on the primary motor cortex (M1) reduces leg muscle activity during a balance task. However, the largest cortical activity observed by electroencephalography (EEG) during reactive balance control is localized to the supplementary motor area proper (SMAp), which has abundant projections to M1 and functions in elaborating complicated movements and regulating posture. SMAp activity during reactive balance responses is associated with clinical balance measurements, but the role of this cortical activity in balance-correcting muscle activity remains unclear. We hypothesize that the SMAp activity plays a causal role in standing balance control. The hypothesis was tested by applying transcranial magnetic stimulation to create a transient “virtual lesion” on the SMAp during backward support-surface perturbations. Each perturbation triggered a TMS or sham stimulation, targeting the SMAp leg region at the activity onset that starts at 80-120ms after a balance perturbation. During the perturbation, the electromyographic (EMG) responses of the participant’s leg muscles were recorded, with the main muscle responses to balance control beginning around 80-100ms. Simultaneously, motion capture recorded their kinematics during the balance perturbation. We predict the active TMS condition induces greater postural instability and a significant reduction in the leg EMG activity during the long-latency response period, which is the involuntary muscle activity occurring after 100ms and before the voluntary activity in response to a perturbation. Preliminary findings indicate that the active TMS targeting SMAp condition decreased the long-latency response activity of the lower-limb muscles, as compared to the sham TMS condition. Corresponding to the decrease in muscle activity, the body sway was greater and the joint angle illustrated a smaller deceleration of the body during the perturbation. Therefore, our initial results suggest that the cortex modulated part of the long-

latency response in leg muscles and helped stabilize human posture in balance control. Identifying a causal relationship between SMAp and muscle activities could provide a target for neuromodulation strategies aimed at enhancing balance.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.045/LBA124

Topic: E.06. Posture and Gait

Title: Enhancing diagnosis of vestibular schwannoma through task-specific gait analysis via machine learning classification

Authors: *S. SÁNCHEZ MANSO[1], L. C. KOHLER VOINOV[2], R. ARYAN[1], K. E. CULLEN[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Tsinghua Univ., Beijing, China

Abstract: Vestibular schwannoma (VS) patients exhibit different gait patterns, rendering diagnosis through classification of those patterns complicated. Machine learning (ML) techniques can aid in performing more accurate classification and a comprehensive understanding of how VS patients differ from each other. We recorded kinematic data from 32 VS subjects (ages 26-81) and 32 controls (ages 25-74) as they performed gait-related tasks, including a baseline task (regular gait, RG), a challenging task for all VS (ambulating backwards, AB), and a task with varying difficulty for different VS (gait with vertical head turns, VHT). Inertial measurement units on their ankle and back recorded 3-dimensional linear acceleration and angular velocity. Each recording was segmented into gait cycles to train and test a convolutional neural network classifier model. For the ankle sensor, RG presented an accuracy of 68.13% for controls and 61.42% for VS, showing on the baseline how healthy subjects are easier to classify than VS. Intuitively, in a lower dimensional space created by the model's feature selection, the controls occupy a cluster more condensed than the VS, whose distribution is more spread out, being harder to identify and classify. For AB, both control (78.45%) and VS (69.28%) accuracy improved drastically. This reflects the task difficulty for all VS samples, more homogeneous now, squeezing their feature cluster while also moving it away from the control one. However, for VHT, challenging only for some VS subjects, the accuracy gain appears for healthy, 77.68%, but not VS, 60.54%. This time the VS cluster drifts away from the control one without becoming tighter. VS samples behave as a whole more distant to controls but unalike from each other as the task affects them differently depending on diagnosis specifics. We

see the same tendencies on the back sensor, getting 68,19% and 65,59% for RG, 71,60% and 73,10% for AB, and 71,11% and 60,68% for VHT, for control and VS. The differences between feature clusters by task can be seen when performing a low-dimensional data representation with a U-map. Lastly, for the back sensor, we checked how many VS subjects were consistently misclassified: 10 for RG, 7 for AB, and 12 for VHT, supporting our previous finding. Our results highlight the task selection importance in VS classification. ML models are notably improved by using data from a task that, by its nature, maximizes the difference between groups, while minimizing variability within each. We reinforce the importance of ML techniques in the diagnosis and study of diseases where kinematic differences arise, as they provide new and valuable insight to discuss further clinical consequences.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.046/LBA125

Topic: E.06. Posture and Gait

Title: Rehabilitation of balance and gait in people after stroke - a clinical evaluation of a stretch reflex training tool - a pilot study

Authors: *K. GLOECKLER[1], D. NICKEL[2], A. SINN[2], J. WÄCHTERSHÄUSER[3], A. K. THOMPSON[4], N. MRACHACZ-KERSTING[5], U. G. KERSTING[6];
[1]Neuromechanics and Musculoskeletal Biomechanics, [2]Inst. of Biomechanics and Orthopaedics - German Sport Univ. Cologne, Cologne, Germany; [3]Univ. Konstanz, Konstanz, Germany; [4]Dept. of Hlth. Sci. and Research, Col. of Hlth. Professions, Med. Univ. of South Carolina, Awendaw, SC; [5]Albert Ludwig Univ. of Freiburg, Freiburg, Germany; [6]Biomechanics and Orthopaedics, German Sport Univ. Cologne, Cologne, Germany

Abstract: Operant conditioning has been shown to reduce the H-reflex and improve gait in patients with central nervous system lesions. Further, stretch reflex (SR) conditioning has shown success in healthy subjects suggesting a more direct link to motor function. This study aimed to evaluate the efficacy of a novel SR training tool (pedal) on reflex response and movement function. Three patients (57-67 years, > 2 years post-stroke, 1 male) completed the 10-week study, alongside regular rehabilitation. In each session, patients stood with the affected leg on the pedal inducing ankle dorsiflexion pertubations (10° at ~200°/s) to elicit the SR. Soleus SR size was measured by surface EMG for immediate visual feedback. The intervention comprised 6 baseline sessions followed by 24 training sessions, inducing 225 reflexes each. During training, patients aimed to reduce the SR based on the feedback. SR, spasticity (Tardieu scale), gait (6-

Min Walk Test, 2-Min Treadmill Walk Test) and balance (manual assessment of Mini BESTest, Limits of Stability (LoS in cm²; C-Mill, Motek) and Postural Stability (PS in cm/s; C-Mill, Motek), were measured and descriptively compared before and after the intervention. Results: Patient 1: SR -30%, Tardieu: no change, 6-Min Walk Test +38%, treadmill speed +25%, Mini BESTest +5%, PS -62%, LoS -86%. Patient 2: SR -6%, Tardieu: no change, 6-Min Walk Test +8%, treadmill speed +44%, Mini BESTest -12%, PS +6%, LoS +39%. Patient 3: SR +45%, Tardieu: no change, 6-Min Walk Test +7%, treadmill speed -25%, Mini BESTest +7%, PS +12%, LoS +411%. Results indicate a link between improvements in functional measures and successful SR down-conditioning. Patients perceived the conditioning training as highly beneficial, particularly in terms of improved perception of the paretic side and reported a general muscle relaxation. Therefore, further research should consider psychological aspects. Additionally, individual differences in the ability to concentrate on the visual feedback were observed. Testing cognitive ability could help to identify any connection to reflex adaptation. A further extension of the training period by 2 weeks, as suggested previously, may also be relevant for future studies. In conclusion, we observed changes in stretch reflex response accompanied by functional improvements using the new training tool. A clinical study is needed to provide conclusive results.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.047/LBA126

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R01NS123116

Title: The transcriptomic landscape of spinal V1 interneurons implicates a specific molecular subset in the control of locomotor speed

Authors: *A. TREVISAN[1], K. HAN[2], P. D. CHAPMAN[2], A. KULKARNI[3], J. HINTON[2], I. KLEIN[4], M. I. GABITTO[5], V. MENON[6], G. GATTO[7], J. BIKOFF[2];
[1]Developmental Neurobio., [2]St. Jude Children's Res. Hosp., Memphis, TN; [3]St Jude Children's Res. Hosp., Memphis, TN; [4]Neurol. Department, Univ. Hosp. of Cologne, Cologne, Germany, 50931 Cologne, Germany; [5]Allen Inst. for Brain Sci., Seattle, WA; [6]Columbia Univ., New York, NY; [7]Neurol., Univ. Hosp. Cologne, Cologne, Germany

Abstract: Neural circuits in the spinal cord are composed of diverse sets of interneurons that play a crucial role in shaping motor output. Despite progress in revealing the cellular architecture

of the spinal cord, the extent of cell type heterogeneity within cardinal interneuron classes remains unclear, hindering our understanding of the organization of the spinal motor infrastructure. Through a focus on a single cardinal class of spinal interneurons, here we present a comprehensive atlas of V1 interneuron diversity across postnatal development using single-nucleus transcriptomics. We find that cell-type diversity is largely preserved across postnatal development, providing insight into the molecular taxonomy that distinguishes both known and novel V1 clades from birth to adulthood. Interestingly, the transcription factor Engrailed-1 (En1), which delineates the parental V1 population, plays a critical role in the development of a highly restricted V1 subset while sparing the vast majority of V1 interneurons. En1 global and conditional knock-out mice exhibit slowed locomotor rhythm but do not exhibit hyperflexion, suggesting a dissociation between these two previously defined phenotypes that are observed upon ablation or inhibition of the larger V1 population. Beyond serving as a molecular resource for this neuronal population, our study highlights how deep neuronal profiling provides an entry point for the study of rare, specialized cell types in the spinal motor system.

Disclosures: A. Trevisan: None. **K. Han:** None. **P.D. Chapman:** None. **A. Kulkarni:** None. **J. Hinton:** None. **I. Klein:** None. **M.I. Gabitto:** None. **V. Menon:** None. **G. Gatto:** None. **J. Bikoff:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.048/LBA127

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R01NS130483

Title: V2a neurons are not required for local rhythmogenesis in zebrafish spinal cord

Authors: *C. TIAN[1], S. BELLO ROJAS[1], M. W. BAGNALL[2];
[1]Neurosci., Washington Univ. In St. Louis, Saint Louis, MO; [2]Washington Univ., Saint Louis, MO

Abstract: Locomotion is produced by spinal cord central pattern generators (CPG) composed of rhythmogenic neural circuits. To identify the source of this innate rhythmicity, the unit burst generator model proposes that the rhythmogenic neural population must provide both recurrent excitatory input back on itself and to motor neurons for direct motor output. In adult zebrafish, work suggests that *chx10+* V2a neurons provide local recurrent excitation for other V2a neurons and motor neurons to initiate and regulate locomotion, making them one possible candidate. However, in systematic mapping of V2a neurons output along the rostrocaudal axis of the spinal cord, we find in young zebrafish that V2a neurons make robust synaptic connections to other

V2a neurons and motor neurons at long ranges (4-6 segments), and weak, largely indirect connectivity locally. These results suggest that they cannot provide the local recurrent excitation hypothesized to underlie rhythmic motor activity. To test this idea on a functional level, we performed ventral root recordings of NMDA-induced fictive swim in spinalized larval zebrafish, while optically silencing V2a neurons expressing GtACR2, an anion channelrhodopsin. We first calibrated the optical stimuli via digital micromirror device (DMD) to ensure localized inhibition of V2a spiking. In current clamp recordings from V2a neurons *in vivo*, we determined that a 568 nm optical stimulus localized over the segment of the recorded neuron can inhibit all evoked spiking selectively within that segment. We next tested whether silencing V2a neurons in this spatially delimited fashion abolished the motor output. We found instead that local optical inhibition of V2a neurons did not affect motor activity. To test whether V2a neurons contribute to rhythm generation more broadly, we used a more effective 470 nm stimulus whose wavelength matches the absorption peak wavelength of GtACR2. In calibration experiments, we found that this optical stimulus suppressed spiking by more than 85% over a ~5 segment range, unlike the more localized inhibition provided by 568 nm light. During fictive locomotion, this optical stimulus robustly inhibited motor activity by 90%. Therefore, we conclude that the inhibition of V2a activity within one local segment is not sufficient to affect the motor output of spinal CPG. However, silencing the V2a neurons in at least 5 segments significantly reduces motor output. Our overall data suggest that V2a neurons do not provide the local excitation required for the rhythmogensis. Instead, they may be crucial for overall excitatory drive of other network elements that underlie local rhythmogenesis.

Disclosures: C. Tian: None. **S. Bello Rojas:** None. **M.W. Bagnall:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.049/LBA128

Topic: E.07. Rhythmic Motor Pattern Generation

Support: The Kavli Foundation Exploration Award
NSF IOS 1755098
Alfried-Krupp Fellowship

Title: Habitat- and species-specific temperature resilience in pattern generating circuits

Authors: *W. STEIN[1], S. HARZSCH[2];
[1]Illinois State Univ., Normal, IL; [2]Univ. of Greifswald, Greifswald, Germany

Abstract: Temperature fluctuations pose significant challenges to the nervous system of poikilothermic animals that lack active temperature regulation. Decapod crustaceans, key species

with massive impacts on food webs in marine coastal ecosystems, are particularly affected by rising habitat temperatures and heatwaves caused by global warming. The continuous functioning of their nervous system in changed habitat temperatures is critical for survival because it controls vital functions like heartbeat, respiration, digestion, and sensory abilities. This raises the question how resilient the nervous system is to temperature fluctuations, whether resilience is species- and habitat-dependent, and which cellular and circuit mechanisms enable temperature resilience.
Using the pyloric and gastric mill central pattern generators of the stomatogastric nervous system, we investigate temperature resilience mechanisms across decapod crustacean species that live in distinct temperature habitats. The pyloric and gastric mill motor patterns control aspects of feeding and can be recorded *in vitro* in all species. They are also generated by homologous neurons, enabling a comparative evaluation of habitat- and species-dependent neuronal properties and responses that facilitate temperature resilience.
The pyloric rhythm showed habitat- and species-specific differences in temperature resilience: When the isolated nervous system was challenged with high saline temperatures, rhythmic activity in species from colder and more stable habitats (subtidal and benthic) ceased at significantly lower temperatures than in intertidal species that experience rapid and more frequent habitat temperature fluctuations (subtidal/benthic species: *Cancer borealis*: 26.9 ± 1.4°C (N=10); *Cancer magister*: 24.9 ± 3.7°C (N=9); intertidal species: *Carcinus maenas*: 33.4 ± 1.3°C (N=10); *Hemigrapsus sanguineus*: 31.7 ± 3.0°C (N=10); *Callinectes sapidus*: 34.7 ± 3.5°C (N=17); $P<0.05$, One-Way Anova). Acclimation to higher habitat temperatures shifted the range of temperature resilience: *C. maenas* acclimated to 8°C crashed at 33.4 ± 3.5°C (N=10) and at 37.4 ± 1.1°C (N=9; $P<0.05$, T-test) when acclimated to 15°C. Thus, neuronal temperature resilience correlates with, and responds to, environmental temperature conditions.

Disclosures: W. Stein: None. **S. Harzsch:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.050/LBA129

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF Grant 1736019

Title: Physiological effects of Acute Exposure to MPTP on the Mammalian Spinal Central Pattern Generator Network for Locomotion

Authors: E. BOAMAH[1], *M. E. DIAZ-RIOS[2];
[1]Biol. and Neurosci., [2]Bowdoin Col., Brunswick, ME

Abstract: Despite current understanding on the toxic effects of the parkinsonism drug, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahdropyridine), on Substantia Nigra pars compacta neurons, its effect on neural circuits localized within the spinal cord that control locomotion remains elusive. MPTP crosses the blood-brain-barrier and can interact with the vesicular monoamine transporter 2 (VMAT2) or the mitochondria's complex I inducing neurotoxicity and reported parkinsonian symptoms in mouse models. We used the isolated lumbar region of the neonatal (P0-P6) mice spinal cord as a model to understand MPTP's effect on neural circuits that control hindlimb locomotion. Locomotor activity was induced via the application of serotonin (9-18 μM) and NMDA (6 μM), which has been previously shown to induce motor activity in this preparation. Motor neuron activity was obtained through suction electrode recordings of lumbar ventral roots related to flexor (L2) and extensor (L5) muscle activity in the presence of MPTP at 50 μM, 75 μM, and 100 μM concentrations. We assessed three parameters related to motor neuron activity including burst amplitude, burst duration, and cycle period. A 50 μM MPTP exposure produced variable response in amplitude for both L2 and L5; for example, amplitude increased in some preparation while it decreased in others. Cycle period increased for both ventral roots significantly for L2. At 75 μM concentration, burst amplitude increased for L5 but decreased for L2 while cycle period increased for both ventral roots. For both concentrations, burst duration remained unaffected except for L5-related activity at 75 μM where it was increased. An application of 100 μM of MPTP generally disrupted all motor activity irreversibly. The differential response in amplitude suggests that MPTP potentially exerts its effect on motor neurons via two distinct mechanisms: interaction with VMAT2 to disrupt neurotransmitter packaging and release, effectively decreasing amplitude. Alternatively, MPTP could interact with mitochondria's complex I, leading to ATP depletion and buildup of free radicals, inducing toxic excitation as seen via an increase amplitude. Overall, our results indicate that burst duration was not impacted, suggesting that MPTP might not be impacting the interneurons responsible for the CPG's control on motor neuron excitability; however, an increase in cycle period also suggests that MPTP might be impacting motor neurons indirectly by disrupting the speed of the network which is controlled by CPG interneurons. Our results provide an insight into how MPTP exerted neurotoxicity on neural circuits localized within the lumbar spinal cord.

Disclosures: E. Boamah: None. **M.E. Diaz-Rios:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.051/Web Only

Topic: E.08. Respiratory Regulation

Support: NIH Grant R01HL147279
NIH Grant R01HL133862

W.T. Gill Summer Fellowship

Title: Sex differences in respiratory response to two forms of oxytocin delivery following fentanyl administration in rats

Authors: *I. S. ABDULLAH, S. KAUR, J. B. ESCOBAR, J. WAINWRIGHT, O. DERGACHEVA, D. MENDELOWITZ;
Pharmacol. & Physiol., George Washington Univ. Sch. of Med. and Hlth. Sci., WASHINGTON, DC

Abstract: Although Naloxone remains the primary treatment for opioid-induced respiratory depression (OIRD), it often precipitates severe withdrawal-related side effects (e.g., nausea, vomiting, aggressive behavior). Previous research in rats suggests Oxytocin as a promising adjunct treatment for OIRD. These studies mostly involve male animals and typically use a single form of systemic Oxytocin (e.g., intranasal spray or intraperitoneal (IP) injection), leading to novel questions about its mechanisms of action and potential sex differences driving respiratory responses to opioids. This study examines the patterns of respiratory recovery following IP Fentanyl injection and subsequent administration of two forms of Oxytocin (chemogenetically-stimulated (endogenous) and exogenous) as a reversal agent in male and female Sprague-Dawley rats. 3 groups of 8 rats each (3 groups of males and 3 groups of females) received a 0.5 mg/kg dose of IP Fentanyl. They were then randomly treated with either IP Clozapine-N-Oxide (CNO), IP Oxytocin, or IP saline. The rats treated with CNO were previously infected with DREADDs in the paraventricular nucleus at 5 days old, approximately 4 months before the Fentanyl study. Respiratory Frequency, Minute Ventilation, and Rate of Apneic events were measured using whole-body Plethysmography recordings over 4-hour periods in unrestrained animals. Our results demonstrated that females experienced significantly greater respiratory depression after Fentanyl administration ($p = 0.0235$). Both IP Oxytocin ($p = 0.0246$) and IP CNO ($p = 0.0361$) induced greater recovery of baseline respiratory frequency compared to IP saline following OIRD. Chemogenetic stimulation exhibited a more sustained effect ($p = 0.0192$) compared to systemic injections of Oxytocin. Female animals showed the greatest recovery with IP Oxytocin administration within the first hour of recovery ($p = 0.036$), with CNO performing comparably to saline. Conversely, males had a greater respiratory response to CNO compared to IP Oxytocin throughout the recovery period.Our findings suggest sex-specific differences in respiratory depression and recovery patterns after Fentanyl administration, highlighting distinct roles of exogenous versus endogenous Oxytocin pathways in modulating respiratory function. Given that endogenous Oxytocin facilitates a more gradual recovery and exogenous Oxytocin induces a more rapid effect, future research should explore their combined use to optimize respiratory recovery.

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Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.052/LBA130

Topic: E.08. Respiratory Regulation

Support: FAPESP (2018/15957-2 and 2021/08833-8)
CNPQ (309338/2020-4)
CAPES (#88887.635569/2021-00)

Title: Baseline respiratory pattern and responses to hypercapnia of adenosine A_{2A} receptors knockout mice exposed to sustained hypoxia

Authors: *K. RODRIGUES[1], D. J. MORAES[2], B. H. MACHADO[3];
[1]Physiol., Univ. of Sao Paulo - USP, Ribeirão Preto, Brazil; [2]Physiol., Sch. of Med. of Ribeirao Preto, USP., Ribeirao Preto, Brazil; [3]Physiol., Sch. Med. Ribeirao Preto, USP, Ribeirao Preto, Brazil

Abstract: There is evidence that adenosine A_{2A} receptors modulate the synaptic transmission in the brainstem pathways responsible for the cardiovascular and respiratory reflexes. Recent studies from our laboratory documented that adenosine A_{2A} receptors knockout (KO_{A2A}) mice exposed to normoxia (control) or sustained hypoxia (SH) presented changes in the baseline ventilatory parameters, indicating a role for these receptors in the generation of breathing. Herein, we evaluated the baseline respiratory pattern and the respiratory responses to hypercapnia/acidosis of Balb/C [Wild Type (WT)] and KO_{A2A} mice previously exposed to SH using the *in situ* working heart-brainstem preparation (WHBP). WT and KO_{A2A} mice (6-8 weeks old) were exposed to normoxia or SH protocol (24h, FiO_2 0.1). The impact of SH on respiratory and autonomic parameters during baseline conditions and in response to hypercapnia/acidosis were evaluated. In the WHBP, we recorded phrenic (PN), abdominal, (AbN), cervical vagus (cVN) and thoracic sympathetic (tSN) nerves activities of control and SH groups. CO_2 in the perfusate was increased from 5% (normocapnia) to 7% and then to 10%. All experimental protocols were approved by the institutional ethical committee (#076/2021). In normocapnia and hypercapnia (7%), the frequency of PN was significantly higher in the KO_{A2A} (n=8) than in WT (n=9) mice (2.05 ± 0.45 vs 0.28 ± 0.04 Hz, $P<0.001$ and 1.35±0.94 vs 0.31±0.06 Hz, $P= 0.04$, respectively). The incidence of AbN active expiration of KO_{A2A} group (n=6) was significantly lower in both hypercapnic challenges (7%: 6.1±3.1 vs 52.3±4.2 %, P=0.03 and 10%: 15.7±6.7 vs 61.4±12.3 %, P=0.01) than in WT group (n=8). SH increased the incidence of baseline AbN active expiration in WT, but not in KOA_{2A} mice. These data support the concept that adenosine acting on A_{2A} receptors plays an important role in modulating the baseline respiratory frequency as well as in generating active expiration in response to sustained hypoxia or hypercapnia/acidosis.

Disclosures: K. Rodrigues: None. **D.J. Moraes:** None. **B.H. Machado:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.053/LBA131

Topic: E.09. Motor Neurons and Muscle

Support: NIH R01 NS125298
NIH R01 NS091010
NIH R01 DC018545
NIH R01 MH128746
NSF 2024776
UCSD Kavli Institute for Brain and Mind

Title: Hierarchical interhemispheric interaction of motor cortex underlies an asymmetric bimanual skill

Authors: *Y. Y. HU[1], A. WU[1], B. YU[1], T. KOMIYAMA[1,2];
[1]Univ. of California San Diego, San Diego, CA; [2]Halıcıoğlu Data Sci. Inst., Univ. of California San Diego, La Jolla, CA

Abstract: Coordinated bimanual motor behavior is a fundamental skill in daily life, yet the neural circuitry underlying the execution of such tasks remains unclear. We investigated the role of interhemispheric connectivity between the left and right primary motor cortex (M1) during an asymmetric bimanual motor task. Mice were trained to press a lever with one limb while concurrently turning a wheel with the other limb. After achieving proficiency, we disrupted the connectivity between the two M1 regions via corpus callosum lesions, which impaired the wheel-turning behavior without affecting the lever-pressing behavior, suggesting an asymmetric interaction between M1 hemispheres. Furthermore, optogenetic inactivation of each hemisphere led to asymmetric effects; inactivation of the lever-contralateral hemisphere (LCH) impaired the movements of both limbs and reduced movement-related activity in the wheel-contralateral hemisphere (WCH). In contrast, inhibiting WCH only affected the wheel-turning movement without affecting the lever-pressing behavior or the LCH activity. These results suggest that two M1 hemispheres interact in a hierarchical manner to control the bimanual skill, with the LCH playing a dominant role controlling both limbs, partly through the control of the WCH activity. We propose that hierarchical interactions of M1 hemispheres ensure the coordination of bimanual movements in asymmetric bimanual skills.

Disclosures: Y.Y. Hu: None. **A. Wu:** None. **B. Yu:** None. **T. Komiyama:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.054/LBA132

Topic: E.09. Motor Neurons and Muscle

Support: American Heart Association, GRNT27760156

Title: Using pose estimation data to analyze the sample entropy of infant movement

Authors: *M. R. ROSALES[1], J. HEATHCOCK[2];
[1]Sch. of Hlth. and Rehabil. Sci., [2]The Ohio State Univ., Columbus, OH

Abstract: Introduction: Pose estimation (PE) has promise to analyze infant movement to better understand the neural correlates of early human movement. Previously, our lab validated a method for quantifying infant movement using PE. Another measure that adds to the robustness of measuring movement is sample entropy (SE). SE is a measure of the repeatability of a signal. For human movement, this is a powerful measure that depicts if an individual is moving randomly with lots of variability (i.e. high SE) or performing constant repetitive behaviors (i.e. low SE). This study furthers movement analysis using PE by examining the differences in arm and leg SE between infants with typical development (TD) and congenital heart disease (CHD). Methods: Twelve 3-month-old infants (N=6 TD and N=6 CHD) engaged in a 15-minute contingency learning paradigm, where movement of the right leg would activate a mobile. Video data was imported and processed using MediaPipe's full body model, and custom python and MATLAB scripts. The scripts quantified infant leg and arm acceleration using the ankle and wrist markers for both sides. From the movement data, we quantified sample entropy for the movement of each limb using a custom MATLAB script. Wilcoxon rank sum tests were used to determine differences in sample entropy between CHD and TD participants, and Pearson's r was used to describe the effect size. Results: There was no statistical difference between the groups for sample entropy for left and right arm and leg movement ($p>0.05$). Infants with TD tended to have larger sample entropies for both side and limbs; and there was a medium effect for left leg movements ($r=0.32$) and a low effect for left ($r=0.25$) and right ($r=0.13$) leg movements and right arm movements ($r=0.13$). Conclusion: These novel data show that we can quantify the complexity of infant movement (i.e. SE). Since PE only requires a video, future studies aimed at understanding the neural correlates of infant movement can be conducted in lower income areas of the world and in situations where devices like wearable sensors cannot be placed on a child (e.g. a neonatal intensive care unit). Thus, opening new and inexpensive avenues for the analysis of infant movement and the early detection of developmental disabilities.

Disclosures: M.R. Rosales: None. **J. Heathcock:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.055/LBA133

Topic: E.09. Motor Neurons and Muscle

Title: Changes in symmetry of motor unit control during isometric dorsiflexion in chronic stroke

Authors: *J. LEVINE[1], X. YU[2], J. L. PONS[3];
[1]Northwestern Univ., Evanston, IL; [2]Legs + Walking Lab., Shirley Ryan AbilityLab, Chicago, IL; [3]L+W AbilityLab, Cajal Institute, Spanish Res. Council, Chicago, IL

Abstract: Following stroke, people exhibit impaired motor control. High-density EMG (HD-EMG) and decomposition reveal spinal motor neuron activity, providing insight into motor impairments. Investigations of motor unit (MU) firing in chronic stroke found reduced discharge rates (DRs) in affected compared to unaffected limbs, with varying results on coefficient of variation (CoV) of DR. We hypothesize that level of lower limb impairment will be related to impaired modulation of MU activity, and differences will be evident with changes in muscle length. Six individuals (4 females) with chronic stroke were recruited, and HD-EMG was recorded over tibialis anterior during submaximal trapezoidal dorsiflexion at 20% maximal voluntary contraction at two ankle angles (neutral 0°, 10° plantarflexion) for both limbs. Additionally, patients performed the 10 meter walk test (10MWT), which is clinically used to stratify patient impairment into community (COM, >0.8m/s) and limited community (LIM, 0.4-0.8m/s) ambulation. Covariation of force (FCoV), average DR, CoV DR, and CoV of cumulative spike train (sum of all MU spikes, CST) were computed over the plateau, as well as symmetry (impaired/unimpaired). Repeated measures ANOVA assessed effects of limb and angle (α=0.05). FCoV was significantly greater on the impaired than unimpaired limb (0.17±0.09, 0.068±0.04, p=0.02) and was greater at 0° than 10° without significance (0.14±0.09, 0.10±0.08, p=0.11). On average, 24±8 MUs were decomposed, yielding at least 12 MUs across subjects, limbs, and angles. Comparison of MU metrics revealed no significant difference across angles (p>0.05), so data were combined. DR was significantly less on impaired limbs (8.66±1.5pps, 10.83±1.5pps, p=0.046), while CoV DR (0.20±0.05) and CoV CST (4.01±1.0) did not differ across angles or limbs (p>0.05). 10MWT speed ranged from 0.42 to 1.28m/s, with three patients classified as COM and three as LIM. When comparing COM and LIM, COM had significantly greater FCoV (0.11±0.08, 0.23±0.04, p=0.02), with greater symmetry for DR (0.93±0.2, 0.70±0.09, p=0.03) and CoV CST (0.96±0.2, 1.6±0.3), while CoV DR was more symmetric but did not reach significance (1.10±0.09, 1.55±0.5, p=0.08). While decreased DR on impaired limbs aligns with previous research, 10MWT speed classified limited community ambulators with reduced ability to modulate force and greater asymmetry in control of MUs. These results suggest that level of lower limb impairment in a dual-limb task is related to the ability to modulate force and MU firing rates symmetrically. Further work is required to elucidate whether MU activity can be a useful tool to stratify patients post-stroke.

Disclosures: J. Levine: None. **X. Yu:** None. **J.L. Pons:** None.

Late-Breaking Poster

LBA005: Theme E Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA005.056/LBA134

Topic: E.09. Motor Neurons and Muscle

Support: Canadian Institute of Health Research (FDN154274)

Title: Effective Feeding by a Neuromuscular System

Authors: *H. ZHANG[1], I. S. CHANDOK[5], R. GAO[2], S. RASOULI[6], T. AHAMED[7], B. MULCAHY[8], A. D. SAMUEL[5], V. VENKATACHALAM[6], M. ZHEN[8,1,3,4];
[1]Dept. of Physiol., [2]Div. of Engin. Sci., [3]Dept. of Mol. Genet., [4]Dept. of Cell & Systems Biol., Univ. of Toronto, Toronto, ON, Canada; [5]Physics, Harvard Univ., Cambridge, MA; [6]Dept. of Physics, Northeastern Univ., Boston, MA; [7]HHMI Janelia Res. Campus, Ashburn, VA; [8]Lunenfeld-Tanenbaum Res. Inst., Mount Sinai Hosp., Toronto, ON, Canada

Abstract: Effective food capture and ingestion is a universal and essential motor behavior. C. elegans feeds on bacteria suspended in liquid using a muscular pump comprising eight muscle cell types. These cells generate patterned contraction and relaxation to produce two motor programs: pumping, which draws, filters, and traps bacteria at its anterior isthmus; peristalsis, which transports trapped bacteria via the posterior isthmus to the grinder. Pumping and peristalsis programs are selectively coupled through pm5, a single muscle cell of the isthmus. During pumping, the anterior of pm5 contracts and relaxes, while the posterior of pm5 remains relaxed. Following some pumping events, the posterior of pm5 performs peristalsis, contracting anti-phasically to the pumping motion of the anterior portion of pm5[1-3].
We want to address two main challenges that this system needs to resolve for effective feeding: 1) Efficient capture of bacteria in a low Reynolds number environment; 2) Optimal transitions between bacteria gathering and ingestion. We present the following progress:
1) We developed imaging pipelines allowing high-resolution visualization of muscle contraction and food distribution during C. elegans feeding. Based on the muscle contraction profile, we built a fluid dynamics model that recapitulates food particle transport. Simulation of this model showed that temporal delay in posterior segments of the pharynx is necessary for efficient food capture during pumping, and simultaneous posterior pm5 contraction with anterior pm5 relaxation is crucial for effective transport during peristalsis.
2) pm5 receives spatially differentiated synaptic inputs from three motor neuron types, M2, M3, and M4. We combine experimental and model perturbation to examine how neuronal inputs contribute to effective food capture and transport. Our ongoing work implicates an essential involvement of M4's excitatory input for a dynamically and spatially controlled posterior pm5 muscle activity. We aim to delineate the circuitry that regulates the dynamic coupling between pm5 activity and these motor neurons between food capture and transport.
1. Avery. & Shtonda. Exp. Biol. 206, 2441-2457 (2003).2. Avery, L. & Horvitzt. Neuron 3, 473-

485 (1989).3. Fang-Yen, C., Avery, L. & Samuel, A. D. T. Proc. Natl. Acad. Sci. 106, 20093-20096 (2009).

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.001/LBA1

Topic: F.01. Neuroethology

Support: NIMH Center for Compulsive Behaviors Fellowship
1ZIAMH002950

Title: Area prostriata modulates escape behavior to threat arising from the visual periphery

Authors: *R. T. LINGG[1], G. NNAMDI[1], K. YU[2], J. O'MALLEY[3], H. WANG[5], Y. LENG[6], H. A. TEJEDA[7], M. A. PENZO[4];
[1]NIMH, Bethesda, MD; [2]Natl. Inst. of Mental Hlth., Rockville, MD; [3]Natl. Inst. of Mental Hlth., Sterling, VA; [4]Natl. Inst. of Mental Hlth., Bethesda, MD; [5]NIH, Natl. Inst. of Mental Hlth., Bethesda, MD; [6]Unit on The Neurobio. and Affective Memory, Natl. Inst. Mental Health/NIH, Bethesda, MD; [7]Hugo Tejeda, NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD

Abstract: Survival in complex and dynamic environments requires mitigating risk of predation while simultaneously preventing starvation. Foraging animals will often avoid areas where, or times when, the risk of predation is high to decrease the likelihood that the organism is attacked when seeking food. Escape behaviors become critical if the animal is unable to avoid attack. Successful escape behavior requires rapidly detecting an advancing threat, computing the most likely route to preventing injury or death, and must be balanced against the loss of resources incurred by vacating a foraging area. Importantly, as hunger increases, animals prioritize food seeking at the expense of escape. In ecological situations, threatening stimuli often arise from the visual periphery unexpectedly. When starved, attentional resources are directed toward appetitive stimuli located towards the center of the visual field at the expense of monitoring the periphery. Here, we characterize a limbic visual processing area known as area prostriata (APr) involved in the detection of a rapidly advancing threat occurring in an organism's peripheral visual field. Using the looming threat task in combination with calcium imaging we show APr activity is increased following presentation of an overhead looming threat in freely moving mice, an effect associated with neurons that express the genetic marker for pituitary adenylate-cyclase-activating polypeptide (PACAP). Then, using head-fixed microendoscope imaging of single-cell APr

activity we observed excitatory APr responses to looming stimuli were greatest for rapid (300 °/s) stimuli occurring near the far periphery (i.e. 120° along the azimuthal plane), relative to stimuli presented toward center field. Excitatory APr responses to peripheral visual stimuli were abolished when mice were food restricted for 24hrs. 24hr food restriction also prevented escape to an overhead looming stimulus, an effect associated with increased cFos in the midline thalamus (i.e. PVT). *In vitro* recording of APr neurons demonstrated optogenetic excitation of PVT fibers in APr modulates activity of APr^{PACAP+} cells and APr neurons that project to the midbrain superior colliculus (SC); a region commonly regarded as integral to the initiation of escape. These results are consistent with an interpretation that APr is involved in guiding escape behavior, particularly when the stimulus provoking escape arises from the visual periphery, and that APr is sensitive to alterations in internal state. Further research is aimed at how metabolic stress alters visual processing of threat, and the role of this PVT - APr - SC circuit in mediating this process.

Disclosures: R.T. Lingg: None. **G. Nnamdi:** None. **K. Yu:** None. **J. O'Malley:** None. **H. Wang:** None. **Y. Leng:** None. **H.A. Tejeda:** None. **M.A. Penzo:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.002/LBA2

Topic: F.01. Neuroethology

Support: Fondecyt 1210169
Fondecyt 3220871

Title: Developmental correlation of orbital orientation, "innate" escape responses and retinal specializations in a diurnal rodent, the Octodon degus

Authors: A. R. DEICHLER[1], L. F. LOPEZ JURY[2], M. RUIZ-FLORES[1], N. I. MÁRQUEZ[1], J. MPODOZIS[1], *G. MARÍN[1];
[1]Facultad de Ciencias, Univ. de Chile, Santiago, Chile; [2]Max Planck Inst. for Brain Res., Frankfurt am Main, Germany

Abstract: Binocular vision depends on the proper orientation and conjugation of the eyes and orbits, and the concomitant development of retinal specializations. Mammals display a wide diversity of eye orientation and retinal specializations, from extremely lateralized eyes in prey species, usually featuring retinas with visual streaks, to highly convergent and frontalized eyes in hunters and skilled manipulators, featuring retinas with areas centralis or high acuity foveas. Developmental interactions presumably contribute to coordinate these morphological features, which must be further linked to postnatal behavior. Here, exploring a public 3D CT scan data set

of mammalian skulls (20 species), we show that orbits increase their convergence during development in all mammals analyzed, suggesting that the reorientation of the eyes during development is tightly linked to orbital development. To further investigate this correlation and its possible influence on the maturation of behavioral responses and the development of the retina, we studied the precocial diurnal rodent *Octodon degus*, as this species is born with open eyes and displays active motor behaviors right after birth. We found that the eyes and orbits of this species converge in parallel during postnatal development, to expand the dorsal binocular field from approximately 20° at P5 to around 60° in adults. Additionally, we found the probability to escape from aversive stimuli is very low at initial stages and that increases progressively when the stimulus is presented overhead, consistent with the increased expansion of the dorsal binocular field. Furthermore, regions of higher-acuity in the retina such as the area centralis and visual streak develop progressively from an initial, relatively uniform retinal ganglion cell distribution. These findings illustrate how postnatal changes in eye and orbit orientation collectively contribute to the configuration of the binocular visual field and correlate with changes in retinal topography and behavior. Moreover, they provide valuable insights to understand the mechanisms driving the diversity of form and function of binocular vision during mammalian evolution.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.003/LBA3

Topic: F.01. Neuroethology

Support: Brain and Behavior Research Foundation NARSAD

Title: A 3D whole-face movement analysis system to uncover underlying physiology in mice

Authors: *I. NOZAL MARTIN[1,2], K. DARUWALLA[1], A. FRANKEL[1], D. NAGLIC[1], Z. AHMAD[1], H. X. HOU[1];
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Neurobio. and Behavior, Stony Brook Univ., Stony Brook, NY

Abstract: Synchronous movements of the entire face, from chewing to grimacing, offer significant insights into internal physiological processes. Mice, with discernible facial responses and evolutionarily conserved mammalian facial movement control circuits, provide an ideal model to unravel the link between facial movement and internal physiological states in mammals. However, existing frameworks lack the spatial or temporal resolution to track motion

of the entire mouse face, due to its small and conical form factor. We introduce Cheese3D, a computer vision system that first captures high-speed 3D motion of the entire mouse face (including ears, eyes, whisker pad, nose, and jaw) using a calibrated six-camera array. We selected a set of 17 anatomically-informed geometrical features (distances, angles, areas, and volumes in 3D space) constructed from shapes defined by facial keypoints. Adult C57BL/6J mice of both sexes were used for the experiments. We first verified the accuracy of the geometrical features against measurements of the same mice acquired statically on a 3D scanner. Furthermore, we validated the necessity of having all six cameras to accurately measure facial details by omitting cameras. To measure the sensitivity of Cheese3D to detect and measure small, localized facial movements, we sought to explicitly quantify keypoint jitter in our setup in a control experiment using motionless periods. We detected patterns of small movements during ketamine-induced anesthesia and showed that time since injection can be predicted through whole-face dynamics. We further tested Cheese3D on movements that are vigorous in amplitude by recording mice as they consumed crunchy food. We identified behavioral dynamics corresponding to distinct modes of eating, consistent with what would be expected from ingestion with incisors and mastication with the molars. This set of experiments reveals the underexplored potential of mouse whole-face dynamics as a readout of physiological processes that are not otherwise visible (i.e., anesthesia depth, food location, muscle engagement). Cheese3D sensitively captures high-resolution facial movements in small and larger temporal scales, while keeping physical interpretability, and offers a platform to predict neural activity in future studies.

Disclosures: I. Nozal Martin: None. **K. Daruwalla:** None. **A. Frankel:** None. **D. Naglic:** None. **Z. Ahmad:** None. **H.X. Hou:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.004/LBA4

Topic: F.01. Neuroethology

Support: NIH Grant T32NS115667

Title: Periodic spike sequences emerge in biological neural networks with dominant inhibition

Authors: *D. SEDERMAN, D. Z. JIN;
Penn State Univ., University Park, PA

Abstract: A recent work (Cogno et al., Nature, 2024) reported the observation of ultraslow oscillations in the medial entorhinal cortex of mice with periods of tens of seconds to minutes. These oscillations lead to long periodic sequences of neural activity that are thought to be critical

for coupling neurons and circuits over extended time scales during episodic memory formation. However, it is unclear how such sequences arise from neuronal dynamics. Here, we show computationally that long spike sequences can arise in biological neuronal networks with dominant inhibition and are driven by external inputs. Our work builds on a previous analytical study of a theoretical model of pulse-coupled leaky integrate-and-fire neurons (Jin, PRL, 2002), which showed the prevalence of spike sequence attractors in random networks with global inhibition. We expand the model to incorporate biological realism, including multi-compartmental models for neurons, axonal delays, noisy fluctuations of membrane potentials, and, importantly, the mediation of inhibition through inhibitory interneurons instead of direct inhibition between all neurons. We find that long periodic sequences emerge in certain parameter regimes in such biologically realistic neuronal networks. Chain-like connectivity between the excitatory neurons is important for the emergence. The mechanism does not require spatially structured connectivity and thus allows random spatial distributions of the neurons that are active adjacent in time. Future work will focus on the role of synaptic plasticity in the formation of chain-like connectivity.

Disclosures: D. Sederman: None. **D.Z. Jin:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.005/LBA5

Topic: F.01. Neuroethology

Title: Central and Sensory Control of Social Homeostasis

Authors: *D. LIU;
Harvard, Cambridge, MA

Abstract: Social grouping increases survival in many species, including humans. By contrast, social isolation generates an aversive state (“loneliness”) that motivates social seeking and heightens social interaction upon reunion. The observed rebound in social interaction triggered by isolation suggests a homeostatic process underlying the control of social need, similar to the physiological drives such as hunger, thirst or sleep, but the neural basis of social homeostasis remains unclear. In this study, I assessed social responses in multiple mouse strains and revealed distinct sensitivity in each strain to social isolation. Two previously uncharacterized neuronal populations in the hypothalamus were uncovered that are activated during either social isolation or social rebound and orchestrate the behavior display of social need and social satiety, respectively. Brain-wide connectivity was revealed between these two populations and the brain areas associated with social behavior, emotional state, reward, and other physiological needs. Intriguingly, social touch was identified to be an essential sensory modality that animals require

to assess the presence of others and fulfill their social need. Together, these data reveal a brain-wide neural system underlying social homeostasis and provide significant mechanistic insights into the nature and function of circuits controlling instinctive social need and for the understanding of healthy and diseased brain states associated with social context.

Disclosures: D. Liu: None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.006/LBA6

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: An animal model of gender-affirming hormone therapy: the effects of testosterone or estrogen on sexual behavior in Long-Evans rats

Authors: *F. GUARRACI[1], C. BAUER[1], M. FIGUEROA[1], I. IRABOR-IGHEDOSA[1], K. PETERSEN[2];
[1]Southwestern Univ., Georgetown, TX; [2]Colorado Col., Colorado Springs, CO

Abstract: The present project was designed to test an animal model of gender-affirming hormone therapy (GAHT) on sexual behavior and physiology. Adult sexually experienced female Long-Evans rats were treated with testosterone enanthate (TE) or oil, twice per week for 4 weeks. TE was used to mimic the masculinizing effects of GAHT prescribed to transmen. Adult sexually experienced male Long-Evans rats were treated with estradiol benzoate (EB) or oil, daily for 4 weeks. EB was used to model the feminizing effects of GAHT prescribed to transwomen. On the last day of hormone treatment, all rats were tested for sexual motivation and behavior using the partner preference paradigm, whereby subjects could spend time near a sexually vigorous male stimulus or a sexually receptive female stimulus. The first phase of the test limited physical contact between the subject and the stimulus animals, allowing for only the transmission of auditory, visual, and olfactory cues. The second phase of the test provided unlimited physical contact between the subject and the stimulus animals. Body weights were recorded weekly and gonads were removed and weighed after the partner preference test. Estrous cyclicity was monitored in the female subjects for the last 10 days of treatment. Finally, female controls received EB (48 hrs) and progesterone (P; 4 hrs) before the partner preference test to synchronize their sexual receptivity, while TE-treated rats received oil. We found TE-treated female rats failed to enter proestrus or estrus during the 10-day observation period. Interestingly, TE-treated female rats were sexually receptive despite not receiving EB+P injections, thus TE could elicit lordosis. Furthermore, TE-treated female rats spent less time with either stimulus animal than controls across both phases of the partner preference test. When physical contact was possible, TE-treated female rats displayed more rejection behaviors. Ovarian weights did not

differ, but TE-treated rats weighed more than controls by the end of the exposure period. In contrast, EB-treated male rats did not differ from controls during the partner preference test. However, testes and body weights were significantly lower than controls at the end of the exposure period. In conclusion, these findings expand our understanding of the effects of GAHT on reproductive health and sexual behavior using an animal model.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.007/LBA7

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NSF GRFP DGE-1343012 to MRB

Title: The effects of mast cell inhibition on brain and social behavior after allergic maternal immune activation in rats

Authors: *M. BREACH[1], X. WEINSTEIN[2], J. ROUSH[2], H. E. AKOURI[2], M. MCDONALD[2], M. FANKHAUSER[2], A. ZALETA LASTRA[1], K. M. LENZ[2];
[1]Neurosci. Grad. Program, [2]Psychology, The Ohio State Univ., Columbus, OH

Abstract: Mast cells are hematopoietic immune cells found throughout the body, including the brain. Though primarily known for their role in initiating the allergic response, emerging work suggests mast cells shape brain development and behavior. For example, allergic inflammation during pregnancy increases the offspring's risk for neurodevelopmental disorders. We previously found that a rat model of acute allergic maternal immune activation (MIA) produces social deficits akin to those seen in neurodevelopmental disorders, and also disturbs dendritic spine density and oxytocin (OT) and vasopressin (AVP) innervation in the social brain. Here, we aim to test the extent to which prenatal mast cell activation contributes to the development of social behavior, both at baseline as well as after allergic MIA. **Methods**: Female rats received sensitization injections of ovalbumin or vehicle. After breeding, pregnant females were randomly assigned to receive no drug or a mast cell inhibitor, ketotifen fumarate, through drinking water from gestational day (GD)14-18. On GD15 or 16, rats were intranasally challenged with ovalbumin or saline. 30 minutes post-challenge, tail vein plasma samples were collected and analyzed for immunoglobulin E to confirm inhibition of the allergic response. Maternal behavior was quantified across 3-4 sessions between postnatal day(P)0-P8. Offspring were tested for neonatal ultrasonic vocalization behavior and juvenile social play behavior prior to brain collection on P31. Brains were processed for immunofluorescence analysis of OT, AVP, and

post synaptic density protein (PSD)-95 in regions relevant to social behavior. Data were analyzed with linear mixed effects analysis and likelihood ratio testing. **Results:** Prenatal mast cell inhibition with ketotifen impaired spontaneous maternal care, specifically in dams that didn't undergo MIA. Ketotifen also improved maternal pup retrieval performance, irrespective of allergen exposure. Regarding the offspring, prenatal mast cell inhibition did not rescue MIA-related changes to ultrasonic vocalizations, juvenile social play, or OT or AVP immunoreactivity in the medial amygdala. Interestingly, prenatal ketotifen exposure alone impaired juvenile social play behavior in rats. **Implications**: Prenatal mast cell inhibition impacted subsequent maternal care and offspring social behavior, suggesting a role for mast cells in programming these outcomes. This study increases our understanding of how mast cells may influence brain and behavioral development, and sheds light on the mechanisms that may contribute to prenatal inflammation as a risk factor for neurodevelopmental disorders.

Disclosures: M. Breach: None. **X. Weinstein:** None. **J. Roush:** None. **H.E. Akouri:** None. **M. McDonald:** None. **M. Fankhauser:** None. **A. Zaleta Lastra:** None. **K.M. Lenz:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.008/LBA8

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Positive chemotaxis to bisphenol A: Potential neuroendocrine disruptor signals impacting growth, development, and behavior of the nematode (Caenorhabditis elegans)

Authors: S. LONG[1], N. JAMES[1], ***G. M. LANGE**[2];
[1]Dept. of Biol., [2]Saginaw Valley State Univ., University Center, MI

Abstract: Environmental osmolarity is a type of neurosensory stimulus for many organisms. While behavioral responses to osmotic change are important for maintaining intracellular osmotic stability, mechanisms shaping the development of these behaviors are not fully understood. In natural environments inhabited by the nematode, *Caenorhabditis elegans*, changes in environmental osmolarity occur frequently. Bisphenol-A is a chemical agent found in many plastics used in everyday life. Bisphenol-A can and does leech from plastics and enters the environment. In this way, this pollutant is inadvertently ingested by organisms. Bisphenol-A has been identified as an endocrine disruptor and impacts the neuroendocrine system and can shape development in a variety of organisms. Data about potential effects of dual stressors of osmotic change and Bisphenol-A exposure are scant and warrant further study. In this research, we created a novel design in which we provided environmental choice to *Caenorhabditis elegans*, and we present findings showing this nematode displays positive chemotaxis towards Bisphenol-A imbued environments compared to control environments. We examine these findings of

positive chemotaxis relative to potential impact this response has on neural signaling and development, and we assess how Bisphenol-A, as an environmental pollutant, may be affecting neuroendocrine development, behavior, and reproductive success in the nematode.

Disclosures: S. Long: None. **N. James:** None. **G.M. Lange:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.009/LBA9

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: CIHR-REDI 202305ED3
BRAIN CREATE NSERC
CIHR

Title: Friend or Foe: Role of CRH^{PVN} neurons in social threat detection

Authors: *I. AKINRINADE[1], M. PARDASANI[2], T.-L. STERLEY[3], T. FUZESI[3], J. S. BAINS[4];
[1]Hotchkiss brain institute, Calgary, AB, Canada; [2]Hotchkiss Brain Inst., Calgary, AB, Canada; [4]Hotchkiss Brain Inst., [3]Univ. of Calgary, Calgary, AB, Canada

Abstract: Our understanding of how animals detect and respond to threat rely on a framework of predator-prey interactions. Threat, however, can also arise from conspecifics. Accurately discerning the potential threat posed by others is vital for building social relationships. How individuals gauge and respond to social threat is not well understood. The corticotropin-releasing hormone neurons of the paraventricular nucleus in the hypothalamus (CRH^{PVN}) control physiological and endocrine responses to threat. They are necessary for the social investigation of a stressed partner that results in the transmission of stress from one individual to another. Whether these neurons are involved in the assessment of the potential threat posed by a conspecific is unknown. Here, we combined precise behavioral analysis with fibre photometry to delineate the relationship of CRH^{PVN} activity with social approach and contact between familiar and unfamiliar mice. We found that CRH^{PVN} activity in resident mice increased during the approach toward an intruder. This increase was significantly larger when the intruder was unfamiliar. This increase in CRH^{PVN} activity was followed by an increase in sniffing behavior that was significantly higher with the unfamiliar intruder. These observations indicate that CRH^{PVN} activity tracks potential social threat. Further investigations are required to determine the scalability and functional consequences of these neural responses.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.010/LBA10

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Ohio Addiction Innovation Fund Grant to KML and BL

Title: Peripartum opioid exposure effects on the maternal brain and behavior in rats: An examination of maternal care, the neuroimmune system, and perineuronal nets

Authors: C. DYE, M. FANKHAUSER, A. WEBB, J. SINGLETON, A. KALATHIL, A. RINGLAND, B. LEUNER, ***K. LENZ**;
The Ohio State Univ., Columbus, OH

Abstract: 7% of pregnant people use opioids. Opioid use during pregnancy can negatively impact maternal and offspring health. Those who use opioids are recommended to use medication assisted therapy (MAT), commonly buprenorphine, to prevent withdrawal symptoms and pregnancy complications. Opioids can bind to TLR4, an immune cell receptor, to impact neuroinflammatory signaling, and we have previously shown that neuroimmune alterations are important for the display of maternal behavior. Here, we used a rodent model to understand the impact of chronic peripartum opioid exposure or MAT on maternal caregiving and neuroinflammation. Female rats (n=8-9/group) were exposed to daily vehicle (VEH), buprenorphine (BUP), or oxycodone (OXY), before, during, and after pregnancy. Opioid exposure reduced gestation length and maternal weight gain. Postpartum maternal caretaking behaviors, including retrieval, huddling and nursing, and pup-directed sniffing and licking, were reduced in opioid-exposed mothers, as measured in pup retrieval tasks and home cage observations. Behavioral fragmentation was also increased in opioid-treated mothers. At postpartum day 8, tissue was collected from brain regions important for facilitating maternal behavior, including the prefrontal cortex (PFC), nucleus accumbens (NAc), preoptic area (POA), amygdala (AMY), and periaqueductal grey (PAG), and processed for immunohistochemistry or qPCR. BUP increased astrocyte (GFAP) staining, while OXY increased microglia (Iba1) staining, with both effects seen only in the PAG. Gene expression analysis also showed regional and treatment differences in immune transcripts. BUP and OXY increased TLR4 in the PFC. BUP increased TNF in the NAc, but decreased IL1B in the POA. OXY increased CD68 in the POA, and IL1B, TNF, and TLR4 in the PAG. No changes were seen in the AMY. We also assessed perineuronal nets (PNNs), extracellular matrix proteins that are important for neuroplasticity and known to be influenced both by pregnancy and by opioids. In the maternal PFC, both OXY and BUP led to significant decreases in PNN immunostaining (WFA), and a corresponding increase in expression of the protease, matrix metalloproteinase 2 (MMP2), which is known to break down PNNs. Analyses of PNNs and related transcripts in other maternal brain

regions are ongoing. Together, these results provide novel evidence of peripartum neuroimmune and perineuronal net alterations following chronic opioid exposure that could contribute to maternal care deficits. Modulating neuroimmune activation could be a potential intervention for care deficits in mothers exposed to opioids during pregnancy.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.011/Web Only

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Voelcker Biomedical Research Foundation
R25NS115552
South Texas Undergraduate Research Opportunities Program

Title: The Influence of Acute Cannabidiol Treatment and Estrous Cycle on Social and Repetitive Behaviors in Adult Female Mice

Authors: A. WINDSCHEFFEL, E. ZHANG, P. PEREZ, P. B. STEWART, D. SANCHEZ, C. MILLER, L. ARNOLD, K. CANTU, *G. G. GOULD;
Physiol., UT Hlth. San Antonio, San Antonio, TX

Abstract: Cannabidiol (CBD) is a nonintoxicating constituent of *Cannabis sativa* that is currently used to manage pain and seizure disorders. Recent research suggests CBD may also alleviate the social deficits associated with autism spectrum disorder (ASD). This study hypothesized that a single dose of acute 15 mg/kg CBD treatment would improve social behavior in adult female BTBR mice, a model of idiopathic autism displaying repetitive behaviors and social interaction deficits. To test this hypothesis, a dose of vehicle or 15 mg/kg CBD was administered to adult female BTBR and C57BL/6 mice. The effects of CBD on autism-relevant behaviors were tested through social interaction sniffing tests 50 minutes after injection, social novelty sniffing tests 60 minutes after injection, a marble burying test 70 minutes after injection, and a social dominance tube test 100 minutes after injection. Additionally, fecal boli were counted after social novelty tests, and the blood glucose was measured following all behavior testing. In female mice, the estrous cycle did not significantly influence any behavior. Moreover, CBD treatment effects were only significant on the number of fecal boli in BTBR mice and marble burying in C57BL/6 mice at 15 mg/kg CBD.

Disclosures: A. Windscheffel: None. **E. Zhang:** None. **P. Perez:** None. **P.B. Stewart:** None. **D. Sanchez:** None. **C. Miller:** None. **L. Arnold:** None. **K. cantu:** None. **G.G. Gould:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

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Program #/Poster #: LBA006.012/LBA11

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Simons Society of Fellows Junior Fellowship 855220
NIH R35GM143051
Searle Scholarship
Klingenstein-Simons Fellowship in Neuroscience
Sloan Foundation Fellowship

Title: The genetic causes and behavioral consequences of glucocorticoid evolution in monogamous mice

Authors: *J. MERRITT[1], S. LOCKWOOD[1], A. BENDESKY[2];
[1]Zuckerman Inst., [2]Zuckerman Mind Brain Behavior Inst., Columbia Univ., New York, NY

Abstract: Resilience to stress is in part controlled by the secretion and regulation of the levels of glucocorticoids. In mice of the genus *Peromyscus*, a pair of sister species have unprecedented divergence in the adrenal gland. Oldfield mice have a 9-fold larger adrenal cortex than deer mice, which corresponds with a 30-fold difference in the circulating CORT (corticosterone) -- the primary rodent stress hormone. Further, oldfield mice provide more care for pups, and exhibit reduced anxiety-like behavior but increased susceptibility to infection relative to deer mice. To understand the genetic basis and phenotypic consequences of CORT levels, we generated 769 F_2 hybrids and quantified parental behavior, anxiety-like behavior, and CORT levels in the hair. Quantitative genetic mapping revealed two loci centered on the glucocorticoid receptor (GR) and on the corticosteroid binding globulin (CBG) that together explain 29% of variation in CORT levels. In F_2s, the oldfield alleles of these genes enhance parental behavior and inhibit anxiety-like behavior, whereas the deer alleles have the opposite effect. To study these loci in detail, we generated backcross mice. Mice with the oldfield GR are much more anxious than either pure species, but mice with the oldfield allele at both GR and CBG behave like oldfield mice. These results suggest that CBG buffers the effects of GR. Oldfield GR has 4 amino acid substitutions and oldfield CBG has 10 substitutions relative to deer mice, some of which occur in functional domains of each protein. Next, we tested the 4 amino acid differences in GR in isolation and in combination using luciferase assays. We found that oldfield GR is less sensitive to CORT, and these results are consistent with RNA-seq data indicating allele-

dependent CORT effects on gene expression. Taken together, the genetic dissection of CORT levels offers new opportunities to understand the mechanisms by which behavioral diversity arises.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

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Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH grant MH113007 to JD
Synergy European Research Council (ERC) grant "OxytocINspace" 101071777 to VG
SFB Consortium 1158-3 to VG
German-Israeli Project cooperation (DIP) GR3619-1 to VG

Title: Vasopressin and oxytocin, acting via oxytocin receptor (OTR), excite Type III, OTR- and CRF-expressing neurons of dorsolateral bed nucleus of the stria terminalis ($BNST_{DL}$) and reduce anxious arousal

Authors: *J. DABROWSKA[1], W. FRANCESCONI[2], V. OLIVERA[3], F. BERTON[4], S. LOSEE OLSON[5], R. CHUDOBA[6], L. MONROY[6], Q. KRABICHLER[7], V. GRINEVICH[8];
[1]Chicago Med. Sch. RFUMS, North Chicago, IL; [2]Dept. of Cell. and Mol. Pharmacol., Rosalind Franklin Univ. of Med. and Scien, North Chicago, IL; [3]Cell. and Mol. Pharmacol., Rosalind Franklin Univ. Sch. of Grad. and Postdoctoral Studies, North Chicago, IL; [4]Dept. of Cell. and Mol. Pharmacol., Rosalind Franklin Univ., North Chicago, IL; [5]Chivago Med. Sch., NORTH CHICAGO, IL; [6]Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL; [7]German Ctr. for Mental Health, Heildelberg Univ., Mannheim, Germany; [8]German Ctr. for Mental Health, Heildelberg Univ., Heidelberg, Germany

Abstract: Interoceptive signals dynamically interact with the environment to shape appropriate defensive behaviors. Hypothalamic hormone and neuromodulator, arginine-vasopressin (AVP), regulates internal states related to thirst and circadian rhythmicity. The dorsolateral BNST ($BNST_{DL}$) expresses oxytocin (OTR) and AVP receptors but their integrated role in modulating $BNST_{DL}$ activity is unknown. Here we show that in male rats, AVP directly excited Type III $BNST_{DL}$ neurons (P=0.0007, F(0.9966, 9.966)=23.05, n=11, mixed effects analysis), which required OTR transmission (with OTR antagonist P=0.3949, F(1.419, 11.35)=0.9149, n=9.) These excitatory effects of AVP were confirmed in fluorescent OTR-$BNST_{DL}$ Type III neurons from OTR-Cre transgenic rats (P<0.0001, F(1.267,11.40)=31.89, n=10). As Type III neurons were previously shown to express mRNA for corticotropin-releasing factor (CRF), we show that

both AVP (P=0.0057, F(1.392, 8.351)=11.82, n=7) and selective OTR agonist, TGOT (P=0.0167, F(1.647, 9.882)=6.823, n=7) excited fluorescent CRF-$BNST_{DL}$ neurons from CRF-Cre rats. Considering the role of $BNST_{DL}$ in avoidance and fear-related behaviors, we next demonstrated that chemogenetic silencing of OTR-$BNST_{DL}$ neurons significantly reduced exploration of open arms in the elevated plus-maze (P=0.0307, n=43, un-paired t-test) and increased anxious arousal in the fear-potentiated startle (P=0.0077, n=43). Finally, to determine the source of AVP inputs to the $BNST_{DL}$, we used AVP-Cre rats and showed that neurons from the suprachiasmatic (SCN), supraoptic, and paraventricular nuclei of the hypothalamus send AVP projections to the $BNST_{DL}$. Notably, optogenetic tetanic light stimulation of the SCN fibers in the $BNST_{DL}$evoked AVP release and excited $BNST_{DL}$ neurons (P=0.0251, F(1.739, 10.43)=5.611, n=7, RM ANOVA) via OTR (P=0.4261, F(1.945, 5.836)=0.9831, n=4). We demonstrate how OTR-$BNST_{DL}$ neurons exited by hypothalamic AVP inputs play a major role in regulating $BNST_{DL}$ excitability, overcoming threat avoidance, and reducing anxious arousal following fear conditioning. Therefore, changes in the activity of internal state-sensitive hypothalamic inputs will directly impact OTR-$BNST_{DL}$ neurons' activity to shape appropriate, physiologically relevant defensive behaviors.

Disclosures: J. Dabrowska: None. **W. Francesconi:** None. **V. Olivera:** None. **F. Berton:** None. **S. Losee olson:** None. **R. Chudoba:** None. **L. Monroy:** None. **Q. Krabichler:** None. **V. Grinevich:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.014/LBA13

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIMH Grant 2R01MH113007

Title: Circadian Control of oxytocin receptor-expressing (OTR) neurons in dorsolateral Bed Nucleus of the Stria Terminalis ($BNST_{DL}$) via Hypothalamic Vasopressin (AVP) Projections

Authors: *L. M. MONROY[1], S. LOSEE OLSON[2], Q. KRABICHLER[3], V. GRINEVICH[3], J. A. DABROWSKA[2];
[1]Cell. and Mol. Pharmacol., [2]Ctr. for Neurobio. of Stress Resilience and Psychiatric Disorders, Dept. of Cell. and M, Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL; [3]Dept. of Neuropeptide Res. in Psychiatry, Central Inst. of Mental Health, German Ctr., Heidelberg Univ., Heidelberg, Germany

Abstract: The bed nucleus of the stria terminalis (BNST) regulates stress-related physiological and behavioral responses, notably, fear and anxiety-like behaviors. The BNST receives inputs

from many hypothalamic nuclei that regulate wake/sleep cycle, such as suprachiasmatic nucleus (SCN) of the hypothalamus. Our recent studies demonstrate that arginine-vasopressin (AVP) has a direct excitatory effect on oxytocin receptor (OTR)-expressing neurons in dorsolateral BNST ($BNST_{DL}$), and these neurons also express striatal-enriched protein tyrosine phosphatase (STEP). However, the source of AVP inputs in the $BNST_{DL}$ are elusive. Hence, we used AVP-Cre transgenic rats (Cre-recombinase under the AVP promoter) injected with Cre-dependent pAAV-hSyn-FLEx-mGFP-2A-Synaptophysin-mRuby into the SCN and we show that SCN sends AVP-containing inputs to the $BNST_{DL}$. To determine whether the SCN and $BNST_{DL}$ have synchronous expression of activity markers, we quantified immunoreactivity patterns for AVP and STEP in the SCN and $BNST_{DL}$, respectively, across four zeitgeber times (ZT 1-1.5, 11, 13, 23) in 17 rats housed in 12:12 light-dark cycles. We found varying levels of AVP expression in the SCN across the four zeitgebers. Two-Away ANOVA revealed that STEP expression in $BNST_{DL}$ neurons was highest at ZT 1 and lowest at ZT 23 ($F_{3,13}$= 14.20, p = .0002), suggesting that expression of STEP in $BNST_{DL}$-STEP neurons might be directly affected by circadian rhythmicity. To test whether chemogenetic activation of SCN-AVP neurons or inhibition of OTR-BNST affects fear and anxiety-like behaviors during elevated plus-maze (EPM) or contextual fear conditioning, we used 21 male and 35 female AVP-Cre transgenic rats injected with Cre-dependent pAAV-hSyn-DIO-hM3D(Gq)-mCherry DREADDS into the SCN and 31 male and 29 female OTR-Cre transgenic rats (Cre-recombinase under the OTR promoter) with Cre-dependent pAAV-hSyn-DIO-hM4D(Gi)-mCherry DREADDS in the $BNST_{DL}$. Contextual fear was not affected by chemogenetic activation of SCN-AVP neurons nor inhibition of OTR-BNST neurons in males and females. Two-way ANOVA revealed a trend that chemogenetic activation of SCN-AVP neurons increases freezing time in the open arms in males and females ($F_{1,52}$= 3.868, p = .0546). Two-way ANOVA also revealed that chemogenetic inhibition of OTR-BNST neurons increased percent of time spent in the open arms, notably in males ($F_{1,56}$= 8.292, p = .0056). In conclusion, the anatomical and functional connectivity between the SCN and $BNST_{DL}$ implies that changing physiological conditions, particularly the sleep/wake cycle, through AVP prompt, may affect OTR-BNST neurons' activity and BNST-dependent behaviors.

Disclosures: L.M. Monroy: None. **S. Losee olson:** None. **Q. Krabichler:** None. **V. Grinevich:** None. **J.A. Dabrowska:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.015/LBA14

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIA Grant R01AG084473

Title: Estrogen loss in a mouse model of menopause creates vulnerability to obesity-related cognitive and metabolic deficits

Authors: *N. D. SCHARTZ[1], J. SUNG[1], A. N. LAGASSE[1], A. K. ODLE[2], S. W. BARGER[1]; [1]Univ. of Arkansas for Med. Sci., Little Rock, AR; [2]Neurobio. and Developmental Sci., Univ. of Arkansas For Med. Sci., Little Rock, AR

Abstract: Menopause marks the end of a woman's ovarian cycling, dominated by a loss of circulating estrogens as depletion of ovarian follicles occurs. Though typically considered a reproductive transition, the perimenopause stage consists of primarily neurological symptoms, including a drop in the cerebral metabolic rate of glucose (CMRglc) and a shift to alternative energy substrates; this coincides with a rise in neurological symptoms. Peri- and post-menopausal women have greater Alzheimer's disease-associated brain biomarkers, including amyloid β (Aβ) deposition, decreased glucose metabolism, and lower gray and white matter volume, compared to premenopausal women and to men. Similarly, diet-induced obesity (DIO) is associated with reduced CMRglc and higher risk of cognitive dysfunction in males of multiple species. In the present study, we tested the hypothesis that estrogen protects non- and premenopausal females from the metabolic and cognitive perturbations seen in males suffering from DIO. Two-month-old C57BL/6N female mice were treated with 4-vinylcyclohexene dipoxide (VCD) or vehicle (sesame oil) for 20 days at a dose of 160 mg/kg/day (i.p.) to induce ovarian follicle failure. Two weeks after the final dose, mice were implanted with a 90-day timed-release 17β-estradiol (βE2) pellet or a placebo. Subsequently, mice were put on a western diet (WD) (42% fat, 34% sucrose) or standard chow (normal diet, ND). After 5 weeks on WD, mice were tested for cognitive function (Y maze), glucose tolerance, and CMRglc. DIO was manifest as significant weight gain in all mice fed WD, although VCD-treated mice gained weight significantly faster than vehicle and VCD-βE2 mice. VCD-WD mice had a deficit in spatial working memory as shown in the Y maze spontaneous-alternation test when compared to VCD-ND mice ($p<0.05$), and this deficit was prevented by βE2 treatment ($p<0.05$). VCD-WD mice exhibited impaired glucose tolerance compared to VCD-WD-βE2 ($p<0.05$), and reduced CMRglc compared to VCD-ND mice ($p<0.01$). Based on these findings, the resilience of female mice against DIO is dependent on βE2 levels. Loss of βE2 due to ovarian failure, similar to the process of menopause, exacerbated the effects of DIO, resulting in cognitive deficits, impaired glucose tolerance, and reduced glucose utilization in the brain. These results were not observed in VCD-treated mice on normal diet or in VCD-WD mice that had βE2 levels restored. These findings are important for considerations of hormone replacement therapy as regards the risk for vascular dementia and other forms of cognitive impairment related to Type-2 diabetes and metabolic syndrome.

Disclosures: N.D. Schartz: None. **J. Sung:** None. **A.N. Lagasse:** None. **A.K. Odle:** None. **S.W. Barger:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.016/LBA15

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: CONAHCYT CVU 1147969
VIEP-BUAP 00231

Title: Participation of TRPV1 receptor in the cellular development of uterus in CD1 mide induced with Polycystic ovary syndrome

Authors: *C. A. ZERÓN ALVARADO[1], A. CARRASCO CARBALLO[3], L. MARTINEZ MENDIETA[2], V. ALATRISTE[4];
[1]Lab. de Neuroendocrinología, [2]Lab. de Neuroquímica, Benemérita Univ. Autónoma De Puebla, Puebla, Mexico; [3]Lab. de Elucidación y Síntesis Orgánica, [4]Lab. de Neuroendocrinología, Benemérita Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: Polycystic ovary syndrome (PCOS) is a neuroendocrine disorder that affects women of reproductive age, causing infertility, implantation failures and abortions due to uterine morphological changes. In our laboratory we studied the transient receptor potential to vanilloid member 1 (TRPV1) as a modulator in cell reproduction biology. TRPV1 has been found in the uterus and its sensory fibers that communicate to the central nervous system (CNS), also is activated by capsaicin. At low concentrations of capsaicin cell proliferation and differentiation are promoted, however at high concentrations cell death is induced. We hypothesized that stimulation of TRPV1 receptors (via sensory pathways) with low capsaicin concentrations modulates uterine cell development in mice with PCOS. We worked with P20 old CD1 female mice divided into 5 experimental groups (control, vehicle, EV, EV/Caps 1 nM and EV/Caps 10 nM, n=8 per group). PCOS induction with estradiol valerate (EV) (40mg/kg s.c.) was performed on P24 (EV, EV/Caps 1 nM and EV/Caps 10 nM) and capsaicin administrations in the L3-L4 vertebrae region (EV/Caps 1 nM and EV/Caps 10 nM s.c.) were performed on days P64, 67, 70, 73. Finally, on P76, animals' euthanasia was performed. First, we evaluated the EV model by determining the first vaginal opening (FVO), recording a variation of weight and estrous cycle through time. Our results showed no statistical differences between FVO´s groups, a significant decrease in weight in EV/Caps 10 nM group (days P64-P76) and a permanent estrous cycle after EV administration that persists in groups EV, EV/Caps 1 nM and EV/Caps 10 nM. After this, we evaluated the uterus of the experimental groups by measuring its relative weight, the thickness of uterine layers, also evaluating morphological quality with H&E staining and TRPV1 receptor by immunohistochemistry. The relative weight of uterus between the groups showed no statistical differences. The EV group showed endometrial hyperplasia, increased epithelial thickness with aberrant cellularity, a decrease in perimetrium thickness, and a reduction in the immunoreactivity in TRPV1 in the epithelium, the endometrium, and the myometrium. The EV/Caps 1nM and EV/Caps 10 nM groups showed improvements in the cellular morphology of the epithelium and endometrial glands, also an increase in the number of glands and the thickness of the endometrium, the myometrium and the perimetrium. In addition, we found an increase on TRPV1 levels in the epithelium, endometrium and the perimetrium. In conclusion, we propose

capsaicin at concentrations of 1 and 10 nM improves abnormalities of uterine cell development in CD1 mice induced to PCOS through TRPV1 agonism.

Disclosures: C.A. Zerón Alvarado: None. **A. Carrasco Carballo:** None. **L. Martinez Mendieta:** None. **V. Alatriste:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.017/Web Only

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: National Natural Science Foundation of China 82271732
National Natural Science Foundation of China 82071603
National Natural Science Foundation of China 82001502
National Natural Science Foundation of China 82201888

Title: The in-vivo properties and functional subtypes of GnRH neurons

Authors: Y. LIU[1], X. SHEN[1], ***Y. ZENG**[2,1], A. E. HERBISON[3], Y. KUANG[1], L. WANG[1]; [1]Shanghai Ninth People's Hosp., Shanghai, China; [2]Shanghai 9th Peoples Hosp. Affiliated to Shanghai Jiaotong Univ. Sch. of Med., Shanghai, China; [3]Physiology, Develop. and Neurosci., Univ. of Otago, Cambridge, United Kingdom

Abstract: Although the gonadotropin-releasing hormone (GnRH) neurons play a pivotal role in mammalian fertility, their in vivo activity and functional classification during ovulation and across reproductive cycles still remain elusive. By integrating in vivo electrophysiological recording with chemogenetic technology, we successfully identified GnRH neurons in freely moving mice. Recordings obtained revealed that the baseline firing rates of rostral preoptic area (rPOA) GnRH neurons were significantly higher during proestrus compared to metestrus and estrus stages of the cycle. Continuous 20-hour recordings showed surge-like activity in subpopulations of GnRH neurons (~46.67%) during the proestrus stage, with the remainder of GnRH neurons exhibiting basal rhythmic firing patterns. Their similar waveform characteristics facilitate their identification for subsequent in vivo electrophysiology studies. This study represents a significant milestone in functionally classifying GnRH neurons and holds great importance for investigating neuroendocrine regulation on female reproduction.

Figure 1

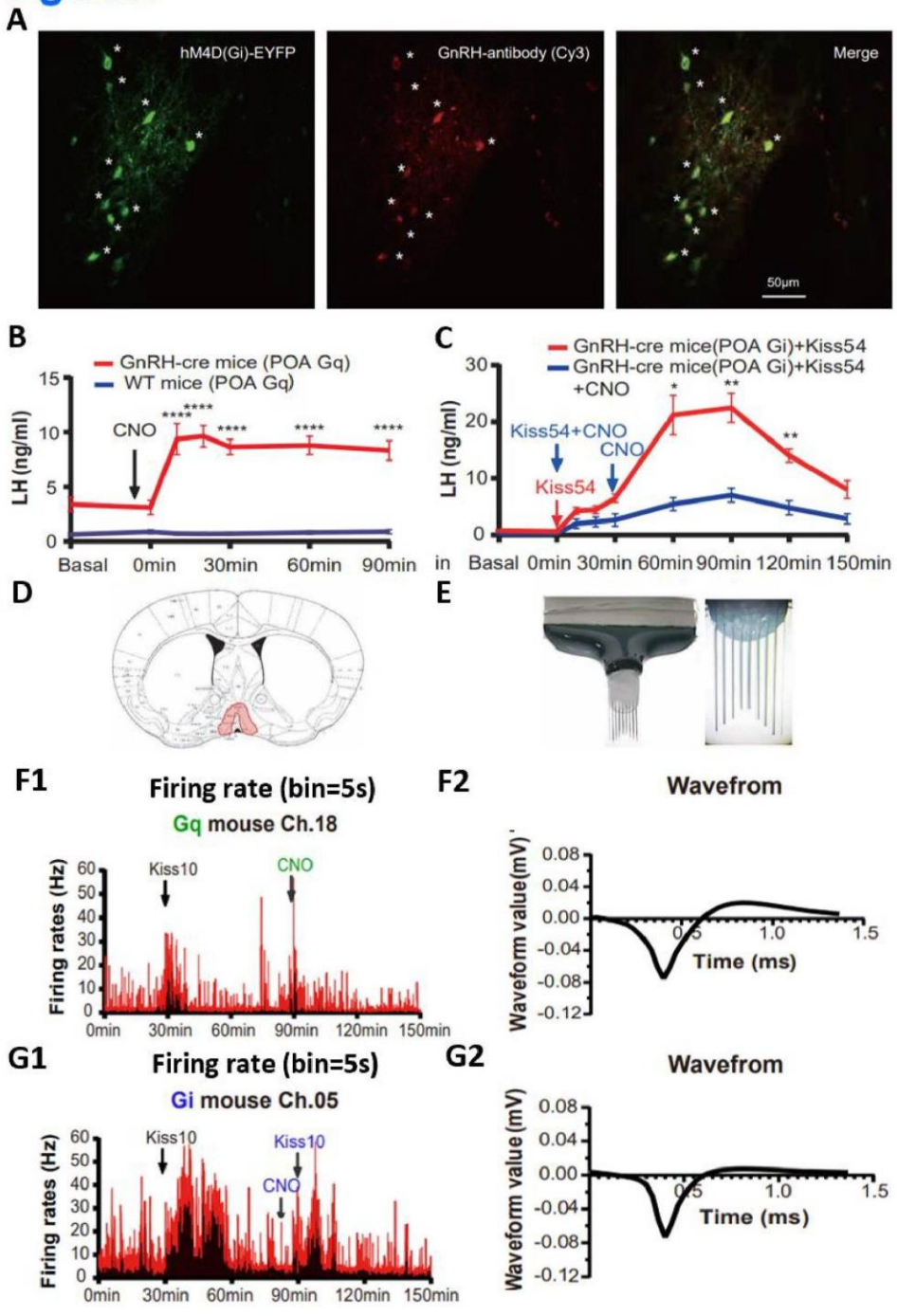
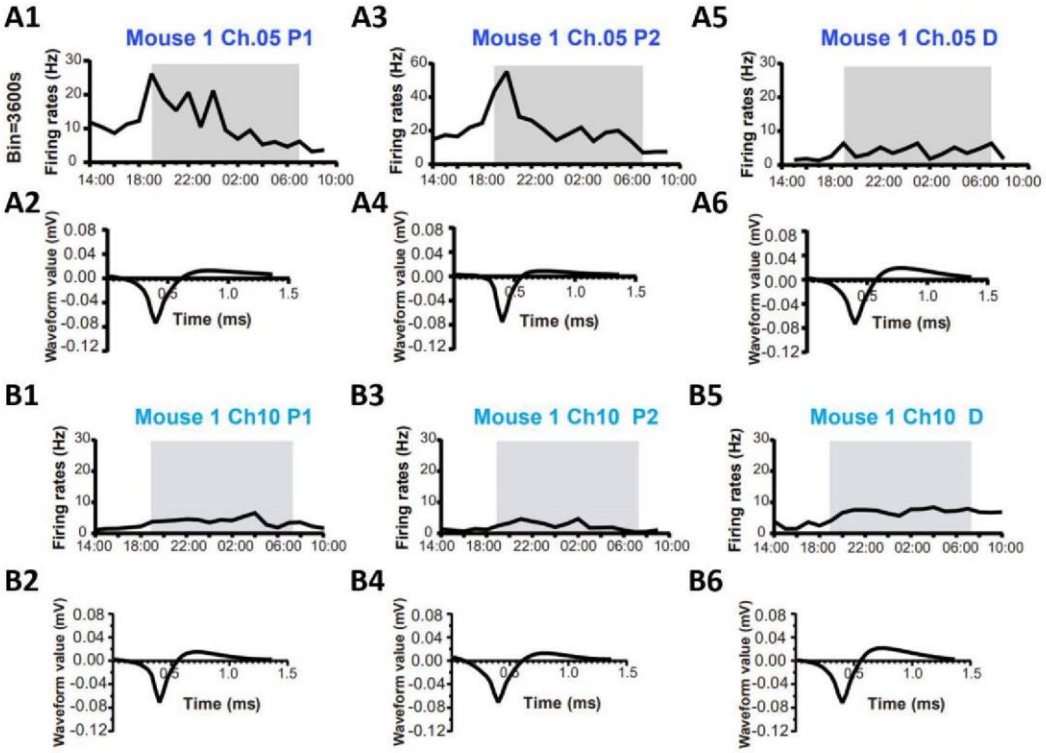

A
hM4D(Gi)-EYFP
GnRH-antibody (Cy3)
Merge
50μm
B
GnRH-cre mice (POA Gq)
WT mice (POA Gq)
LH (ng/ml)
CNO
Basal 0min 30min 60min 90min
C
GnRH-cre mice(POA Gi)+Kiss54
GnRH-cre mice(POA Gi)+Kiss54 +CNO
Kiss54+CNO
CNO
Kiss54
Basal 0min 30min 60min 90min 120min 150min
D
E
F1
Firing rate (bin=5s)
Gq mouse Ch.18
Kiss10
CNO
Firing rates (Hz)
F2
Wavefrom
Waveform value(mV)
Time (ms)
G1
Firing rate (bin=5s)
Gi mouse Ch.05
Kiss10
Kiss10
CNO
G2
Wavefrom
Waveform value (mV)
Time (ms)

Figure 2



Disclosures: Y. Liu: None. **X. Shen:** None. **Y. Zeng:** None. **A.E. Herbison:** None. **Y. Kuang:** None. **L. Wang:** None.
Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.018/LBA16

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Sip by Sip: Sex Differences and Behavioral Effects on Alcohol Pharmacokinetics

Authors: *S. E. HEBERT[1], N. BUSH[3,1,2], A. CUSHNIE[2,1], M. SINCLAIR[1], H. AHMED[4,1], J. BOISSONEAULT[1];
[1]Dept. of Anesthesiol., [2]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN; [3]Ctr. for Alcohol and Addiction Studies, Brown Univ., Providence, RI; [4]Dept. of Psychology, Univ. of Wisconsin, Madison, WI

Abstract: Background: Alcohol is one of the most commonly used substances in the United States, contributing to significant individual and societal costs. Recent research demonstrates that drinking topography (i.e., rate of intake) has important associations with alcohol-related consequences above and beyond quantity consumed or peak blood alcohol concentration (BAC). However, findings regarding the link between drinking topography and BAC are largely limited to observational studies and potential sex-dependent effects remain unclear. This is important given established sex differences in alcohol pharmacokinetics due to sex differences in body composition and alcohol metabolism.
Method: 34 healthy adults over the age of 21 (M = 26, SD = 6.72; 52.9% female) freely drank up to two 5% alcohol-by-volume beverages throughout a one-hour session in a virtual reality bar environment. Beverages were placed on a Bluetooth scale, allowing measurement of drink weight and calculation of the volume and interval of individual sips. Estimated BAC (eBAC) was calculated using a three-compartment pharmacokinetic modeling equation updated with each sip. Independent t-tests were conducted to examine sex-dependent effects on eBAC. Multilevel modeling (MLM) was used to characterize the effect of drinking rate (grams of ethanol consumed per second) on the lagged rate of acceleration of the eBAC on the ascending limb.
Results: Analyses indicated males had greater sip volume t(32.0) = 2.28, p = 0.029, Mdiff = 8.91, d = 0.784), sip volume variability t(32.0) = 2.48, p = 0.019, Mdiff = 5.11, d = 0.851) and total ethanol consumption t(32.0) = 2.35, p = 0.025, Mdiff = 5.24, d = 0.809) than females. MLM results suggested that greater time from the first sip was associated with faster eBAC acceleration (b = 0.027, p = < .001, 95% CI = [0.019, 0.035]). The interaction of rate of consumption with time was a significant predictor of eBAC acceleration such that faster rate of consumption and longer time since first sip was associated with a faster eBAC acceleration (b = 0.006, p = < .001, 95% CI = [0.004, 0.009]).
Conclusion: Findings indicate sex-dependent effects on behavioral drinking patterns may have important implications for the higher binge drinking rates seen across males. Faster rate of consumption over time was associated with a faster eBAC rise until the next sip, especially as the length of the session increased. This is likely due to carryover effects because the starting eBAC of each sip will be partially dependent on each previous sip. This suggests that intervening earlier in a drinking session and modifying how fast an individual drinks may be an important target for harm reduction interventions.

Disclosures: S.E. Hebert: None. **N. Bush:** None. **A. Cushnie:** None. **M. Sinclair:** None. **H. Ahmed:** None. **J. Boissoneault:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.019/LBA17

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: The puberty blocker, leuprolide, alters the inflammatory marker, uPAR, and extracellular matrix regulator, TIMP2, in the adolescent rat brain.

Authors: *A. JOHNSON[1], A. P. AUGER[2];
[1]UW-Madison, Madison, WI; [2]Psychology, Univ. Wisconsin, Madison, Madison, WI

Abstract: Puberty blockers, such as leuprolide, are gonadotropin-releasing hormone agonists that delay the onset of puberty. This blockade is most commonly used to treat disorders such as gender dysphoria in adolescents. Puberty is also a time of increased vulnerability to anxiety and depression, which have been associated with increased inflammatory states. Urokinase plasminogen activator receptor, uPAR, is a biomarker associated with the activation of inflammatory responses coded by the Plaur gene. Stressful stimuli has been correlated to upregulation of uPAR levels. As puberty and adolescence is a time period of vulnerability to stressors, we wanted to examine if pausing puberty altered the levels of uPAR within the adolescent hippocampus and amygdala. Additionally, uPAR has been implicated in the regulation of factors that alter the extracellular matrix (ECM). Specifically, uPAR activation leads to regulation of the opposing extracellular matrix proteins MMP-2, matrix metalloproteinase 2, and TIMP-2, tissue inhibitor of metalloproteinase 2. These proteins serve vital roles in ECM remodeling and synaptic plasticity in these brain regions. Previously, we observed a decrease in anxiety-like behavior in a rodent model after the administration of puberty blockers. Now, we are using this blockade to understand the relationship between puberty and its corresponding role in inflammatory reactions. Through the use of a multiplexed qPCR approach, we measured mRNA expression of Plaur, MMP-2 and TIMP-2 genes in the adolescent hippocampus and amygdala. Within the adolescent hippocampus, we find that treatment with leuprolide lowered uPAR mRNA levels in males and females. Within the amygdala, we found a sex difference in the levels of TIMP-2 mRNA, with females having higher levels of TIMP-2 mRNA than males. Furthermore, leuprolide increased the levels of TIMP-2 mRNA in both males and females. Since puberty is a time of physiological restructuring, it is not unexpected that pausing puberty would alter factors related with ECM remodeling. Together, these data that puberty blockers may have anti-inflammatory characteristics and prevent ECM degeneration of different adolescent brain regions.

Disclosures: A. Johnson: None. **A.P. Auger:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.020/LBA18

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: AHA 23PRE1019923

Title: Estrogenic re-mapping of the metabolic response to an energy deficit

Authors: *P. VANDER[1], F. SUN[1], W. HONG[2], S. CORREA[3];
[2]Neurobio. and Biol. Chem., [3]Dept. Of Integrative Biol. and Physiol., [1]UCLA, Los Angeles, CA

Abstract: Endothermy is an adaptation that can be traced back hundreds of millions of years and is critical for nearly every aspect of mammalian biology. Despite the advantages associated with a stable internal temperature, endothermy is energetically expensive. To conserve energy when food is scarce, mice have evolved the ability to reversibly enter a regulated state of hypothermia and hypometabolism, known as torpor. We have found that circulating 17β-estradiol, a potent estrogen, inhibits fasting-induced torpor in ovariectomized female mice, yet the signaling mechanisms underlying this estrogenic re-mapping of the metabolic response to an energy deficit remain largely unknown. Recent studies have identified the medial preoptic area of the hypothalamus (MPO) as the central regulator of torpor. MPO neurons that express estrogen receptor alpha have been identified as central coordinators of torpor, and MPO neurons that are activated during torpor broadly express estrogen receptors, suggesting that circulating estrogens may directly modulate torpor-driving neurons in the MPO. To test the hypothesis that circulating estrogens inhibit torpor by acting directly on estrogen-sensitive neurons in the MPO, we delivered 17β-estradiol (E2) directly to the MPO before inducing torpor with a 48-hour fast. Surprisingly, we found that E2 delivered to the MPO was sufficient to inhibit fasting-induced torpor in gonad-intact, but not ovariectomized, female mice. These data demonstrate that E2 signaling in the MPO is insufficient to inhibit torpor on its own and that there are likely MPO-independent nodes in the body that circulating estrogens act on to inhibit torpor. However, our data also demonstrate that E2 signaling in the MPO does play a role in tuning the torpor response when endogenous gonadal hormones are present, suggesting that the MPO can sense estrogens and engage the appropriate effector circuits to inhibit torpor in certain physiological contexts. Together, these data advance our understanding of how circulating estrogens inhibit torpor in mice - a critical step towards the broader goal of understanding how circulating estrogens influence energy expenditure, and how these pathways can be manipulated to improve metabolic health.

Disclosures: P. Vander: None. **F. Sun:** None. **W. Hong:** None. **S. Correa:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.021/LBA19

Topic: F.03. Stress and the Brain

Title: Neutrophil elastase promotes stress-susceptibility and is modulated by fluoxetine treatment

Authors: *A. TAVALLAEI[1], L. F. PARISE[2], K. CHAN[2], F. CATHOMAS[2], R. DURAND-DE CUTTOLI[2], A. V. AUBRY[2], J. ALVAREZ[2], T. DRESCHER[2], R. L. FISHER-FOYE[2], L. LI[2], H.-Y. LIN[2], S. J. RUSSO[2];
[2]Neurosci., [1]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Background: Peripheral immune dysregulation, including upregulation of pro-inflammatory signaling, is found widely in depression. So far as stress plays a role in the onset of depression, research has also shown that neutrophils are upregulated after chronic stress. Interestingly, using the chronic social defeat stress model we find that neutrophil elastase, a secreted neutrophil serine protease, is upregulated in stress-susceptible mice. The ongoing question remains to what extent this depression-associated peripheral imbalance can be modulated by currently available antidepressants (i.e., fluoxetine). Additionally, we tested the functional relevance of directly modulating elastase to either promote or blunt stress susceptibility. Methods: Adult male C57BL/6 mice were exposed to 10 days of chronic social defeat stress and then stratified by their interaction ratio (>1=resilient (RES), <1=susceptible (SUS)). SUS mice received chronic fluoxetine (160 mg/L in drinking water) and elastase levels were measured by ELISA after 4 weeks of treatment. A separate cohort of defeated mice were separated by phenotype and instead of fluoxetine, SUS mice were treated with Alvelestat, a neutrophil elastase inhibitor. In parallel, RES mice received chronic recombinant elastase treatment to precipitate a susceptible phenotype. Results: Mice that received chronic fluoxetine after stress showed a reversal of social avoidance and an attenuation of neutrophil elastase activity. Interestingly, recombinant administration of elastase only modestly facilitated a SUS phenotype in RES mice whereas attenuating elastase activity was sufficient to promote resilience, similar to that seen after chronic fluoxetine treatment. Conclusion: Neutrophil elastase could be a novel peripheral biomarker of stress susceptibility and a viable target for antidepressant treatment. Additionally, neutrophil elastase could be an indicator of positive antidepressant treatment response.

Disclosures: A. Tavallaei: None. **L.F. Parise:** None. **K. Chan:** None. **F. Cathomas:** None. **R. Durand-De Cuttoli:** None. **A.V. Aubry:** None. **J. Alvarez:** None. **T. Drescher:** None. **R.L. Fisher-Foye:** None. **L. Li:** None. **H. Lin:** None. **S.J. Russo:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.022/LBA20

Topic: F.03. Stress and the Brain

Support: Grant-in-Aid for Scientific Research 22K07480
Grant-in-Aid for Scientific Research 22K07404

Title: Chronic Stress Exacerbates Viral Infection-Induced Sickness Behaviors and Neuroinflammation

Authors: *B. LKHAGVASUREN[1], T. OKA[2], C. ERDENEBAATAR[3], Z.-P. PANG[4], N. SUDO[5];
[1]Kyushu Univ., Fukuoka, Japan; [2]IUHW Narita Hosp., Narita, Japan; [3]Brain and Mind Res. Inst., Ulaanbaatar, Mongolia; [4]Child Hlth. Inst. of New Jersey, Rutgers Univ., New Brunswick, NJ; [5]Kyushu University, Grad. Sch. of Med. Scie, Fukuoka-Shi, Japan

Abstract: Post-viral fatigue syndrome (PVFS) is characterized by persistent sickness responses following viral infection. This study investigates the hypothesis that chronic stress predisposes individuals to develop PVFS. Mice were subjected to chronic stress prior to a viral mimic challenge (poly I:C). We assessed sickness behaviors, including fever, fatigue, pain, and depressive-like behavior. Chronic stress significantly attenuated grip strength ($p<0.001$), spontaneous locomotor activity ($p<0.01$), and the febrile response to poly I:C while increasing mechanical allodynia ($p<0.001$) and prolonged immobility in the forced swim test ($p<0.05$). Furthermore, we observed that minocycline and RU486, targeting microglial activation and glucocorticoid receptors respectively, attenuated PVFS-like symptoms ($p<0.001$). Preliminary histological data suggest altered activation patterns in brain regions implicated in stress and immune responses indicating potential neuroinflammatory mechanisms underlying these behavioral changes. These findings provide evidence that chronic stress is a risk factor for developing PVFS and highlight the importance of neuroinflammation in the pathophysiology of this condition.

Disclosures: B. Lkhagvasuren: None. **T. Oka:** None. **C. Erdenebaatar:** None. **Z. Pang:** None. **N. Sudo:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.023/LBA21

Topic: F.03. Stress and the Brain

Support: NIMH F31 MH121023
Silo Pharma
NICHD R01 HD101402
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For the Love of Travis Foundation
Columbia University SURF Program
Columbia University School of General Studies

Title: Sex Differences in the Synergistic Effects of (R,S)-Ketamine and Prucalopride on Neural Activity

Authors: *T. MONIZ[1], B. K. CHEN[1,2], C. A. DENNY[3,2];
[1]Neurobio. and Behavior, Columbia Univ., New York, NY; [2]Div. of Systems Neurosci., Res. Fndn. for Mental Hygiene, Inc. (RFMH) / New York State Psychiatric Inst. (NYSPI), New York City, NY; [3]Psychiatry, Columbia Univ. Irving Med. Ctr., New York, NY

Abstract: Sex is a significant risk factor in Major Depressive Disorder (MDD), with women experiencing depression and taking antidepressants at twice the rate of men. Given that MDD presents differently in men and women, it is crucial to study sex-specific treatments, as women often experience distinct symptoms and may respond differently to treatments, making targeted interventions essential. Current treatments are limited by non-specific side effects, inefficacy in Treatment Resistant Depression (TRD), and delayed onset. Serotonin type IV receptors (5-HT_4Rs) and N-methyl-D-aspartate receptors (NMDARs) have both been implicated in the pathophysiology of depression, and targeting these receptors with (*R,S*)-ketamine and prucalopride, respectively, has demonstrated rapid antidepressant effects in preclinical models. Previous results have found that combined administration of (*R,S*)-ketamine and prucalopride exerts additive effects against stress by attenuating learned fear in male mice and suppressing behavioral despair and hyponeophagia in both sexes. Here, we aimed to further understand the underlying mechanisms of these sex-specific behavioral changes by characterizing the neural circuits affected by combined (*R,S*)-ketamine and prucalopride treatment in both sexes. Male and female mice were treated with a single injection of saline, (*R,S*)-ketamine, prucalopride, or a combined dose of (*R,S*)-ketamine+prucalopride (K+P) one week before exposure to contextual fear conditioning. C-fos and parvalbumin (PV) expression in the medial prefrontal cortex (mPFC) and hippocampus (HPC) was analyzed using immunohistochemistry and network analysis. In male mice, K+P treatment increased c-fos and PV expression as well as the correlated activity of inhibitory PV^+ interneurons in the mPFC and HPC regions. In contrast, in female mice, K+P treatment selectively decreased c-fos expression in the mPFC without altering PV expression or c-fos in the HPC. These findings suggest that the mPFC could be a potential target for female-specific treatments for MDD, highlighting the importance of considering sex differences in the development of therapeutic strategies. This research underscores the potential of (*R,S*)-ketamine and prucalopride to offer a novel, sex-specific treatment option for MDD. Further research into the distinct neural mechanisms in females is essential for developing more effective and tailored interventions for depression, ultimately improving outcomes for a significant portion of the population affected by MDD.

Disclosures: T. Moniz: None. **B.K. Chen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Authors BKC and CAD are named on provisional patent applications for the prophylactic use of (R,S)-ketamine, 5-HT4Rs agonists, and other compounds against stress-related psychiatric disorders and Alzh. **C.A. Denny:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Authors BKC and CAD are named on provisional patent applications for the prophylactic use of (R,S)-ketamine, 5-HT4Rs agonists, and other compounds against stress-related psychiatric disorders and Alzh.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.024/Web Only

Topic: F.03. Stress and the Brain

Title: Investigation regarding the physiological effects of cobalt on physiological functions in Drosophilia, crayfish, and crab: behavior, cardiac, neural, and synaptic properties

Authors: *J. K. SCHWAMBURGER[1], K. BROCK[2], A. TAUL[2], J. NADOLSKI[4], J. KIM[5], S. M. BIERBOWER[6], R. L. COOPER[3];
[1]Univ. of Kentucky, Wheelersburg, OH; [3]Dept Biol, [2]Univ. of Kentucky, Lexington, KY; [4]Benedictine, Lisle, IL; [5]Model Lab. Sch., Richmond, KY; [6]Physiol., Univ. of Texas Hlth. Sci. Ctr., San Antonio, TX

Abstract: Cobalt, a metallic element found naturally in the earth's crust, is essential to survival. It is the active center of cobalamins such as vitamin B12 and is also a micronutrient for bacteria, algae, and fungi. The effects of cobalt (II) chloride, $CoCl_2$, are dependent on the dosage. High dosage or chronic exposure of $CoCl_2$ can have negative effects such as carcinogenic properties, intoxication, and cardiomyopathy known as "beer drinker's cardiomyopathy." This investigation was designed to test the acute effects of a high cobalt dose on physiological functions including behavioral, cardiac, neural, and synaptic properties in *Drosophila*, crayfish and crab. Using 1 mM of $CoCl_2$, there was decreased neural transmission at the neuromuscular junction (NMJ) in both crayfish and *Drosophila* larvae. In the crayfish proprioceptive organ there were no conclusive results due to variability. At the crab proprioceptive organ, activity was increased after 10 minutes when immersed in 1 mM $CoCl_2$. Heart rate decreased and almost stopped at 1 mM $CoCl_2$ in larval *Drosophila*, and this in situ preparation was able to recover a regular heart rate after rinsing with saline. Systemic injections in crayfish hemolymph produced no significant effects on heart rate. All crayfish responded to tail taps as normal. There were no behavioral effects in larval *Drosophila* within 24 hours of consuming food with 1 mM $CoCl_2$, with mouth hook movements and body wall movements unaffected. This did however cause a slightly decreased lifespan of adult *Drosophila*. This indicates that 1 mM CoCl2 has differing effects depending on the tissue and organism.

Disclosures: J.K. Schwamburger: None. **K. Brock:** None. **A. Taul:** None. **J. Nadolski:** None. **J. Kim:** None. **S.M. Bierbower:** None. **R.L. Cooper:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.025/LBA22

Topic: F.03. Stress and the Brain

Support: NIH Grant DA059237

Title: Acute minocycline treatment attenuates physical withdrawal symptoms but does not impact later cognitive development in rat model of neonatal opioid withdrawal syndrome (NOWS)

Authors: S. L. MILLS-HUFFNAGLE[1], T. MCFADDEN[1], O. LOWDEN[2], R. SERPA[1], E. TUFANO[1], *J. E. NYLAND[1];
[1]Penn State Col. of Med., Hershey, PA; [2]The Pennsylvania State Univ., University Park, PA

Abstract: Introduction: Approximately 50-80% of NOWS infants require medication for symptom management, which primarily consists of opioids. This seems paradoxical given recent preclinical evidence of neuroinflammation as a result of *in utero* opioid exposure, as well as clinical observations of poor cognitive outcomes in those previously diagnosed with NOWS. Thus, there is a need to evaluate non-opioid agents for NOWS treatment. Given that minocycline has effectively reduced opioid withdrawal symptoms in adult rats, this study investigated minocycline to reduce withdrawal symptoms and evaluate cognitive effects in a rat model of NOWS. **Methods:** In this ongoing study, 6 pregnant dams received heroin (2 mg/kg/day) via osmotic minipump from embryonic day 14 (E14) - postnatal day 10 (PN10). From PN8 - PN10, neonates received 45 mg/kg minocycline (i.p.; n = 30) or saline (n = 30). On PN10, all neonates received 5 mg/kg naloxone (s.c.) to precipitate withdrawal, followed by recording of locomotor activity; a measure of neonatal rat withdrawal. To evaluate cognitive function, a subset of rats (n = 26) completed the Morris Water Maze (MWM) at PN22-24. **Results:** There was no difference in PN10 weight between the saline and minocycline groups (t = 0.129, $p = 0.89$); however, within the saline group, females (n =17) weighed less than males (n =13; t = 2.295 $p = 0.03$). Compared to the minocycline group, the saline group experienced more locomotor activity during withdrawal including total distance moved (t = 1.690, $p = 0.05$), velocity (t = 1.653, $p = 0.05$), and time spent moving (t = 2.238, $p = 0.02$). Within the males, the saline group (n =13) spent more time moving when compared to the minocycline group (n = 17; t = 2.685 $p = 0.01$); however, subsequent analyses did not show a sex by drug interaction effect (F (1, 59) = 2.800, $p = 0.10$). Additionally, within the saline group, there was a trend for males to spend more time moving than females (t = 1.815, $p = 0.08$); however, this did not hold after controlling for body size (F (1, 27) = 2.744, $p = 0.11$). There was no difference in the rate of completion of the MWM between the saline (n = 13) and minocycline (n = 13) groups (F (1, 24) = 0.054, $p = 0.82$) or the number of crossovers after escape platform removal (t = 1.203, $p = 0.12$). **Conclusion:** Acute minocycline may attenuate physical withdrawal symptoms in rat neonates exposed to heroin and experiencing naloxone-precipitated withdrawal. Additionally, minocycline may not affect cognitive functioning at the juvenile timepoint. Future work will test neonatal ultrasonic vocalizations as a secondary measure of withdrawal, as well as later cognitive functioning at the adolescent and adulthood timepoints.

Disclosures: S.L. Mills-Huffnagle: None. **T. McFadden:** None. **O. Lowden:** None. **R. Serpa:** None. **E. Tufano:** None. **J.E. Nyland:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.026/LBA23

Topic: F.03. Stress and the Brain

Title: Quantifying behavioral response to alarming and novel stimuli in larval zebrafish

Authors: *B. HADIWIDJAJA[1], L. COLLINS[2], A. AMBROSINI[3], S. THIBERGE[3], H. SEUNG[4];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Inst. of Neurosci., Univ. of Oregon, Burlington, NJ; [4]Princeton Neurosci. Inst., [3]Princeton Univ., Princeton, NJ

Abstract: Consistent increases in global temperatures due to climate change is predicted to have critical implications on the habitat of aquatic animals, such as that of Danio rerio. Previous works have produced inconsistent results on the effect of rearing in high temperatures on behavioral response to alarming and benign cues. It was suggested that elevated temperatures during the development of larval zebrafish reduces overall locomotion, as measured by swimming distance. Other papers have reported increased distance traveled and swimming speed for zebrafish raised in increased temperatures. To help clarify these inconsistent results, we first recorded fear responses to benign or alarming olfactory and visual stimuli for zebrafish raised in normal (28° Celsius) and raised (32° Celsius) temperatures. Fear responses primarily include immediate fleeing or increased motility after exposure. For olfactory response, we used an alarming stimulus known as schreckstoff (a chemical cue released by injured conspecifics) and glutamic acid, a benign cue. For visual response, we used a looming stimulus as an alarm cue and a rotating pinwheel as a benign cue. In analyzing zebrafish mobility in response to alarming or benign cues, results indicate a lack of difference in fear response to the cue and the control condition. There is no indicative difference in responses to both cues within the same temperature groups. Between temperature groups, 32° C raised fish exhibit reduced motility. These results can be noted for both visual and olfactory groups. Significant differences in fear responses between temperature groups are likely supported by a difference in neuronal activity patterns as the zebrafish are presented with alarming or benign stimuli. With light bead microscopy, we found preliminary evidence that we can reliably record from multiple brain areas. Future analysis of fear response should consist of imaging the olfactory bulb and optic tectum as the zebrafish are exposed to various alarm and benign cues. Additionally, it will be beneficial to evaluate the downstream pathways which are developmentally affected by increased rearing temperatures, such as the habenula, which has been implicated in experience-dependent regulation of fear responses in larval zebrafish.

Disclosures: B. Hadiwidjaja: None. **L. Collins:** None. **A. Ambrosini:** None. **S. Thiberge:** None. **H. Seung:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.027/LBA24

Topic: F.03. Stress and the Brain

Support: NSF Graduate Research Fellowship
USDA Congressional Grant

Title: Age-dependent effects of social isolation on honey bee brain gene expression

Authors: *M. E. FLORES[1,2], A. N. GOMEZ LOPEZ[3], S. M. MURPHREE[4], G. E. ROBINSON[4,1,2];
[1]Neurosci. Program, [2]Carl R. Woese Inst. for Genomic Biol., [3]Crop Sci. Program, [4]Dept. of Entomology, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Adult worker honey bees exhibit behavioral maturation, age-related behavioral shifts that underlie colony division of labor. Because honey bee larvae undergo complete metamorphosis as pupae, completely restructuring their body plan, including the brain, prior to eclosing as adults, they provide a unique model to study how early-life experiences and environmental information affect adult brain and behavior. We used newly developed methods to rear bees in the laboratory and compared brain gene expression of 5th instar larvae and 1-day-old adults reared either in social isolation or under natural colony conditions. Statistical analyses of bulk RNA gene expression data (whole head for larvae and brain for adults) to identify DEGs were performed using a Wilcoxon Rank Sum Test, with p-values adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR < 0.05). Social isolation affected gene expression in adults (N = 24), but not larvae (N = 8). Social isolation had no effect on larval gene expression but did cause differences in ~2,400 genes in adults. To provide functional information for these genes, orthologs to the *Drosophila melanogaster* genome for ~600 DEGs with a log-fold change > 0.5 were used to identify Gene Ontology (GO) terms for each list of up- or down-regulated genes using the R package "gProfiler2." Upregulated genes were enriched for terms related to development. Downregulated genes were enriched for terms related to sensory perception and metabolism. Future studies will study the possible behavioral consequences of the social isolation effects on adult brain gene expression and why larvae are insensitive to social isolation, but adults are.

Disclosures: M.E. Flores: None. **A.N. Gomez Lopez:** None. **S.M. Murphree:** None. **G.E. Robinson:** None.

Late-Breaking Poster

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Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.028/LBA25

Topic: F.03. Stress and the Brain

Support: NIDA Grant DA060266-01

Title: Resource scarcity-induced genomic alterations in the basolateral amygdala: a focus on retrotransposons

Authors: *A. CUARENTA, D. A. BANGASSER;
Neurosci. Inst., Georgia State Univ., Atlanta, GA

Abstract: Retrotransposons are mobile elements within the genome capable of autonomous transposition via RNA intermediates. Long interspersed element 1 (L1) is a retrotransposon that comprises 17% and 23% of the human and rat genome, respectively, and has been implicated in several psychiatric disorders including depression, schizophrenia, and bipolar disorder. L1 was previously thought to be quiescent during typical development through epigenetic suppression; however, recent research has demonstrated that L1 is influenced by environmental experiences such as maternal care and early life adversity. My previous research revealed L1 copy number was increased in the juvenile amygdala after neonatal predator odor exposure in rats, a model of early life adversity. The neonatal predator manipulation reduces juvenile play and play is negatively correlated with L1 inserts in the amygdala. I am now extending this work to another early life adversity model. Currently, our lab uses a limited bedding and nesting (LBN) model to mimic a resource scarce environment, which is a form of early life adversity. Despite the low nesting materials provided, dams in LBN provide enhanced maternal care and male offspring are less impulsive and self-administer less morphine in adulthood than male rats raised in control housing. I used RT-qPCR to investigate whether LBN experienced during the first week of life altered the retrotransposon, L1, in the basolateral amygdala (BLA) genome later in adulthood. Our analysis demonstrates that male and female rats exposed to the LBN model as pups have fewer L1 copies in the BLA genome as adults compared to controls. This intriguing result demonstrates that the LBN model is impacting the BLA genome by reducing L1 copy number. We are now extending this research to investigate whether this change is cell-type specific. Understanding whether there are specific cell-types being impacted by LBN is an important step in understanding how early life adversity is directly altering the genome and potentially future behavior.

Disclosures: A. Cuarenta: None. **D.A. Bangasser:** None.

Late-Breaking Poster

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Program #/Poster #: LBA006.029/LBA26

Topic: F.03. Stress and the Brain

Support: NRF-2022R1I1A4053049
MSIT 2022R1A5A8019303

Title: Comparing the effects of different exercise modes on mood symptoms and EEG activity

Authors: *K. YUK[1], J. LIM[2], S. KIM[2], K. TAE YEON[2], H. MOON[2];
[1]Physical Educ., [2]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Anxiety and depression are mental illnesses that occur frequently in overall population. Previous research suggests that aerobic and resistance exercises both contribute to the alleviation of anxiety and depression symptoms. In addition, recent studies suggest that different types of exercises may modulate different mechanistic pathways in terms of mood. Existing research suggests that electroencephalography (EEG) can be utilized as a tool to measure electrophysiological changes in mood disorders. However, there is no research comparing which type of exercise is more effective for alleviating mood symptoms and changing mood-related EEG activities. This research investigates the different effects of each type of exercise on mood symptoms and EEG activities. We conducted a cross-over design; two groups participating in 6-week aerobic and resistance exercises 2 times per week with a 3-week washout period. The Score of Hospital Anxiety and Depression Scale (HADS) was measured to evaluate the severity of mood symptoms. The EEG analysis was conducted to verify brain wave pattern changes. EEG of 10 regions (Fp1, Fp2, F3, F4, T7, T8, P3, P4, O1, O2) was recorded. We calculated values of theta/beta ratio (TBR), total theta relative power, frontal alpha asymmetry (FAA), and Higuchi Fractal Dimension (HFD). Lastly, we conducted an Enzyme Linked Immunosorbent Assay (ELISA) to confirm the changes in cortisol levels, which is known to elevate in patients with anxiety and depression. Questionnaire results exhibited that both types of exercise contributed to the alleviation of anxiety and depression from mild to normal levels. However, the average score change deviation within each group of participants revealed that aerobic exercise (AE) decreased the score of HADS-A ($p < 0.05$), while resistance exercise (RE) improved HADS-D compared to CTL ($p < 0.05$). Our results parallel with the results of our pilot study, which reported that AE and RE (once per week) respectively reduced BAI and BDI scores. In EEG analysis, a significant decrease of TBR in the left frontal region ($p < 0.05$) was observed after AE. Next, we evaluated values of HFD, TBR (ch5, 6), and FAA as depression-specific biomarkers. However, both interventions did not cause a difference within all groups. Lastly, a trend of reduced levels of cortisol ($p = 0.0942$) was identified after participating in RE. In conclusion, our results suggest the possibility that different types of exercise may alleviate different mood symptoms and moreover lead to different EEG changes. To the best of our

knowledge, this is the first study to compare two types of exercise in terms of mood symptoms and EEG changes.

Disclosures: K. Yuk: None. **J. Lim:** None. **S. Kim:** None. **K. Tae Yeon:** None. **H. Moon:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

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Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.030/LBA27

Topic: F.03. Stress and the Brain

Support: R01MH127214

Title: The long term effects of early life adversity on anxiety and social behaviors

Authors: *C. CHRISTENSEN[1], S. V. BLAGBURN-BLANCO[2,1,3], L. A. DENARDO[2,1]; [2]Physiol., [1]UCLA, Los Angeles, CA; [3]Med. Scientist Training Program, UCLA, Los Angeles, CA

Abstract: Early life adversity (ELA) is a major risk factor for developing mental health disorders. ELA occurring during key periods affects brain development, specifically in reward and stress-related brain regions. Previous literature has shown that certain pairings of ELA with a second hit of stress prime the brain to be over responsive to stress, and alter affective behaviors. This project aims to understand the impacts of ELA and a later social isolation (SI) stress on the brain development and behavior. Previous research has shown that mice who experience SI during key developmental time points show a decrease in later social interaction. Through a limited bedding and nesting (LBN) protocol, an ELA model for resource deprivation in rodents, followed by a second hit of SI stress, this project has investigated ELA's long term impacts on changes to behaviors associated with anxiety-like behaviors and social interaction. After one- or two-hit stress protocols, mice were tested through behavioral assays including the open field test, elevated zero maze, and sociability test. LBN mice showed increased anxiety compared to SI mice and LBN-SI mice, suggesting that, following LBN, SI may promote later resilience in anxiogenic environments. In social behavior assays, LBN, SI and LBN-SI mice all have a similar magnitude decrease in social interactions compared to standard reared mice. These results suggest that experiencing LBN during development has a differing long term effect between anxiety and social behaviors. Additionally, LBN does not appear to prime the brain for an over response to a second hit of SI stress in the domains of social and anxiety-like behaviors. These findings advance our understanding of rodent models of ELA, and provide insight into the nature of the additive effects of early adversity followed by juvenile social isolation.

Disclosures: C. Christensen: None. **S.V. Blagburn-Blanco:** None. **L.A. DeNardo:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.031/LBA28

Topic: F.03. Stress and the Brain

Support: ORWH-NIMH 3U54MH118919
ORWH-NIMH 3U54MH118919-04S3

Title: Increased Anxiety-like Behavior and Stress Responses in Adult Female Rat Offspring of Resiquimod-Injected Dams

Authors: M. MARTINEZ[1], *S. TOBET[2];
[1]Univ. of Arizona Col. of Medicine-Phoenix, Phoenix, AZ; [2]Colorado State Univ., Fort Collins, CO

Abstract: Maternal immune activation (MIA) can occur during pregnancy due to exposure to infectious diseases or other stressors. Resiquimod (RQ), a toll-like receptor 7 agonist, induces systemic inflammatory responses and mimics responses to viral infections. The current project investigates the degree to which late-gestation MIA with RQ impacts offspring development, anxiety-like behavior, and neuroendocrine function. Pregnant rat dams received a single vehicle (phosphate-buffered saline) or RQ (1 mg/kg, s.c.) injection on gestation day 18. We conducted an open field test to assess anxiety-like behavior and assessed plasma corticosterone (CORT) responses following restraint stress in separate cohorts of rats before puberty (postnatal day (PND) 23-28) and after puberty (9-10 weeks of age). In-utero MIA exposure did not affect birth weights or early-life developmental milestones (i.e., the timing of eye opening and righting reflex). However, the female offspring of RQ-injected dams experienced a significant delay (~1 day) in vaginal opening, suggesting delayed pubertal onset. Before puberty, MIA did not affect open field assessments or CORT levels in response to restraint. After puberty, there was a significant effect of RQ ($F(1,13)=7.046$, $p=0.0198$) to increase anxiety-like behavior. Specifically, post hoc analysis revealed that the adult female offspring of immune-activated dams spent significantly less time in the center zone ($p=0.0244$) than their controls. Plasma CORT concentrations following 20 minutes of restraint tended to be higher in the offspring of RQ-injected dams ($F(1,12) = 3.133$, $p=0.1021$). In summary, the results of the open field test indicate that the adult female offspring of immune-activated dams display increased anxiety-like behavior. This group also displays trends of dysregulation of the hypothalamic-pituitary-adrenal axis based on the restraint plasma CORT concentrations. Moreover, the data suggests that these effects manifest post-puberty, indicating a role for gonadal hormones and/or aging in programming these changes. These studies contribute to our growing understanding of the long-term consequences of MIA on the offspring.

Disclosures: M. Martinez: None. **S. Tobet:** None.

Late-Breaking Poster

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Program #/Poster #: LBA006.032/LBA29

Topic: F.03. Stress and the Brain

Support: NIH grant R01MH123686
NIH-MARC U-STAR training grant number T34GM136498

Title: The effect of Tsc22d3 knockout on synapse density and cognitive performance following stress exposure during adolescence

Authors: *N. V. BUGARIN[1], A. Y. FLORES[3], C. CHINN[6], J. ROUNDS[4], M. A. WOOD[2], G. LUR[5];
[1]Neurobio. and Behavior, [2]Neurobiol & Behavior, Univ. of California Irvine, Irvine, CA;
[4]Neurobio. & Behavior, [5]Neurobio. and Behavior, [3]Univ. of California, Irvine, Irvine, CA;
[6]Neurobio. and Behavior, UC Irvine, Irvine, CA

Abstract: Adolescent stress is a well-known risk factor for cognitive deficits and neuropsychiatric disorders. The central mechanism thought to underlie these cognitive impairments is stress-induced disruption of synaptic communication in brain regions including the hippocampus, anterior cingulate cortex (ACC), posterior parietal cortex (PPC), and basolateral amygdala (BLA). Tsc22d3 is a gene regulating the expression of glucocorticoid-induced leucine-zipper (GILZ) that is thought to play a role in the brain's response to prolonged stress. Our preliminary data shows significantly increased GILZ expression in male mice ACC, PPC, and amygdala after repeated exposure to multiple concurrent stresses (RMS) during adolescence. RMS and other chronic stress paradigms cause impaired learning, increased anxiety, and synapse loss. We hypothesized that GILZ was a mediator of stress effects and therefore knocking out GILZ would mitigate negative outcomes following RMS. We anticipated stressed GILZ KO mice to demonstrate cognitive performance and anxiety levels similar to unstressed cohorts. Additionally, we expected GILZ KO mice would exhibit attenuated loss of excitatory and inhibitory synapses following stress. To test our hypothesis, we assigned male wildtype or GILZ KO mice to control or stress (10 days of RMS starting on postnatal day 30) cohorts. All mice were tested for visuospatial working memory by measuring spontaneous alterations in a Y-maze paradigm. To assess anxiety phenotypes we used an elevated plus maze (EPM) and measured time spent in the closed arms. To determine the effect of GILZ KO on synapse density, we used immunohistochemical staining of PSD 95 and Gephyrin to label excitatory and inhibitory synapses, respectively, in the hippocampus, ACC, PPC, and BLA. Our preliminary Y-Maze data showed no effect of GILZ KO on spontaneous alternation. In the EPM,

GILZ KO and wildtype stressed cohorts indicated a stress-induced increase in anxiety by a greater amount of time spent in the closed arms, however, we did not see a genotype effect in this behavior either. Our immunohistochemistry data showed that stressed GILZ KO mice exhibited a greater loss of excitatory synapses in hippocampus and the PPC compared to wildtype. Conversely, in the BLA, stressed GILZ KO mice exhibited a greater gain in inhibitory synapses than wildtypes. Our findings indicate that GILZ KO has a marked effect on synaptic puncta counts in the PPC, Hippocampus, and BLA regions in stressed mice. Instead of mediating the stress effect, this preliminary data suggests GILZ has a protective effect on synapses in multiple brain regions, although the behavioral effects remain unclear.

Disclosures: N.V. Bugarin: None. **A.Y. Flores:** None. **C. Chinn:** None. **J. Rounds:** None. **M.A. Wood:** None. **G. Lur:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

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Program #/Poster #: LBA006.033/LBA30

Topic: F.03. Stress and the Brain

Support: Office of Naval Research (ONR)

Title: Dynamics of Periodic and Aperiodic Brain Activities in Homeostatic and Allostatic State During Acute Cold-Water Immersion Military Field Training

Authors: *W. ZHENG[1,2], R. WELLER[1,2], N. ROBERTS[3], D. JONES[1];
[1]Warfighter Performance Dept., Naval Hlth. Res. Ctr. (NHRC), San Diego, CA; [2]Leidos Inc., San Diego, CA; [3]Marine Corps Mountain Warfare Training Ctr., Bridgeport, CA

Abstract: Military operations in cold environments may increase heat loss, impair task performance, and endanger service members' health. While much has been learned on physiological responses to cold, very little is known on how the brain responds to cold while concurrently attempting to perform cognitive tasks. To address this gap, we monitored heart rate, core temperature, and brain activities with high-density electroencephalogram (EEG) while service members performed two cognitive tasks (Simple Reaction Time and Delayed Match-to-Sample) during field cold-water immersion (CWI). Thirty-six participants were immersed to the neck for 10 min in an icy pond (~1.6°C). Data were collected in seven conditions: baseline (indoors), pre-immersion (outdoors), immersion (in water), post-immersion (outdoors with wet clothes), and at 0, 15, and 60 minutes of rewarming. After separation of the periodic and aperiodic EEG components with the FOOOF (Fitting Oscillations and One-Over-F) toolbox, the abundance of the θ, α, β, and γ band oscillations and the offset/exponent of the 1/f components were computed to profile the rhythmic and nonrhythmic brain activities, respectively. Analysis

of heart rate and core temperature revealed a sequential transition from the homeostatic state in baseline and pre-immersion condition into two allostatic states. The first allostasis was achieved during the 10-min CWI, within which core temperature was maintained at baseline level (37.4 ± 0.2 ^{o}C), heart rate increased substantially (ANOVA, $p < 0.01$, same statistics in the rest of the abstract), and response time in cognitive tasks slowed significantly. The second allostasis was achieved during the 15-min rewarming period as core temperature decreased and stabilized at a significantly lower level (35.9 ± 0.6 ^{o}C), heart rate increased to the highest level, and cognitive task performance declined further. Notably, distinctive patterns of brain activities were manifested in each of the two allostatic states. In the first state, only θ band abundance increased significantly and both the offset and exponent remained unchanged compared to baseline. In the second state, α and β abundance increased, θ and γ abundance decreased, and both the offset and exponent decreased significantly compared to baseline. These results revealed dynamically changing patterns of brain activity associated with homeostatic state changes during field CWI. Understanding the complexity of brain-body interactions during CWI is vital to improving cognitive performance and preventing hypothermia not just in military operations but also in a variety of human activities across multiple sectors of modern society.

Disclosures: W. Zheng: None. **R. Weller:** None. **N. Roberts:** None. **D. Jones:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.034/LBA31

Topic: F.03. Stress and the Brain

Support: NARSAD Young Investigator grant to LRV and FY
National Institutes of Mental Health grants K08MH12616 to LRV
MHR01107435 to SP

Title: BNST Pathways involved in Avoidance Generalization

Authors: *R. MASROOR[1], W. SMITH-PETERS[2], F. YASMIN[2], V. KONDEV[3], S. PATEL[2], L. E. ROSAS-VIDAL[2];
[2]Dept. of Psychiatry and Behavioral Sci., [1]Northwestern Univ., Chicago, IL; [3]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: PTSD is a psychiatric disorder characterized by emotional distress triggered by reminders of a traumatic event. Fear generalization and avoidance of trauma reminders are core symptoms of PTSD and are critical to understanding its pathophysiology. The bed nucleus stria terminalis (BNST) is crucial for mediating anxiety and fear generalization (Lebow and Chen, 2016). It is unknown, however, if BNST mediates generalization of avoidance. BNST projects to

ventral tegmental area (VTA) and the dopamine neurons of VTA have been implicated in the fear generalization (Jo YS et al., 2018). Additionally, the basomedial amygdala (BMA) has been shown to alleviate anxiety and fear-related freezing and signal safety and also projects to BNST (Adhikari et al., 2015). Thus, we hypothesize that BNST to VTA projections could promote generalization of avoidance, whereas BMA to BNST projection is needed to reduce generalization. To test this hypothesis, we used optogenetics in an avoidance-conflict task in male mice to test if activating the BNST-VTA pathway aggravates avoidance generalization. Similarly, we used optogenetic inhibition to test if the BMA-BNST pathway is required to suppress generalization. Our optogenetic experiments suggest that BNST-VTA promotes generalization to safe and uncertain stimuli, whereas BMA-BNST is required to suppress generalization to uncertain stimuli. Using slice electrophysiology, we show that BNST receives glutamatergic inputs from BMA. This is in line with the idea that BNST integrates safety information from BMA and gates the expression of avoidance generalization through selective activation of outputs to VTA.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

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Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.035/LBA32

Topic: F.03. Stress and the Brain

Support: NIH Grant K08-MH130802
NIH Grant R01-MH108665

Title: Regulation of fear memory acquisition by Foxp2 transcription factor in the mouse amygdala

Authors: *O. PONOMAREVA[1,2], E. CATT[3], S. KINI[3], K. J. RESSLER[1,2];
[1]McLean Hosp., Belmont, MA; [2]Harvard Med. Sch., Boston, MA; [3]Northeastern Univ., Boston, MA

Abstract: Post-Traumatic Stress Disorder (PTSD) is a common, debilitating mental illness with a high economic burden and limited available personalized treatments. Recent Genome-Wide Association Studies (GWAS) identified the transcription factor Forkhead box P2 (*FOXP2*) as a target implicated in PTSD. Foxp2 has been previously associated with language learning and neuropsychiatric disorders; however, its role in adult emotional learning is unknown. In adult mice, *Foxp2* mRNA is expressed in clusters of Intercalated Cells surrounding the basolateral amygdala. Intercalated Cells are functionally important for conditioned fear response and fear

extinction, with activation of the ventromedial Intercalated cluster being particularly important for retrieval of extinction memories. Despite its strong association with PTSD and localization in a region highly implicated in fear extinction, the role of the Foxp2 transcription factor in modulating fear-related behaviors in the amygdala remains unknown. The aim of the current study is to test the hypothesis that Foxp2 regulates specific components of fear learning through its interaction with the Wnt signaling pathway in the Intercalated Cells of the amygdala. We show that Wnt transcription is active in the Intercalated Cells of adult male and female mice during fear learning with neutral Conditioned stimulus (tone) followed by an aversive Unconditioned stimulus (mild foot shock), and that *Foxp2* mRNA is dynamically regulated after fear learning in male mice. Following RNAi-mediated knockdown (KD) with Foxp2 shRNA targeting Foxp2 expression in the medial Intercalated Cell cluster of the amygdala, we find that mice with reduced Foxp2 expression acquire fear learning at a significantly lower rate than their control counterparts. We find no difference in time ambulating, total distance travelled in an open field task, or total duration rearing during fear learning. An ongoing goal of this study is to further describe the functional role of Foxp2 and its modulators in adult fear learning and memory and identify pharmacological targets for a more personalized treatment of trauma and stressor-related disorders.

Disclosures: O. Ponomareva: None. **E. Catt:** None. **S. Kini:** None. **K.J. Ressler:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Alto Neuroscience. F. Consulting Fees (e.g., advisory boards); Acer, Bionomics, Jazz Pharma. Other; Sage, Boehringer Ingelheim, Brain and Behavior Research Foundation, Brain Research Foundation.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.036/LBA33

Topic: F.03. Stress and the Brain

Support: CIHR PJ8 179866
CIHR PJT 183587
NSERC 840107

Title: Diminished social memory and hippocampal correlates of social interactions in chronic social defeat stress susceptibility

Authors: A. LAROSA[1], A. WONG[2], ***T. WONG**[2];
[1]Neurosci., McGill Univ., Verdun, QC, Canada; [2]Douglas Res. Ctr., Verdun, QC, Canada

Abstract: Background: The susceptibility to chronic stress has been associated with depression, a mood disorder which highly implicates the hippocampus. Hippocampal contribution to stress susceptibility has been supported by findings in mice following chronic social defeat stress (CSDS). However, little is known of the role of hippocampal activity in determining the development of stress susceptibility.
Methods: We used the UCLA miniscope to longitudinally measure the activity of dorsal CA1 hippocampal neurons across CSDS. Apart from examining the representation of social information by these neurons, we also compared social memory in mice that were susceptible or resilient to CSDS.
Results: We observed more stable dCA1 correlates of social interaction and social memory in CSDS resilience. Such changes were absent in CSDS susceptible mice and accompanied by greater social memory impairments.
Conclusions: CSDS susceptibility may be supported by hippocampal social cognitive processes, reflected in diminished hippocampal representations of social information and a greater impairment in social memory.

Disclosures: A. Larosa: None. **A. Wong:** None. **T. Wong:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.037/Web Only

Topic: F.03. Stress and the Brain

Title: Investigation regarding the physiological effects of sodium selenite on physiological functions inDrosophila,crayfish and crab: behavior, cardiac, neural, and synaptic properties

Authors: *J. BIDROS;
Biol., Univ. of Kentucky, Lexington, KY

Abstract: Selenium is an essential element, comprising the 21stamino acid (selenocysteine) and ensuring the functionality of selenoproteins. Selenoproteins maintain cellular health and support the immune system. Additionally, sodium selenite can be beneficial when used in therapeutic treatments. It has been shown to inhibit ferroptosis during spinal cord injury. However, it can also be biologically harmful depending on its concentration and form of exposure. Overexposure can lead to death, but the mechanisms and series of pathological actions are not fully understood. This investigation examined the effects of acute sodium selenite exposure in relatively high concentrations (1 mM and 5 mM) on marine crab (Callinectes sapidus) sensory nerves; stretch-activated channels (SACs) in the muscle receptor organ of a freshwater crayfish; synaptic transmission at the crayfish and larval Drosophila neuromuscular junctions; and the myogenic heart of larval Drosophila. Systemic exposure of sodium selenite in crayfish hemolymph resulted

in organism death after 2 hours. The development and survival of Drosophila through dietary exposure to sodium selenite was observed as well. When the food was laced to a 1 mM concentration, larvae died in 24 hours and adults died in 3 days. This indicates that the effects vary between acute exposure on tissue and chronic exposure of one or two days in intact animals.

Disclosures: J. Bidros: None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.038/LBA34

Topic: F.03. Stress and the Brain

Support: NIH Grant 5R21HD109368-02

Title: Ascending projections from CRFR2-expressing cells in the midbrain dorsal raphe to the medial preoptic area and nucleus accumbens of recently parturient rats

Authors: *T. A. MEINHARDT, J. S. LONSTEIN;
Michigan State Univ., East Lansing, MI

Abstract: The midbrain dorsal raphe (DR), the source of most forebrain-projecting serotonin neurons, influences postpartum maternal caregiving and affective behaviors in female laboratory rodents. These postpartum behaviors are derailed by the stress-related neuropeptide, corticotropin releasing factor (CRF), acting on its two receptor subtypes (CRFR1 and CRFR2) that are both expressed in the DR. These receptors alter DR neuronal activity to affect serotonin release and signaling in forebrain regions, such as the medial preoptic area (mPOA) and the nucleus accumbens (NAc), that are critical for postpartum caregiving and affective behaviors. Previous work from our lab found that recently parturient rats had more *CRFR2* (but not *CRFR1*) mRNA-expressing cells in the rostral DR compared to nulliparae, suggesting a potential role of CRFR2 receptors in the early postpartum resilience to stress. Whether or not, and how many, of these DR neurons expressing *CRFR2* project to the mPOA and NAc has not been investigated. In the current study, we injected retrograde cholera toxin subunit b (CTb) conjugated to Alexa Fluor 488 into either the mPOA or NAc on pregnancy day 15, then used *in situ* hybridization to visualize *CRFR2* and CTb-positive cells in the DR of recently parturient rats. This study is revealing previously uncharacterized anatomical connections between DR *CRFR2*-expressing cells and the mPOA and NAc, helping to explicate how stress can affect serotonin input to hubs in the maternal behavior brain network, with implications for maternal stress, peripartum affective disorders, and impaired infant caregiving.

Disclosures: T.A. Meinhardt: None. **J.S. Lonstein:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.039/LBA35

Topic: F.04. Neuroimmunology and Neurovirology

Support: Mike Dunkle Summer Research Endowed Fund
Summer Research at University of Puget Sound

Title: Characterization of kynurenic acid in the nervous system of the pond snail helisoma duryi

Authors: *V. DEPINTO;
Biol., Univ. of Puget Sound, Tacoma, WA

Abstract: The kynurenine (KYN) pathway, a major metabolic pathway in L-tryptophan (TRP) catabolism, is implicated in the formation of neurotransmitters serotonin and melatonin. Dysregulation of the KYN pathway is associated with multiple neuroinflammatory and neurodegenerative diseases, including Alzheimer's disease, schizophrenia, multiple sclerosis (MS), and various cancers. However, much is still unknown regarding KYN activity in the CNS, including the location and pathophysiological role of its metabolites. Invertebrate species provide a unique model to study neural mechanisms and behavioral processes involved in neuronal growth and localization. KYN genes have been localized in different tissues of the gastropod mollusk Lymnaea, with expression in the central nervous system as well. To date however, there have been no studies locating actual neurons containing KYN in the snail brain. We use immunohistochemical stains to locate KYN in the central nerve ring and buccal ganglia of the pond snail Helisoma duryi. Brains were isolated from adult snails (n = 20, 4-10mm in diameter), fixed using 4% PFA, and stained using anti-Kynurenine. Positive staining was found in neurons in the buccal ganglia and the circumesophageal ganglia including the cerebral, pedal, parietal, and visceral ganglia. Immunoreactivity was also found in processes such as the cerebrobuccal connectives, the buccal and cerebral commissures, and nerves from the visceral and pedal ganglia. Given the importance of KYN to brain health, its localization in the snail nervous system can provide a new model to study its role in the function and survival of healthy neurons.

Disclosures: V. DePinto: None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.040/LBA36

Topic: F.04. Neuroimmunology and Neurovirology

Title: Tnf-responsive neurons in the bed nucleus of the stria terminalis mediate sickness behaviour

Authors: *T. HEPLER[1], O. HASHIMOTO[1], A. TYNAN[1], K. J. TRACEY[2], S. S. CHAVAN[3]; [1]Feinstein Inst. for Med. Res., Manhasset, NY; [2]Res. Admin., [3]Inst. for Bioelectronic Med., Feinstein Inst. For Med. Res., Manhasset, NY

Abstract: Tumor Necrosis Factor (TNF), a proinflammatory cytokine, has been well-studied for its role in the progression of inflammatory diseases. Physiological changes driven by TNF markedly increase morbidity by exacerbating inflammatory diseases. However, the neural networks that regulate TNF-mediated effects are not yet known. Here, we identify the bed nucleus of the stria terminalis (BNST) as a central regulatory node in the physiological response to TNF. Administration of TNF significantly increases serum IL-6 (control vs. TNF; 26.8±8.3 vs. 484.8±110.5 pg/ml; p=0.006) and MCP-1 (control vs. TNF; 242.5±75.2 vs. 1531.0±305.8 pg/ml; p<0.0001) 2 hours post systemic injection. A significant decrease in minimum core body temperature (control vs. TNF; -1.3±0.2 vs. -2.1±0.2 ºC; p<0.03) and activity level (control vs. TNF; 9.4±1.4 vs. 3.8±0.4 AUC; p=0.003) is also observed following TNF adminstration. We utilized activity-dependent TRAPing technology to identify neurons activated in response to TNF administration. Our studies identified distinct neuronal populations in the BNST, paraventricular nucleus of the hypothalamus (PVN), paraventricular thalamic nucleus (PVT), and nucleus tractus solitarius (NTS) in response to TNF. Selective chemogenetic activation of TNF-responsive BNST neurons recapitulates inflammatory phenotype in the absence of exogenously administered TNF (IL6: control vs. TNF; 24.1±4.3 vs. 252.3±75.4 pg/ml; p=0.02 and MCP-1: control vs. TNF; 204.3±38.0 vs. 803.3±247.5 pg/ml; p=0.04), and also induces a significant decrease in minimum core body temperature (control vs. TNF; -0.9±0.2 vs. -5.3±1.1 ºC; p=0.008) and a trend towards reduced activity (control vs. TNF; 13.4±2.1 vs. 9.9±1.9 AUC; p=0.2). Taken together, our data identifies a neuronal node in the brain, the BNST, that is sufficient for mediating TNF associated physiological responses.

Disclosures: T. Hepler: None. **O. Hashimoto:** None. **A. Tynan:** None. **K.J. Tracey:** None. **S.S. Chavan:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.041/LBA37

Topic: F.04. Neuroimmunology and Neurovirology

Title: SARS-CoV-2 S1 spike protein induces a temporal systemic inflammatory response that promotes long-term behavioral changes

Authors: *L. MERINO GALAN[1], J. M. HEMENWAY[1], H. L. JAGANA[1], S. ORTIZ ESPINOSA[2], M. HATHAWAY[1], A. RAJENDRAN[3,1], T. JACKSON[1], N. RECHE-LEY[1], A. KHANNA[1], S. SARKAR[1,3], V. KALIA[1,3], S. S. PATTWELL[1,3,2];
[1]Ben Towne Ctr. for Childhood Cancer Res., Seattle Children's Res. Inst., Seattle, WA; [2]Human Biol. Div., Fred Hutchinson Cancer Ctr., Seattle, WA; [3]Univ. of Washington, Seattle, WA

Abstract: The COVID-19 pandemic continues to affect millions of people globally, with increasing reports of persistent neurological manifestations such as fatigue, anxiety, and cognitive impairment, often referred to as Long-COVID. Understanding its etiology and the related neuropathological alterations is crucial for addressing ongoing public health challenges. The S1 subunit of the SARS-CoV-2 spike protein plays a critical role in viral entry into host cells by binding to the ACE2 receptor. Additionally, emerging evidence shows that the S1 protein can detach from the virion, its serum levels are associated with disease severity in patients, and it can induce systemic immune activation. This suggests that the soluble S1 protein alone might trigger host immune responses and neuroinflammation, inducing neurological symptoms even in the absence of viral particles. However, the exact mechanisms and extent of its impact remain unclear. This study aimed to investigate the short- and long-term effects of SARS-CoV-2 S1 spike protein on systemic inflammation, neuroinflammation, and behavior. K18-hACE2 adult mice (both females and males, > 3 months old), genetically engineered to express the human ACE2 receptor, were administered the S1 spike protein intravenously (5 ug, 10 ug and 20 ug) and monitored over 2 months for signs of neurotoxicity and behavioral changes. Our findings reveal that the S1 protein induces a dose-dependent and temporal systemic inflammatory response, characterized by elevated levels of inflammatory cytokines such as GM-CSF, IFN-λ, IL-2, IL-13, MIP-1α and MIP1-β and CCL5. This initial inflammatory response diminished over time, yet residual inflammation persisted. Flow cytometry and histopathological analysis of brain tissue indicated no evidence of increased systemic immune cell infiltration. Neurologic screening exams and open field tests conducted 2 months post-inoculation revealed significant changes. Mice exhibited subtle neurological abnormalities, particularly in postural adjustment and balance and marked anxiety-like behaviors, without altered locomotor activity and spatial working memory. This suggests a correlation between the systemic inflammatory state induced by the S1 protein and long-term neuropsychiatric alterations. These behavioral changes align with clinical observations in human Long-COVID patients, providing a potential mechanistic link between S1 protein-induced inflammation and lasting neuropsychological effects that might be amendable to therapeutic intervention.

Disclosures: L. Merino Galan: None. **J.M. Hemenway:** None. **H.L. Jagana:** None. **S. Ortiz Espinosa:** None. **M. Hathaway:** None. **A. Rajendran:** None. **T. Jackson:** None. **N. Reche-Ley:** None. **A. Khanna:** None. **S. Sarkar:** None. **V. Kalia:** None. **S.S. Pattwell:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.042/LBA38

Topic: F.04. Neuroimmunology and Neurovirology

Support: Ohio State University Foods for Health
ASPIRE Medical Research Program

Title: Anthocyanin- and galactooligosaccharide-rich diet increased gut microbiome diversity and increased inflammatory cytokines but failed to protect against LPS-induced sickness

Authors: *F. AREGA, T. BECK, J. JORDAN, A. GENTRY, D. CHANG, M. ANTONIUS, R. BRUNO, Y. VODOVOTZ, K. M. MARTENS, C. VONDER HAAR;
The Ohio State Univ., Columbus, OH

Abstract: Inflammation can result in cognitive impairments and anti-inflammatory interventions are of great interest to mitigate this. Dietary interventions may have multimodal actions, including via the gut-brain axis. In the current study, a diet of blueberries rich in anthocyanins and the prebiotic galactooligosaccharide (GOS) was used to enhance gut microbe diversity and increase levels of antioxidants. Behavioral and physiological outcomes were measured to determine if this diet would mitigate deficits associated with acute administration of lipopolysaccharide (LPS), a pro-inflammatory component of bacterial cell walls. In a behavioral study, rats were fed experimental diet or control for eleven weeks and then injected with LPS (1 mg/kg) or vehicle. The elevated plus maze (EPM), the forced swim test (FST), and the Morris water maze (MWM) were used to measure anxiety-like behavior, depressive-like behavior, and spatial learning ability, respectively. At 15 days post-injection, IBA-1 immunohistochemistry staining of microglia was performed. In an acute study, rats were given the experimental diet or control for six weeks, then injected with LPS or vehicle. Brains were collected 48 hours post-injection to assess for acute LPS and diet effects. IBA-1 immunohistochemistry for microglia was performed and inflammatory markers TNF-α and IL1-β quantified in brain tissue with ELISA. Blueberry/GOS diet increased alpha and beta diversity in the gut microbiome but did not mitigate the effects of LPS on the gut. LPS-induced sickness increased anxiety-like behavior in the EPM but was mitigated by the diet. LPS had no effect on forced swim or MWM. The diet alone significantly improved MWM spatial learning in control rats. LPS injections generated a sickness response and likely inflammation. At an acute timepoint, diet increased TNF-α and IL1-β levels in the hippocampus and prefrontal cortex. Diet nor LPS increased microglia number at both timepoints. Further work is needed to understand discrepant response of blueberry diet on anxiety compared to other behavioral assessments.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.043/LBA39

Topic: F.04. Neuroimmunology and Neurovirology

Support: CAPES
CNPq
FAPEMIG
IBRO

Title: Disruption of immune homeostasis mediates neural and behavioral alterations induced by cocaine

Authors: *M. SILVA[1], R. RIBEIRO[2], T. SILVA DE SOUZA[2], L. MOREIRA[2], N. ROCHA[2], R. BRITO[2], L. MAGALHAES[2], J. SOUZA[3], G. GOMES[2], H. DE BARROS FERNANDES[2], S. TAVARES ARAÚJO SANTOS[2], R. FERNANDES[2], V. R. SANTOS[4], S. OLIVEIRA[2], L. BUENO[2], R. FUJIWARA[2], A. SILVA DE MIRANDA[2], A. C. OLIVEIRA[2];
[1]Univ. Federal De Minas Gerais, Belo Horizonte, Brazil; [2]Federal Univ. of Minas Gerais, Belo Horizonte, Brazil; [3]Federal Univ. of Minas Gerais, BH, Brazil; [4]Federal Univ. of Minas Gerais, Belo Hozionte, Brazil

Abstract: INTRODUCTION: Different data suggest that cocaine binds in the complex MD-2/TLR4, being recognized as an exogenous substance and leading to neuroinflammation. However, the role of microglia activation and TLR4 in cocaine induced behavioral abnormalities is still poorly understood. METHODS: Mice were treated with microglial depletor PLX3397 and subjected to behavioral sensitization induced by cocaine . Thereafter, their brains were removed for analysis of number and morphology of microglia cells, as well as quantification of CX3CL1 and BDNF levels. In addition, mice were treated with the TLR4 receptor biased agonist MPLA or TLR4-/- mice were submitted to behavioral sensitization, and to microglia phenotypic analysis by flow cytometry. All procedures were approved under the protocol CEUA 325/2022. RESULTS: PLX3397 treatment reduced Iba-1+ cells and attenuated behavioral sensitization. In the partial depletion group, the drug also increased activation of remaining microglia cells. Animals treated with PLX3397 + cocaine showed altered CX3CL1 in the striatum, hippocampus and in the PFC, as well as BDNF, in comparison with the animals treated with only cocaine. Besides, CX3CL1 and BDNF levels presented a correlation among the cocaine-induced behavioral sensitization. Moreover, MPLA treatment reduced cocaine-induced hyperlocomotion, while TLR4-/- mice showed an increase in cocaine-induced locomotor activity compared to WT animals. Finally, there are different microglia populations between saline, cocaine and cocaine + MPLA and cocaine + TLR4-/-treated animals, with differences in the expression of CX3CR1, CD62L, CD11b, CD44, CD11c, Single H and P2RY12. In addition, cocaine increased monocyte number and activation (Ly6C+), increased lymphocytes TCD8+ and TCD4+ central memory, but not effector memory, which was prevented by MPLA. Cocaine also decreased the dendritic spine

in the brain, which was also prevented by MPLA CONCLUSION: Considering this data, we suggest that disruption in the immune homeostasis may be involved in the neural alterations that occur in neurobiology of cocaine addiction.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.044/LBA40

Topic: F.04. Neuroimmunology and Neurovirology

Support: NIH AA25964

Title: Binge treatment with ethanol-induced spleen atrophy, modulation of signaling pathways of the spleen and behavioral deficits in the adolescent F344 rats.

Authors: *S. CHANG;
Seton Hall Univ., South Orange, NJ

Abstract: Previously, we observed that binge treatment with ethanol (EtOH) differentially induces spleen atrophy in the F344 adolescent rats. In this study, male and female F344 rats were given 3-day EtOH (4.8 g/kg/d; 52% w/v; i.g.), or water, upon pubertal onset. 24 hrs following the last treatment of EtOH, the animals' locomotor activities (LMA) in the Open Field Apparatus using AnyMaze focusing on locomotor activity, freezing, and thigmotaxis. Following the assessment for LMA, the rats were sacrificed, and spleens were collected and weighed to judge the EtOH-induced spleen atrophy (E-SA) differentially. Differential E-SA was observed in male and female rats with more profound effects on the male rats. Using Correlation analysis and Linear Regression analysis, we also found that E-SA correlating with motor deficits, anxiety, and fear in a sex-dependent manner with males more affected than females. RNA was isolated from the spleen to prepare cDNA for RNA-seq analysis. Fold change of each gene was obtained in the spleen of each rat being studied. Core analysis was conducted on the fold changes of each Differentially Expressed Genes (DEGs, adjusted $p<0.05$) to reveal the signaling pathways involved in E-SA. Correlation between the z-score for each signaling pathway and the behavior measurement were also analyzed. In female, Interferon Gamma Signaling, Multiple Sclerosis Signaling Pathway, Nicotine Degradation II, Acute Phase Response, were moderately correlated with most of the LMA measurements. However, in male, Neutrophil degranulation, were

moderately correlated with most of the LMA measurements. Taken together, at the organ level, correlation between behavior deficit and E-SA is more profound in the spleen of the male rats than that of female animals. With the studies of signaling pathways involved in E-SA, correlation between activities of signaling pathways and behavioral deficit was found to be more profound in the spleen of the female rats than that of male rats given binge treatment with EtOH (partially sponsored by R01 AA25964 to SLChang).

Disclosures: S. Chang: None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

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Program #/Poster #: LBA006.045/LBA41

Topic: F.04. Neuroimmunology and Neurovirology

Support: Rudi Schulte Research Institute
Robert McLaren Fund
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Title: Experimental approaches in the development of novel biologics ablating the choroid plexus: our experience using human iPS/ES cells derived choroid plexus organoids

Authors: *C. RICHETTA[1], J. GOTO[2], F. T. MANGANO[5], J. TCHIEU[3], C. SHULA[4], S. STEPHENS[4], G. SEBRING[4];
[1]Cincinnati Children Med. Ctr., Cincinnati, OH; [2]Pediatric Neurosurg., [3]Developmental Biol., [4]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [5]Cincinnati Children's Med. Ctr., Cincinnati, OH

Abstract: ***Experimental approaches in the development of novel biologics ablating the choroid plexus: our experience using human iPS/ES cells derived choroid plexus organoids****Authors:* C. Richetta[1], J. Tchieu[2], G. Sebring[1], S. Stephens[1], C. Shula[1], J. Goto[1] , F.T. Mangano[1]*Affiliations:* 1.Division of Pediatric Neurosurgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA2.Division of Developmental Biology, Cincinnati Children's Medical Center, Ohio, USA *Disclosures:* none.*Funding:* Rudi Schulte Research Institute, Robert McLaren Fund, NIH NINDS 1R21NS127177
Key words: organoids, choroid plexus, adeno-associated viruses
Abstract: Choroid plexus (ChP) is a system of specialized cells producing cerebrospinal fluid (CSF). Hydrocephalus is a common neurological condition where CSF accumulates in the ventricles. Although surgical CSF diversion effectively controls intracranial pressure, most patients suffer long term neurological sequelae. Additionally, surgery carries risks and significant failure rate. ChP tumors require surgical resection as the first therapeutic line. These

lesions are deep seated and highly vascularized posing substantial challenges especially in children. The ability to target and ablate ChP cells through a minimally invasive approach, offers new tools of care for pediatric conditions related to the ChP. ChP cauterization in humans shows no complications compared to patients treated with shunts. Similarly transgenic mice carrying Diphtheria Toxin Human Receptor experience ablation of ChP after administration of Diphtheria toxin and no neurological adverse events. These findings support that ChP ablation is a safe technique.Adeno-associated viruses (AAVs) are commonly employed in brain gene delivery modifying cells function and even inducing cell death. AAVs serotypes 2/5 demonstrated tropism for ChP cells (X.Chen et al.). We designed an AAV expressing a prodrug able to initiate apoptosis of targeted cells. Additionally, we used an AAV (AAV-CMV-EGFP) to assess specificity and biodistribution.We developed an in vitro model to test our AAVs on human Chp cells. We followed Chp organoids protocol (Pellegrini et al.) starting from H-ESC cultures. To promote the Chp fate, BMP4 and CHIR were added at day 10. Cultures were maintained for >80 days. About 50% of our colony produced balloon-like CSF cysts. IHC highlighted expression of FOXJ1 and TTR confirming ChP differentiation along the cysts walls. Organoids were infected at age +30 days with AAV-CMV-EGFP showing tropism for the cysts walls. These findings suggest that AAVs are a valuable tool for targeting of ChP and future treatment of ChP diseases.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.046/LBA42

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Semaglutide diminishes phenotype development of mice in an activity-based anorexia model

Authors: *S. HALL;
Comparative Med., Yale Univ., New Haven, CT

Abstract: Incretin analogs, such as the GLP-1 agonist, semaglutide, emerged as breakthrough treatments for people with obesity, which predominantly stems from overeating. On the other hand, people with anorexia nervosa, a serious psychiatric condition with the highest mortality rate among mental disorders, purposefully starve themselves and frequently exercise compulsively to decrease body weight. Because starvation is highly stressful, incretin analogs may be sought after by subjects with anorexia nervosa to decrease appetite. It is assumed that such intervention would be detrimental. To interrogate this question, we used a mouse model of activity-based

anorexia. In this paradigm, peri-pubertal mice given semaglutide displayed key differences compared to vehicle controls. Semaglutide reduced wheel running, basal metabolic rate, and respiratory exchange ratio of mice compared to the values of their vehicle controls. In addition, one week after returning to ad libitum feeding without wheel access, mice that received semaglutide showed reduced stereotypic behaviors and anxiety compared to control mice. In summary, while counterintuitive, our data show that semaglutide diminishes many of the negative attributes and consequences of anorexia nervosa in an animal model.

Disclosures: S. Hall: A. Employment/Salary (full or part-time):; Yale University.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.047/LBA43

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

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the Research Service of the Veterans Administration
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Title: Identification of Differentially Expressed Genes in the Nucleus Accumbens of Diet-Induced Obesity Prone Rats with RNA-Seq

Authors: *P. BENSING[1], A. HAWLEY[2], M. BRAVO[3], E. M. FEKETE[5], A. SUNDARESAN[2], P. NATARAJAN[2], S. HEAD[2], J. B. FRIHAUF[6], B. E. LEVIN[7], E. P. ZORRILLA[4];
[1]Mol. Med., [2]Scripps Res., La Jolla, CA; [3]Mol. Med., Scripps Res. Inst., La Jolla, CA; [4]Mol. Med., Scripps Res. Inst., San Diego, CA; [5]Committee on the Neurobio. of Addictive Disorders, The Scripps Res. Inst., La Jolla, CA; [6]UC San Diego, La Jolla, CA; [7]VA Med. Ctr., East Orange, NJ

Abstract: Obesity, which affects ~42% of American adults, is disabling and deadly. Current medications require ongoing use and are only effective in some, with major long-term side effects. It remains key to identify molecular bases of obesity risk to develop new targets. Here,

we aimed to identify obesity risk-related genes by determining transcriptome differences in the nucleus accumbens (NAc) of rats selectively bred for vulnerability (DIO) or resistance (DR) to high-fat (HF) diet-induced obesity. In Experiment 1, male DIO and DR rats (n = 18) were exposed to chronic (~6 months) low-fat or HF diet from 120 days of age until sacrifice. In Experiment 2, male DIO and DR offspring (n = 20) from chow- or Western diet-fed dams were studied in a Comprehensive Laboratory Animal Monitoring System (CLAMS) as adults and fed HF diet for 1 week before sacrifice. Total RNA from RNALater-protected NAc punches was subjected to NEBNext Poly(A) mRNA Ultra II poly(A) library prep and sequenced on a NovaSeq S2 flowcell (paired end, 150 bp reads, ~67M/sample). DESeq2 was used to build a multifactor model (Genotype, Early diet, Adult diet), yielding 1511 (Expt. 1) and 116 (Expt. 2) adjusted p-value transcript "hits" for Genotype. Hits significantly altered in both experiments, technically validated by qPCR, and biologically validated in a 3rd cohort of DIO/DR P23 weanlings (n = 10) show the robust approach and include Dus2, Anxa6, Trim56, Psme1ps1, Srek1ps1, and MGC116121 (C18orf21 homolog). We have prioritized understudied genes that were "hits" in both experiments for further study based on enriched striatal neuron expression in single cell atlases and annotation to obesity or addiction traits in genome-wide human studies. These include Dock3, Ube3d, Cacna2d1, Camkk2, Mme, Plcb1, Sez6, Cntnap1, and Rgs7bp. Early and adult diet influences on NAc expression of these genes also will be presented.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.048/LBA44

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NICHD 5K00HD109205
NIDDK U24DK132746-01
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Iris Cantor UCLA Women's Health
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Title: Modulation of temperature in pregnancy by hypothalamic estrogen signaling in mice

Authors: *L. R. CORTES[1], S. CORREA[2];
[1]Integrative Biol. and Physiol., Univ. of California Los Angeles, Los Angeles, CA; [2]Dept. Of Integrative Biol. and Physiol., UCLA, Los Angeles, CA

Abstract: Pregnant mammals display significant changes in core body temperature (Tc). Circadian fluctuations in Tc are blunted, and there is a dampening of Tc towards the end of pregnancy. Our work aims to pinpoint the neurobiological processes contributing to maternal thermoregulation. In ovariectomized female mice, estrogen administration decreases core temperature. Circulating estradiol levels increase in the end of pregnancy and could underlie a decrease in Tc. We previously found that activation of estrogen receptor alpha (ERa) neurons in the medial preoptic area (MPO) decreases temperature in non-pregnant female mice. Thus, we hypothesize that estrogen sensitive neurons in the MPO coordinate maternal changes in Tc. Estrogens fine-tune biological processes by engaging estrogen signaling. This process involves estrogen receptors binding to estrogen response elements (EREs), where they are able to modify gene expression. We hypothesize that pregnancy is linked to greater estrogen signaling in thermoregulatory MPO neurons. We use a novel reporter (NeuroSeeER) that fluorescently visualizes cells with high levels of estrogen signaling. NeuroSeeER expresses enhanced green fluorescent protein (eGFP) in response to the binding of ERE sites, as well as, FusionRed in cells expressing Cre. We stereotaxically delivered this reporter to the MPO and report more eGFP+ cells (i.e., estrogen signaling) in mice that are in pregnancy day 16 compared to non-pregnant controls. Next, we tested the hypothesis that estrogen signaling in the MPO is required for maternal thermoregulatory adaptations. We ablated ERα in the MPO and monitored core temperature in control and KO mice throughout pregnancy. We report that eliminating ERα expression in the MPO increases Tc and the circadian amplitude of Tc. Thus, ERα KO blunts the changes in core temperature associated with pregnancy. This work expands our understanding of one aspect of physiology that is noticeably altered by pregnancy.

Disclosures: L.R. Cortes: None. **S. Correa:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.049/LBA45

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant U19-NS123717
NIH Fellowship F31NS118949
NIH Grant R01DA050159

Title: Reevaluating BOLD signal interpretation during high arousal brain states

Authors: *P. DORAN[1], P. D. PEREZ[1], S. KURA[1], B. C. RAUSCHER[1], D. BALOG[1], N. X. CHAI[1], K. KILIÇ[1], G. CHABBOTT[1], N. FOMIN-THUNEMANN[1], J. P. STOCKMANN[2], B. FU[2], D. MILLER[2], M. THUNEMANN[1], C. T. FARRAR[2], D. A. BOAS[1], X. YU[2], J.

MANDEVILLE[2], S. SAKADZIC[2], A. DEVOR[1,2];
[1]Boston Univ., Boston, MA; [2]Athinoula A. Martinos Ctr. for Biomed. Imaging, Boston, MA

Abstract: The BOLD fMRI signal increases when the concentration of paramagnetic deoxy-hemoglobin in the blood decreases. When a brain region becomes more active, blood flow to that region not only increases to meet metabolic demands, but it produces an overshoot that results in decreased concentrations of deoxy-hemoglobin in active brain regions. When a mouse becomes aroused, norepinephrine (NE) is released in the cerebral cortex and the pupil dilates. NE is an excitatory neurotransmitter and a vasoconstrictor. Therefore, the BOLD signal may decrease in high arousal states while neuronal activity increases. In this study, we use a multimodal imaging system to investigate the relationship between neuronal activity and the BOLD signal in awake mice. The red fluorescent calcium indicator jRGECO1a is expressed in all neurons to measure neuronal activity. Mice are implanted with curved glass optical windows covering the left hemisphere of the dorsal cerebral cortex. Fluorescent optical probes are imaged using an MRI-compatible fiberscope that utilizes a 5 mm x 5 mm imaging fiber bundle and contains a system of optical components inside the scanner that allows for epi-illumination. Resting-state BOLD fMRI is performed on a 9.4 T system with T2* weighted GE-EPI sequences (0.2 mm in-plane resolution, 0.5 mm slice thickness, TR = 1 sec) and covers the whole brain volume below the optical window. Based on a parallel all-optical study from our lab, we use pupil diameter as a proxy of cortical NE release. During data processing, we perform slice-timing correction, despiking, motion correction, renormalization, alignment and resampling, finally arriving at aligned optical and BOLD data with 10 Hz optical and 1 Hz BOLD time resolution over an approximate 5 mm x 5 mm field of view on the cortical surface. We find that neuronal calcium has a positive correlation with pupil size and the BOLD signal has a negative correlation with pupil size. When pupil size is large, the BOLD signal goes down while neuronal activity increases. Therefore, when the mouse is aroused, changes in the BOLD signal do not reflect changes in neuronal activity as well as when the mouse is at rest. These results have profound implications for the interpretation of fMRI data. Pupil measurements may be valuable in clinical fMRI studies to enable more accurate estimation of neuronal activity.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.050/LBA46

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: A novel mouse model for in vivo evaluation of anti-human CD98HC antibody penetration across blood-brain barrier

Authors: R. LV[1], Z. SHEN[1], C. LI[1], **R. CHHABRA**[2], *Y. TIAN[2], X. ZHOU[1];
[1]Biocytogen Pharmaceuticals (Beijing) Co., Ltd., Beijing, China; [2]Biocytogen Boston Corp., Waltham, MA

Abstract: **Introduction:** The drug delivery to the central nervous system (CNS) remains a major hurdle in treating neurological disorders, largely due to the restrictive permeability of blood-brain barrier (BBB) to large molecules, such as antibodies. While many strategies proposed for brain delivery of antibodies, the leading approach is to utilize the receptor-mediated transcytosis by designing molecules that bind the membrane transport proteins at the luminal surface of the endothelial cells of the BBB. **Objectives:** CD98 heavy chain (CD98HC), also known as 4F2, heterodimerizes with large amino acid transporters (LATs), it is essential for transporting amino acids and other molecules into cells. CD98HC is highly expressed and presented on both luminal and abluminal surfaces of brain vascular endothelial cells in both mice and human. It has been identified as a promising drug delivery target of BBB through proteomic profiling. However, previously developed human CD98HC targeting antibodies do not interact with mouse or non-human primate CD98HC. Therefore, it is urgent to develop scientifically appropriate animal models for assessing the efficacy and safety of anti-human CD98HC antibodies, particularly regarding their ability to penetrate the blood-brain barrier *in vivo*. **Results:** We successfully developed a mouse model expresses humanized hCD98HC proteins, named B-hCD98HC mice. Humanized CD98HC expression was detected on T cells, B cells, and brain vascular endothelial cells of B-hCD98HC mice. The proportions of various immune cells in the spleen, blood, and lymph nodes of B-hCD98HC mice were similar to those of wild-type C57BL/6 mice. The blood biochemistry and blood routine indicators of B-hCD98HC mice were similar to those of wild-type C57BL/6 mice. These results indicate that humanization of CD98HC does not affect the differentiation and development of various immune cells and blood cells. **Conclusions:** Humanized CD98HC protein expressing mouse model, B-hCD98HC, is a novel and unique *in vivo* model for evaluating the ability and safety of anti-human CD98HC antibodies to penetrate the BBB.

Disclosures: R. Lv: None. **Z. Shen:** None. **C. Li:** None. **R. Chhabra:** None. **Y. Tian:** None. **X. Zhou:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.051/LBA47

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: First trimester human umbilical cord perivascular cells modulate lipopolysaccharide-induced blood brain barrier permeability in-vivo

Authors: *F. SIDDIQUI[1], S. MUKHERJEE[1], L. LOPEZ[1], A. GAUTHIER-FISHER[1], C. LIBRACH[2,3,4,5];
[1]Create Res. Program, Toronto, ON, Canada; [2]Create Fertility Ctr., Toronto, ON, Canada; [3]Dept. of Obstetrics and Gynecology, [4]Inst. of Med. Sci., [5]Dept. of Physiol., Univ. of Toronto, Toronto, ON, Canada

Abstract: Introduction: Compromised blood-brain barrier (BBB) permeability is a hallmark of neuroinflammation. However, a robust and safe therapeutic approach to restore perturbed barrier permeability is still lacking. In this study, the immunomodulatory effect of first trimester human umbilical cord perivascular cells (FTM-HUCPVC), a young and potent source of mesenchymal stromal cells (MSC), was tested in a lipopolysaccharide (LPS)-induced in vivo model of BBB breakdown. We previously reported that immunomodulation by peripherally infused MSC was able to exert a neuroprotective effect in an LPS-based model of neuroinflammation and depression. Thus, we hypothesize that HUCPVC may render neuroprotection by regulating BBB signaling.**Methods:** 3 groups of C57BL6 mice, Control, LPS and LPS+HUCPVC were included (*n*=3-4). Blood and brains were collected at 5h and 24h after the injections of LPS (*i.p*; 0.83mg/kg) and HUCPVC (*i.v*; $1x10^6$ cells). A mix of fluorescently tagged dextran dyes (4KD, 70KD) was also injected 10 min before anesthetizing the animals. BBB at both the timepoints was assessed by measuring the transcript levels of tight junctions (TJ), ZO1, OCLN1 and CLDN5 in the isolated brain blood vessels. Severity of BBB damage at these timepoints was studied by quantifying the extravasation of the dyes excited at different wavelengths. This was done by confocal imaging of the brain cryosections and by a permeability assay conducted by obtaining the fluorescence read-out from plasma and brain homogenate samples. **Results:** HUCPVC significantly rescued the LPS-induced downregulation of TJ transcripts in the LPS treatment groups of 5h (*Cldn5*: 2.8 folds, *Ocln1*: 5.3 folds) and 24h (*Ocln1:* 2.9 folds) timepoints. A significantly higher content of 4KD dextran dye was recorded in the brain homogenate of both LPS 5h (2.5-fold) and 24h (10.3-fold) groups. Whereas the 70KD dye was found to be significantly higher in the LPS 24h group (8.9-fold) compared to the LPS 5h treatment group (1.7-fold). However, HUCPVC was found to restore the LPS-induced increased permeability for 4KD (5h: 2.3-fold, 24h: 10.2-fold) as well as 70KD (24h: 10.3-fold) dextran dyes. Confocal imaging of the brain tissues revealed a more prominent extravasation of 70KD dye at 24h timepoint (6.3-fold), which was seen significantly curbed by HUCPVC (4.6-fold). **Conclusion:** The immunomodulatory properties of HUCPVC appear to intervene with LPS-induced perturbed BBB signaling, thus normalizing the BBB permeability. Notably, the infusion of MSC was shown to be beneficial in diffusing the enhanced BBB damage at 24h, a critical time point at which many pathways to neuroinflammation and depression are initiated.

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Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.052/LBA48

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: CIHR-PJT190207

Title: Hyperpolarized ^{13}C-MRI topography corresponds to specific neuronal and glial cell populations in the healthy human brain

Authors: *B. UTHAYAKUMAR[1,3], N. I. C. CAPPELLETTO[1,3], N. D. BRAGAGNOLO[3], J. GILLIS[2], A. CHEN[4], H. SOLIMAN[5], C. CUNNINGHAM[3,1];
[1]Med. Biophysics, [2]Physiol., Univ. of Toronto, Toronto, ON, Canada; [3]Physical Sci., Sunnybrook Res. Inst., Toronto, ON, Canada; [4]GE Healthcare, Taipei, Taiwan; [5]Dept. of Radiation Oncology, Sunnybrook Odette Cancer Ctr., Toronto, ON, Canada

Abstract: Hyperpolarized-^{13}C magnetic resonance imaging (HP-^{13}C MRI) is an imaging technique that enables imaging of ^{13}C-pyruvate and downstream metabolites ^{13}C-lactate and ^{13}C-bicarbonate. Prior work has shown a ^{13}C-metabolite topography governed by factors still under investigation[1]. In this study, HP-^{13}C MRI images were related to the Allen human brain atlas (AHBA) microarray dataset to investigate the correlation between cell populations and regional patterns of ^{13}C-metabolite signal.
Forty-three cognitively normal volunteers (ages 21-77, mean 36, median 28) were scanned using HP-13C MRI. ^{13}C-pyruvate preparation and ^{13}C-metabolic imaging was done using previously described workflows[2]. Anatomical T1 and ^{13}C-metabolite images were registered to the MNI152 atlas and parcellated using the Yeo17 split atlas. Ratios of ^{13}C-lactate/^{13}C-bicarbonate signal (L_B), ^{13}C-lactate/^{13}C-pyruvate signal (L_P) and ^{13}C-bicarbonate/^{13}C-pyruvate signal (B_P) were averaged across all volunteers to create brain maps. Microarray data obtained from the AHBA database (n = 6, ages 24-57) was pre-processed using the standardized Abagen python package (available from 10.5281/zenodo.3451463).
Spearman correlations were calculated between transcripts and 13C-metabolite ratio maps before being ranked for gene set enrichment analysis (GSEA) using the Lake brain celltype genesets with the GSEAPY package. Spatial autocorrelation was accounted for using the brainSMASH package. Enrichment score p-values were corrected for multiple comparisons by controlling the false discovery rate at 0.1, and p-values surviving the FDR cutoff are listed.
Numerous excitatory and inhibitory neurons had significant positive enrichment for the B_P ratio. This can be interpreted as positive correlations between the B_P ratio and the majority of genes representative of the corresponding neuron subtypes. The celltypes surviving the FDR cutoff include the Ex5a ($p = 0.0008$), Ex5b ($p = 0.001$), Ex4 ($p = 0.002$), Ex2 ($p = 0.003$), Ex3b ($p = 0.006$), Ex6a ($p = 0.008$), Ex3c ($p = 0.01$), Ex6b ($p = 0.01$), Ex1 ($p = 0.02$), and Ex3a ($p = 0.04$)

excitatory and In1c ($p = 0.03$), In8 ($p = 0.04$), In4b ($p = 0.04$), and In1b ($p = 0.04$) inhibitory neurons. For the L_P, oligodendrocytes were positively enriched ($p = 0.003$). These results are supported by the literature: regions with higher BP ratios tend to also be regions with higher neuron and synapse densities[3]. In conclusion, B_P signal in HP-13C MRI is related to regional neuron density.

References
1. Casey Y Lee et al. Neuroimage, 204:116202, 2020
2. Benjamin J Geraghty et al. Magnetic Resonance in Medicine, 79(2):643-653, 2018
3. Blue B Lake et al. Science, 352(6293):1586-1590, 2016

Disclosures: B. Uthayakumar: None. **N.I.C. Cappelletto:** None. **N.D. Bragagnolo:** None. **J. Gillis:** None. **A. Chen:** A. Employment/Salary (full or part-time):; GE Healthcare. **H. Soliman:** None. **C. Cunningham:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.053/LBA49

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: RF1NS124778
R01NS122904

Title: Can 23Na MRI be used for functional mapping with a 14 Tesla scanner?

Authors: *X. YU[1], Y. JIANG[2], G. YU[2], X. LIU[2], X. A. ZHOU[2];
[1]Massachusetts Gen. Hosp., Malden, MA; [2]Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Conventional functional MRI (fMRI) methods map brain function based on the hemodynamic responses of vessels coupled to neuronal activity. Their indirect coupling scheme has a fundamental limit on its spatial specificity and temporal characteristics for *in vivo* neuronal activity measurement. The direct measurement of neuronal activity through NMR signal poses as a challenge of neuroimaging. In particular, to identify the “true fMRI” signal directly linked to the neuronal activity—e.g., the action potential (AP) or local field potential (LFP) mediated by transmembrane ion movement—Sodium (^{23}Na) NMR signal measurement offers a promising mapping scheme in comparison with proton-based hemodynamic fMRI. Here, we implemented the reshuffled K-t space FLASH method originally used for single-vessel fMRI mapping to acquire 23Na fMRI images. Each k-space line is first filled in different k-spaces as the function of time (TR=10ms), during a block design (1 electrical pulse per 300ms). The 300ms block will be repeated for the number of 2nd phase encoding multiplied by the number of the 1st phase encoding (Fig 1). For the 3D dataset with 400x400x1500μm resolution, the total scanning time

for a single trial of (30 data points) is 18 seconds. This ultra-fast acquisition scheme enables massive averaging to produce sufficient SNR for 23Na fMRI. By performing alternating electrical stimulation of the forepaw and vibrissal pad of anesthetized rats, we reported negatived 23Na response (NAR) signals in the tens of millisecond scale per electrical pulse in contrast to the positive BOLD signals detected from the forepaw somatosensory cortex (FP-S1) versus the barrel cortex (BC). Although the underlying mechanism of the NAR fMRI signal remains to be investigated, this work demonstrates the feasibility to detect ultrafast 23Na-related signal changes coupled to neuronal activation in rat brains.

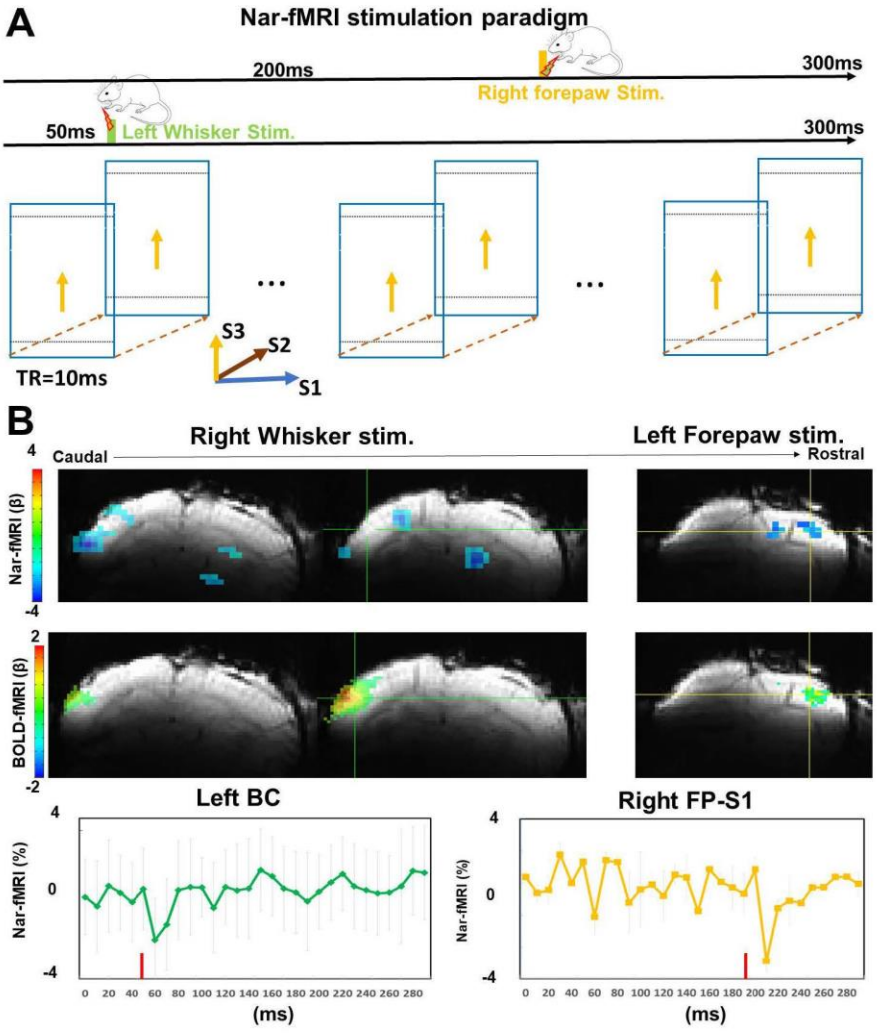

Fig 1. A. NAR-fMRI stimulation paradigm design. **B**. (^{23}Na) Nar-fMRI and (^{1}H) BOLD fMRI of young rats anesthetized with isoflurane. Nar-fMRI maps present negative signals surrounding activated brain regions ($p<-0.05$) and BOLD fMRI maps present activated BC and FP-S1 ($p<0.01$) Lower panel shows the time courses of the Nar-fMRI activated voxels.

Disclosures: **X. Yu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); co-funder of MRIBOT LLC. **Y. Jiang:** None. **G. Yu:** None. **X. Liu:** None. **X.A. Zhou:** None.
Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.054/LBA50

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

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BrainsCAN CFREF
Brain Canada Platform Support Grant

Title: Enhanced fMRI using stimulus-modulated approach to steady-state

Authors: ***R. MATHEW**[1,4], A. EED[2,4], M. KLASSEN[4], S. EVERLING[3,4], R. MENON[2,4]; [1]Neurosci., [2]Med. Biophysics, [3]Physiol., Western Univ., London, ON, Canada; [4]Ctr. for functional and metabolic mapping (CFMM), London, ON, Canada

Abstract: fMRI studies discard the initial volumes acquired during the approach of the magnetization to its steady-state value. Here, we leverage the higher temporal signal-to-noise ratio (tSNR) of these initial volumes to substantially increase the sensitivity of event-related fMRI experiments. We introduce Acquisition Free Periods (AFPs) that allow for the full recovery of the magnetization, followed by rapidly sampled equal-length task or baseline acquisition blocks (AB) of fMRI volumes. When the peak of the hemodynamic response function occurs during the magnetization approach to steady-state within the task AB, we observe an increase in the tSNR by up to 60% compared to the conventional steady-state fMRI approach. We demonstrate the improved sensitivity using head-fixed awake common marmosets (Callithrix jacchus) as subject animals for visual and auditory experiments with a 9.4 Tesla MRI scanner. General Linear Model (GLM) analysis revealed a higher number of active voxels with higher z-values compared to the traditional steady-state sequence. The gain in tSNR is validated using theoretical modeling utilizing solutions from the Bloch equations. In addition to increasing fMRI sensitivity, the AFP allows flexibility for the silent presentation of auditory stimuli or the uncontaminated recording of electrophysiology, improved fMRI-to-anatomic registration, as well as acquiring fMRI data to asynchronous behaviours in the same manner as spike-triggered averaging.

Disclosures: **R. Mathew:** None. **A. Eed:** None. **M. Klassen:** None. **S. Everling:** None. **R. Menon:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.055/LBA51

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Multi-receptor whole-cortex configurations underlying states of wakefulness

Authors: *D. DAVILA[1], M. N. BALIKI[2], A. D. VIGOTSKY[1], L. HUANG[1], A. V. APKARIAN[3];
[2]PM&R, [1]Northwestern Univ., Chicago, IL; [3]Neurosci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Considering the prevalence of general anesthesia in modern medicine, it is remarkable how little is known about its neurobiology. Here, we introduce a novel approach that links spontaneous fMRI activity to the distribution of 19 receptors (Hansen et al. 2023) in the neocortex, and we use the approach to examine reconfigurations of this multidimensional state with changes in wakefulness. We analyzed a dataset of 17 healthy subjects (Kandeepan et al. 2020) where resting-state fMRI was collected for four states of propofol-regulated wakefulness: awake, no propofol; light sedation; deep sedation; and recovery. Network properties of the cortex were examined for functional and receptor-related activity. After standard fMRI preprocessing, differences in brain activity were derived voxel-wise and compared between awake and the other conscious states using paired *t*-tests. We modeled propofol-related changes in the amplitude of low-frequency fluctuations (ALFF) using linear multiple regression with the 19-receptor cortical maps. These models could explain more than 50% of the variance of the change in cortical brain activity across all three sedation levels relative to awake. For light and deep sedation, change in ALFF was mainly explained by 5-HT_{1A}, 5-HT_{2A}, and $mGluR_5$ receptor-related activity (p<0.01), while the recovery state reflected μ-opioid and NMDA receptor-related activity (p<0.01). The appearance of statistically significant explanatory receptors in some contrasts but not others indicates wakefulness-dependent molecular effects. Further network analysis using receptor weighted cortical activity identified how the interaction of 12 receptor pairs tracked levels of wakefulness (p<0.05, FDR corrected). In contrast, the anatomically defined cortical resting state network remained mostly constant across all four conscious states. Our method of mapping multi-receptor distribution to ongoing brain activity seems to reveal novel cortical mechanisms at play during changes in wakefulness state. Engagement of multiple receptors and interactions between receptors characterized varying levels of wakefulness. Our findings may constitute molecular targets to better control states of wakefulness. These results are exploratory and will require future validation.

Disclosures: D. Davila: None. **M.N. Baliki:** None. **A.D. Vigotsky:** None. **L. Huang:** None. **A.V. Apkarian:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.056/LBA52

Topic: F.06. Autonomic Regulation

Support: NIHHBLI Grant 19134-47

Title: Testosterone metabolite, 6beta-hydroxytestosterone generated by cytochrome P450 1B1 promotes angiotensin II-induced hypertension and neuroinflammation via 12/15-lipoxygenase activation in the paraventricular nucleus

Authors: *S. R. DUTTA[1], P. SINGH[2], C. SONG[3], J. SHIN[3], K. U. MALIK[3];
[1]Pharmacol., Univ. of Tennessee Hlth. Sci. Ctr. Neurosci. Inst., Memphis, TN; [2]Pharmacology, Addiction Sci. and Toxicology, Univ. of Tennessee Hlth. Sci. center, Memphis, TN; [3]Pharmacology, Addiction Sciences, and Toxicology, Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: We showed previously that testosterone (TTS) via its cytochrome P450 1B1 (CYP1B1)-generated metabolite 6β-hydroxytestosterone (6β-OHT) in the paraventricular nuclei (PVN) of the hypothalamus promotes angiotensin (Ang) II-induced hypertension (HTN) in male mice. However, the underlying mechanism of 6β-OHT in the development of HTN and neuroinflammation is unknown. Ang II is known to increase the production of arachidonic acid-12/15-lipoxygenase (LOX)-generated metabolite 12(S)-hydroxyeicosatetraenoic acid in male mice. LOX is present in the brain in neural tissue, endothelial cells, microglia, and astrocytes. Therefore, this study was conducted to determine the contribution of central LOX and its relationship to CYP1B1-generated 6β-OHT in Ang II-induced HTN in male mice. Ang II (700 ng/kg/min, subcutaneous, osmotic pump, two weeks) failed to increase systolic blood pressure (SBP, mmHg) measured by tail-cuff in 6β-OHT (15 µg/g by intraperitoneal injection every third day) treated orchidectomized (ORX) LOX knockout (LOXKO) but not wildtype (WT) male mice (Day 0 vs Day 12: 111±5 vs 116±1 and 113±5 vs 176±6, respectively, $P<0.05$, n=4/group). LOX knockdown in PVN (200 nL, bilaterally) by transduction with adenovirus (Ad)-LOX-short hairpin (sh)RNA (7.04x1011 pfu/mL) but not its control Ad-scrambled (Scr)-shRNA (6.4x1011 pfu/mL) minimized a) Ang II-induced increase in SBP in WT mice (Day 12: 192±9 vs 135±2, $P<0.05$, n=4/group); and b) the effect of 6β-OHT injected intracerebroventricularly (1.5 µg/2 µL per alternate day) to restore Ang II-induced increase in mean arterial pressure (mmHg) measured by radiotelemetry in CYP1B1KO mice lacking endogenous 6β-OHT (Day 12: 163±4 vs 114±1, $P<0.05$, n=4/group). Moreover, Ang II-induced increase in the number of GFAP-positive cells, a marker for astrocytes in PVN, was also reduced by transduction with Ad-LOX-shRNA in intact WT male mice (41±2 vs 17±1 per high power field, $P<0.05$, n=3/group). These results suggest that TTS, via its CYP1B1-derived metabolite 6β-OHT, promotes the development of Ang II-induced HTN and neuroinflammation in male mice via activation of LOX in the brain. Thus,

CYP1B1/LOX inhibitors could be useful for treating HTN in young males with heightened renin-Ang system activity.

Disclosures: S.R. Dutta: None. **P. Singh:** None. **C. Song:** None. **J. Shin:** None. **K.U. Malik:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.057/LBA53

Topic: F.06. Autonomic Regulation

Support: CCOM Research Fellowships to KK and HN
MWU Intramural funds to PFM

Title: Central Projections of Nerves innervating the Nasal Passages are Important for Activation of Trigeminal Neurons during Repetitive Diving in Rats

Authors: K. KERNOSEK[1], H. NAMBURI[1], K. DINOVO[2], ***P. MCCULLOCH**[2];
[1]CCOM, [2]Physiol., Midwestern Univ., Downers Grove, IL

Abstract: The diving response is an autonomic reflex characterized by apnea, bradycardia and increased peripheral vascular resistance initiated when animals submerge underwater. To initiate this response, afferent stimulation of the nose and nasal mucosa produces activation of second-order neurons located within the brainstem, specifically the trigeminal medullary dorsal horn (MDH). We investigated whether the central projections from the nose, specifically the anterior ethmoidal nerve (AEN), can provide the anatomic connection that activates MDH neurons during diving. Male Sprague-Dawley rats were trained to repetitively dive through an underwater maze. In these animals the anterograde tracer wheatgerm agglutinin (WGA) was injected into either the nasal passages or AEN to identify the central terminal projections from the nasal passages. These rats then repetitively dived underwater to activate MDH neurons to produce the Fos protein. Other trained rats were used as non-diving controls. Brains from all animals were harvested, and 50 μm brainstem tissue sections were preserved. WGA immunochemistry confirmed nasal afferents terminate primarily ventrally within the superficial laminae of the MDH between the pyramidal decussation caudally and the area postrema rostrally. Within this WGA area of termination, immunohistochemistry further identified MDH neurons that express Fos and thus were activated by repetitive diving. In rats receiving WGA injection into the nasal passages (N=7), 32.34 ± 10.47 MDH neurons/hemisection (mean ± SE) were both Fos and WGA positive in repetitively diving animals (N=3), compared with 4.56 ± 2.09 MDH neurons/hemisection in non-diving control animals (N=4). In rats receiving WGA injection into the AEN (N=12), 30.27 ± 5.14 MDH neurons/hemisection were both Fos and WGA positive in

repetitively diving animals (N=7), compared with 13.92 ± 3.55 MDH neurons/hemisection in non-diving control animals (N=5). Results indicate that repetitively diving rats express significantly more Fos positive MDH neurons within the superficial MDH region that receives nasal afferent terminations compared with non-diving control rats. Additionally, the AEN constitutes the primary innervation of the nasal passages important for activation of MDH neurons during repetitive diving. However, results also suggest that a second nasal nerve besides the AEN provides some innervation of the nasal passages that help activate MDH neurons during repetitive diving. We conclude that central projections from the nasal passages are important for activating MDH neurons during repetitive diving in rats.

Disclosures: K. Kernosek: None. **H. Namburi:** None. **K. DiNovo:** None. **P. McCulloch:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.058/LBA54

Topic: F.07. Biological Rhythms and Sleep

Support: FRM - amorçage d'équipe
ED414 - Bourse doctorale

Title: The importance of the medial prefrontal cortex circadian molecular clock in the depressive phenotype and its modulation by ketamine

Authors: *D. H. SARRAZIN[1,2], W. GARDNER[1,2], T. SERCHOV[1,2,3];
[1]CNRS, Strasbourg, France; [2]Inst. des Neurosciences Cellulaires et Intégratives (INCI), Strasbourg, France; [3]Dept. of Psychiatry and Psychotherapy, Freiburg, Germany

Abstract: Depression is associated with dysregulated circadian rhythms, but the role of intrinsic clocks in mood-controlling brain regions remains poorly understood. We found increased oscillation of clock negative regulatory loop, as well as a phase shift of *Bmal1* expression in the medial prefrontal cortex (mPFC) of a mouse model of depression (depression-like behavior and anhedonia induced by daily 10 min swim sessions for 5 consecutive days). Acute intraperitoneal injection of low-dose ketamine (3 mg/kg) normalizes the intrinsic clock by decreasing expression of negative feedback loop genes, and increases expression of positive elements. Selective disruption of mPFC clockwork with viral *Bmal1*KO in CaMK2a excitatory neurons blocks the development of depressive-like phenotype in our model of depression. Moreover, following a ketamine injection in these CaMK2a-*Bmal1*KO mice, we no longer observe the normalizing effect on the clock seen in WT mice, nor the improvement in the depressive-like phenotype. BMAL1 is involved in the regulation of the synaptic plasticity protein Homer1a, which is

implicated in the antidepressant mechanisms. While mRNA expression of Homer1a is reduced in the mPFC of depressed-like mice, ketamine restores its expression along with positive clock elements such as Bmal1. However, in the CaMK2a-*Bmal1*KO mice, mRNA levels of Homer1a remain unchanged in mPFC following a Ketamine injection. Taking together, our data suggest the importance of the circadian clock in excitatory neurons of the mPFC, both for the development of a depressive-like phenotype and for the effects of ketamine on mood.

Disclosures: D.H. Sarrazin: None. **W. Gardner:** None. **T. Serchov:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.059/LBA55

Topic: F.07. Biological Rhythms and Sleep

Support: Howard Hughes Medical Institute

Title: Four SpsP neurons are an integrating sleep regulation hub in Drosophila

Authors: *X. DAI, J. LE, D. MA, M. ROSBASH;
Howard Hughes Med. Institute, Brandeis Univ., Waltham, MA

Abstract: Sleep is an essential and conserved behavior, yet the cellular mechanisms underlying sleep regulation remain largely unknown. To address the neural mechanisms of sleep drive, here we carry out whole brain calcium-modulated photoactivatable ratiometric integrator (CaMPARI) imaging of Drosophila and show that the activity of the neuropil protocerebral bridge (PB), a part of the central complex, correlates with sleep drive. Through a neural activation screen followed by anatomical and functional connectivity assays, we further narrow down the key player of sleep regulation in the PB to a three layer circuit composed of 4 SpsP neurons and their upstream and downstream synaptic partners: the 4 SpsP neurons act as an integrating hub by responding to ellipsoid body (EB) signals from ~ 40 EPG neurons, and by sending signals back to the EB through ~20 PEcG neurons. Moreover, sleep deprivation enriches the presynapse abundance of SpsP neurons and strengthens the connections of the EPG-SpsP-PEcG circuit, indicating plasticity gating in the circuit in response to sleep drive change. As the SpsP neurons also receive input from the sensorimotor brain region and given their known role in navigation regulation, these neurons probably mediate the negative feedback between sleep and navigation. The data taken together indicate that the four SpsP neurons and their sleep regulatory circuit play an important and dynamic role in sleep regulation.

Disclosures: X. Dai: None. **J. Le:** None. **D. Ma:** None. **M. Rosbash:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.060/LBA56

Topic: F.07. Biological Rhythms and Sleep

Title: Optimizing the temperature of the bed microenvironment to enhance sleep quality

Authors: *G. GARCIA MOLINA[1,3], M. RAO[1], V. CHELLAMUTHU[1], L. MCGHEE[2], T. WINGER[2,4], N. MAKARAM[1], P. CHERNEGA[5], Y. SHCHERBAKOV[6], E. VENEROS[7], R. MILLS[2], M. ALOIA[2,8], K. J. REID[9], E. J. VAN SOMEREN[11], P. C. ZEE[10];
[1]Sleep Number, San Jose, CA; [2]Sleep Number, Minneapolis, MN; [3]Psychiatry, Univ. of Wisconsin-Madison, Madison, WI; [4]Computer Sci. and Engin., Univ. of Minnesota, Minneapolis, MN; [5]GlobalLogic, Kyiv, Ukraine; [6]GlobalLogic, Tarragona, Spain; [7]Nanami, La Paz, Bolivia, Plurinational State of; [8]Dept. of Med., Natl. Jewish Hlth., Denver, CO; [9]Dept. of Neurol., [10]Neurol., Northwestern Univ., Chicago, IL; [11]Netherlands Inst. For Neurosci., Amsterdam, Netherlands

Abstract: Falling asleep is associated with core body temperature (CBT) decrease which persists as sleep progresses. Conversely, the transition from sleep to wakefulness is associated with CBT increase. Heat exchange between the core body and the sleep microenvironment is mediated by cutaneous blood flow which positively correlates with skin temperature. Leveraging the ability of the Sleep Number smart bed to dynamically regulate the temperature of the in-bed microenvironment, we evaluated the effect of 10 temperature programs on sleep. A program consists of a sequence of four temperature settings each applied to four consecutive 2-hour segments in a sleep session. Possible settings included cooling at high, medium and low intensity (HC, MC, and LC respectively), off (OF), and warming at low and medium intensity (LW and MW respectively). Sixteen participants (8M/8F; 44.5 [SD: 6.7] years) recruited among smart bed owners, enrolled in a study consisting of 14 nights within their homes. For each night, ballistocardiography-based objective sleep estimates from the smart bed were collected. The sequence of programs was the same for all participants and included 4 nights without manipulation (all segments OF). A validated algorithm (Sensors 2022, 22(7):2605) to detect sleep/wake, breathing cycles, and heart beats estimated sleep duration, restful sleep percentage, sleep quality, mean sleep heart rate, time domain heart rate variability, and breathing rate. The sleep quality score (1-100) is a metric that considers sleep duration, level of movement during sleep, bed exit count, resting heart rate, and breathing rate. Linear mixed models were used to estimate the effects of temperature settings of each segment on each of the outcome metrics. The temperature settings were numerically encoded as follows HC=-3, MC=-2, LC=-1, OF=0, LW=1, and MW=2. As compared to all night OF, better sleep quality occurred during nights with warmer first segments ($\beta1$=+5.5; p=0.02) and cooler second segments ($\beta2$=-5.0; p=0.003). Likewise, a higher percentage of restful sleep occurred during nights with warmer first segments ($\beta1$=+1.64; p=0.03) and cooler second segments ($\beta2$=-1.47; p=0.007). While uncorrected for

multiple comparisons, the integrated results at present suggest that a nocturnal microenvironment temperature profile favorable for sleep quality may consist of initial warming which may help with falling asleep and subsequent cooling which may help with sleep maintenance. The validation of these results on a larger sample size is ongoing which may also help identify significantly favorable temperature settings for the third and fourth segments.

Disclosures: G. Garcia Molina: A. Employment/Salary (full or part-time):; Sleep Number Corporation. **M. Rao:** A. Employment/Salary (full or part-time):; Sleep Number. **V. Chellamuthu:** A. Employment/Salary (full or part-time):; Sleep Number. **L. Mcghee:** A. Employment/Salary (full or part-time):; Sleep Number. **T. Winger:** A. Employment/Salary (full or part-time):; Sleep Number. **N. Makaram:** A. Employment/Salary (full or part-time):; Sleep Number. **P. Chernega:** A. Employment/Salary (full or part-time):; Sleep Number. **Y. Shcherbakov:** A. Employment/Salary (full or part-time):; Sleep Number. **E. Veneros:** A. Employment/Salary (full or part-time):; Sleep Number. **R. Mills:** A. Employment/Salary (full or part-time):; Sleep Number. **M. Aloia:** A. Employment/Salary (full or part-time):; Sleep Number Corporation. **K.J. Reid:** None. **E.J. Van Someren:** None. **P.C. Zee:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.061/LBA57

Topic: F.07. Biological Rhythms and Sleep

Title: Chronic sleep restriction enhances cortical structural plasticity in adult rats

Authors: *F. GARCÍA-GARCÍA[1], F. BRAVO[2], M. E. ACOSTA[2];
[2]Inst. de Ciencias de la Salud, [1]Univ. Veracruzana, Xalapa, Mexico

Abstract: For a long time, sleep has been considered to have a restorative function for the brain and the organism. Recently, our group has shown that chronic sleep restriction (CSR) for 7 days/4 hours induces a significant increase in delta FosB expression in the rat's prefrontal cortex (PFC). Delta FosB is a protein that regulates gene expression of proteins related to the neuronal plasticity process. Therefore, the objective of the present study was to determine if CSR induces changes in the dendritic length, branching of the dendritic tree, and dendritic spine morphology of the pyramidal neurons from the PFC. For this purpose, adult male Wistar rats were divided into two experimental groups: control and CSR for 7 days/4 h daily using the gentle handling method. At the end of the experiment, the rats were euthanized, and brains were dissected and processed by Golgi-Cox staining. The structural plasticity was determined using the Sholl analysis. The results showed that CSR increases the dendritic length, the dendritic tree's branching, and the mushroom spine density in neurons of the PFC. In conclusion, CSR could have a restorative role in some neurodegenerative diseases

Disclosures: F. García-García: None. **F. Bravo:** None. **M.E. Acosta:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.062/LBA58

Topic: F.07. Biological Rhythms and Sleep

Title: The role of sleep stages in emotional memory consolidation: distinct functions of REM and slow-wave sleep

Authors: *F. MORADI YAZDI[1], M. MOEINI[2];
[1]Modiran Pishro Res. Co., Tehran, Iran, Islamic Republic of; [2]Modiran Phishro Moaser Res. Co., Tehran, Iran, Islamic Republic of

Abstract: Sleep plays a crucial role in the consolidation of memories, particularly those with emotional significance. This study investigates the distinct functions of REM sleep and slow-wave sleep (SWS) in emotional memory consolidation. Utilizing polysomnography, we assessed memory retention for emotionally charged and neutral stimuli in participants after a full night's sleep. Our findings reveal that REM sleep enhances the consolidation of positive emotional memories, likely due to increased amygdala and prefrontal cortex activity. In contrast, SWS predominantly supports the consolidation of negative memories, facilitated by the hippocampus's activity and associated cortisol release. These results underscore the importance of sleep's temporal dynamics in emotional regulation, suggesting potential therapeutic applications for sleep modulation in treating disorders such as PTSD and depression. This study contributes to a deeper understanding of how specific sleep stages influence emotional memory processing, offering insights into targeted interventions for improving emotional health.

Disclosures: F. Moradi Yazdi: None. **M. Moeini:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.063/LBA59

Topic: F.07. Biological Rhythms and Sleep

Title: Dynamics of sleep and feeding homeostasis in Drosophila glia and neurons

Authors: *A. FLORES VALLE, J. D. SEELIG;
Max Plank Inst. for Neurobio. of Behavior, Bonn, Germany

Abstract: Sleep across species is controlled through a homeostatic process which measures both, the time spent awake as well as the time spent sleeping. Sleep control circuits in the fly have been linked to neurons in a central brain area important for navigation and memory. Identifying cellular correlates of sleep homeostasis in behaving fruit flies has however proven difficult. We have developed a number of methods for characterizing sleep behavior at high resolution and combined these methods with two-photon calcium imaging and cellular resolution optogenetics in the brain of flies navigating in virtual reality over multiple days. Using these techniques, we describe the dynamics of different populations of neurons and glia during sleep and feeding behavior, and identify molecular correlates of sleep related to metabolism. Together, these experiments describe the cellular dynamics and control of identified homeostatic sleep and hunger circuits for the first time in behaving flies.

Disclosures: A. Flores Valle: None. **J.D. Seelig:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.064/LBA60

Topic: F.07. Biological Rhythms and Sleep

Support: Weill Neurohub Fellowship

Title: Neural circuit mechanisms of sickness-induced sleep

Authors: *D. DARMOHRAY[1], Y. YAO[2], J. SIMA[3], Y. DAN[4];
[1]UC Berkeley/HHMI, berkeley, CA; [2]UC BERKELEY, Berkeley, CA; [3]MCB, Univ. of California, Berkeley, Berkeley, CA; [4]Mol. and Cell Biol., Univ. of California, Berkeley, CA

Abstract: Infections and delivery of bacterial endotoxins induce lethargy and adaptive increases in sleep. Bodily sickness is conveyed via the vagus nerve to the nucleus of the solitary tract (NST) which mediates many sickness behaviors including anorexia, adipsia and reductions in movement. The pathways and mechanisms underlying increases in sleep, however, are not known. Here, we show that like bacterial endotoxin (lipopolysaccharide (LPS)), chemogenetic reactivation of NST LPS-TRAP neurons increases non-REM sleep and reduces REM. Axonal tracing of NST-TRAP neurons reveals projection targets in many homeostatic and autonomic related brain regions including paraventricular thalamus, periaqueductal gray, parabrachial nucleus and hypothalamic nuclei. We show that optogenetic terminal stimulation of NST to PB neurons increases nREM sleep. Finally, assessment of classic arousal-promoting

neuromodulatory systems with LPS or NST activation shows differential effects on dopaminergic, cholinergic and noradrenergic signaling.

Disclosures: D. Darmohray: None. **Y. Yao:** None. **J. Sima:** None. **Y. Dan:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.065/LBA61

Topic: F.07. Biological Rhythms and Sleep

Support: 5R01MH060670-21

Title: Learning and memory in rodents associated with non-simultaneous regional sleep states in hippocampus, striatum, and cortex

Authors: *W. PETTIBONE[1], G. R. POE[3], A. M. WIKENHEISER[2], B. BOHALL[1], R. SCHLICHTING[1];
[2]Psychology, [1]UCLA, Los Angeles, CA; [3]Dept. of Integrative Biol. and Physiol., UCLA Chapter, Los Angeles, CA

Abstract: Sleep states inferred from a single brain region are often assumed to reflect the state of the entire brain. However, recent studies suggest that different areas of the brain can simultaneously exhibit multiple sleep states. Considering the significant role of sleep in various forms of learning and memory consolidation, this newly discovered phenomenon of asynchronous sleep could influence how sleep shapes behavior and facilitates learning. We conducted experiments with 13 Long-Evans rats, training them on three tasks over seven days: a motor learning task (the complex ladder), a spatial hippocampal task (the hidden goal task), and a cue-based striatal task (the light-cued circular maze). The rats completed each task entirely before starting the next. During each week, the rats showed continuous behavioral learning, with significant performance improvement initially, followed by a gradual plateau. We recorded sleep activity in the motor cortex, hippocampus, striatum, and prefrontal cortex simultaneously, analyzing each channel to determine the sleep state. Asynchronous sleep was defined as any period during which at least one region was in a different sleep state compared to others. On average, asynchronous sleep constituted about 50% of total sleep time at baseline. There were no significant differences in the time each region spent in different sleep stages. As rats learned each task, the amount of asynchronous sleep time initially increased before returning to near-baseline levels. The number of asynchronous sleep bouts also increased and then decreased. Rats with a larger change in asynchronous sleep showed better task performance the following day. These results indicate that region-dependent learning might be enhanced or modulated through asynchronous sleep states across different brain regions.

Disclosures: W. Pettibone: None. **G.R. Poe:** None. **A.M. Wikenheiser:** None. **B. Bohall:** None. **R. Schlichting:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.066/LBA62

Topic: F.07. Biological Rhythms and Sleep

Title: Oxycodone disrupts sleep architecture and cognition in rats

Authors: *T. LUGO[1], C. ZUVIA[2], G. R. POE[3];
[1]Univ. of California Los Angeles, Los Angeles, CA; [2]UCLA, Riverside, CA; [3]Dept. of Integrative Biol. and Physiol., UCLA Chapter, Los Angeles, CA

Abstract: Chronic consumption of opioids has detrimental effects on sleep which include difficulty falling asleep, maintaining sleep, and altering the time spent in non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Sleep disturbances are associated with an increased risk of addiction and relapse. Withdrawal from drugs is distressing and stress affects hippocampal-learning including memory of spatial locations. Despite the known role of disturbed sleep in addictive behaviors, it is poorly understood. This study aimed to establish a detailed profile of sleep architecture, stress indicators, and hippocampal-dependent learning in control and oxycodone-treated rats. Long-Evans rats (n = 17) were tested on a hippocampus-dependent test (object location memory (OLM)) and a non-spatial memory test (novel object recognition (NOR)). Behavioral tasks were conducted before and after seven days of either saline or oxycodone i.p. injections (3 mg/kg/day). Screw electrodes were implanted over the prefrontal cortex, hippocampus and olfactory bulbs (reference) to record sleep. Nuchal electromyographic electrodes were implanted in the dorsal neck muscles to monitor muscle tone and electrocardiogram electrodes measured heart rate variability, an indicator of stress. 24-hour electrophysiological data were collected before, during, and after injections and scored into sleep categories (Waking, NREM, REM, and Transition-to-REM). In the OLM task, investigation of the object placed in the novel location significantly decreased after oxycodone withdrawal, indicating an impairment in the rats' hippocampal learning strategy ($p < 0.0001$). The control group showed no such impairment. However, exploration of the novel object remained significantly higher than that of the familiar object, indicating that performance in the NOR task was unaffected. Sleep onset latency from return to cage and percent time spent awake increased after oxycodone injections, indicating the development of sleep disturbances due to oxycodone intake and withdrawal. Since sleep is crucial for memory consolidation, understanding these effects will shed light on how opioid use and withdrawal impair cognitive functions, potentially leading to interventions for cognitive deficits in opioid users.

Disclosures: T. Lugo: None. **C. Zuvia:** None. **G.R. Poe:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.067/LBA63

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH NIDDK (R01DK129321)
Huck Metabolic Physiology Chair Funds

Title: Amylin in the amygdala is necessary and sufficient for feeding behavior control

Authors: *S. BYUN[1], S. BÖRCHERS[2], M. R. HAYES[3], K. P. SKIBICKA[1];
[1]Pennsylvania State Univ., State College, PA; [2]Univ. of Gothenburg, Göteborg, Sweden; [3]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Amylin, a pancreatic peptide, has a well-established role in feeding behavior control. Moreover, amylin analogues are already clinically utilized in patients with diabetes, and are under investigation as potential new anti-obesity pharmacotherapies. While area postrema has been recognized as a primary site for mediating amylin's satiating effects, more recent studies expanded this perspective to other brain regions, highlighting that our understanding of neural circuitry underlying actions of amylin on behavior remains incomplete. The central amygdala (CeA) recently emerged as a critical neural substrate for feeding behavior control and reward processing. We found that all components of amylin receptors (CTR, RAMP1-3) are expressed in the CeA; their potential role in physiology or behavior remains unknown. Therefore, here we investigated the potential ingestive and motivated behavior roles of amylin in the CeA of male and female rats. We found that intra-CeA delivered amylin was sufficient to acutely reduce chow intake in both sexes, with this hypophagic effect lasting longer in females. Intra-CeA amylin also potently reduced food-motivated behavior for sucrose. However, when high-fat and sucrose were offered, intra-CeA amylin selectively reduced the high-fat food intake, while sparing the sucrose intake. Pharmacological blockade of CeA amylin receptors increased food intake, but only in female rats. Virogenetic knockdown of CTR resulted in increased body weight gain in females, but not males. Our data indicate the CeA as a novel neural substrate for amylin. They reveal amylin receptors in the CeA are sufficient to alter feeding behavior in both sexes, while necessary only in females, underscoring a sex difference in the necessity of the CeA amylin signaling.

Disclosures: S. Byun: None. **S. Börchers:** None. **M.R. Hayes:** None. **K.P. Skibicka:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.068/LBA64

Topic: F.08. Food and Water Intake and Energy Balance

Support: R01DK129321
Swedish Research Council 2018-00660

Title: Lateral parabrachial nucleus astrocytes control food intake

Authors: D. MISHRA[1], J. E. RICHARD[2], S. BÖRCHERS[3], K. EEROLA[4], J.-P. KRIEGER[5], ***K. SKIBICKA**[6];
[1]Inst. of Neurosci. and Physiol., Gothenburg Univ., Gothenburg, Sweden; [2]Neurosci. and Physiol., Goeteborg, Sweden; [3]Univ. of Gothenburg, Göteborg, Sweden; [4]Univ. of Gothenburg, Gothenburg, Sweden; [5]Univ. of Zurich, Switzerland, Switzerland; [6]Penn State Univ., University Park, PA

Abstract: Food intake behavior is under the tight control of the central nervous system. Most studies to date focus on the contribution of neurons to this behavior. However, although previously overlooked, astrocytes have recently been implicated to play a key role in feeding control. Most of the recent literature has focused on astrocytic contribution in the hypothalamus or the dorsal vagal complex. Contribution of astrocytes located in the lateral parabrachial nucleus (lPBN) to feeding behavior control remains poorly understood. Thus, here we first investigated whether activation of lPBN astrocytes affects feeding behavior in male and female rats using chemogenetic activation. Astrocytic activation in the lPBN led to profound anorexia in both sexes under both *ad-libitum* feeding schedule as well as after a fasting challenge. Since astrocytes have a key contribution to glutamate homeostasis, and can themselves release glutamate, and lPBN glutamate signaling is a key contributor to the potent anorexia which can be induced by lPBN activation, we determined whether glutamate signaling is necessary for lPBN astrocyte activation induced anorexia, and found that pharmacological N-methyl D-aspartate (NMDA) receptor blockade attenuated the food intake reduction resulting from lPBN astrocyte activation. Since astrocytes have been shown to contribute to feeding control by modulating the feeding effect of peripheral feeding signals, we further investigated whether lPBN astrocyte activation is capable of modulating the anorexic effect of the gut/brain hormone - glucagon-like peptide-1 (GLP-1) as well as the orexigenic effect of the stomach-produced orexigenic hormone - ghrelin, and found that the feeding effect of both signals are modulated by lPBN astrocytic activation. Lastly, we found that lPBN astrocyte activation induced anorexia is affected by diet-induced obesity challenge, in a sex divergent manner.

Disclosures: D. Mishra: None. **J.E. Richard:** None. **S. Börchers:** None. **K. Eerola:** None. **J. Krieger:** None. **K. Skibicka:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.069/LBA65

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant DK104897

Title: Early life Western Diet exposure impairs vagus nerve-mediated hippocampus cholinergic signaling.

Authors: *L. TIERNO LAUER, S. E. KANOSKI;
Biol. Sci., USC, Los Angeles, CA

Abstract: Early life Western Diet exposure impairs vagus nerve-mediated hippocampus cholinergic signaling.
Authors L. Tierno Lauer[1], S. E. Kanoski[1,2,] † Department of Biological Sciences, University of Southern California, USA **DisclosuresL. Tierno Lauer**: None, **S. E. Kanoski**: None **Abstract:** Chronic exposure to a Western diet (WD) elicits hippocampal (HPC)-dependent memory impairment. One potential unexplored mechanism for these effects involves impaired vagus afferent nerve (VAN) signaling, as VAN signaling promotes HPC function, and WD consumption blunts the capacity of vagally-mediated gut signals to communicate to the brain. The medial septum (MS) is an anatomical relay between the brainstem and the HPC, and the MS extensively innervates the HPC with acetylcholine (ACh)-releasing fibers. Thus, we hypothesized that VAN signaling engages the HPC via MS ACh release, and further, that impairments in this signaling pathway underlie WD-associated HPC dysfunction. Using in vivo fiber photometry and fluorescent ACh sensors (iAChSnFR) in adult (Postnatal day 56-75) male Sprague Dawley rats, we demonstrate that HPC ACh binding is elevated immediately following consumption of a meal (n=10). Additional results revealed that these meal-induced elevations in HPC ACh binding were eliminated in animals who underwent a surgical subdiaphragmatic vagotomy (SDV), thus identifying a role for vagal signaling in mediating postprandial HPC ACh signaling (n=5-6/group). To explore how a WD affects this outcome, we recorded HPC ACh release in animals chronically exposed to a WD during development (Post-natal days 26-56) while consuming a meal during adulthood. Results reveal that, similar to SDV rats, meal-induced elevations in HPC ACh binding were eliminated in the WD group (n=6-8/group). Further, Western blot analyses revealed comparable reductions in HPC protein expression of vesicular ACh transporter, an indicator of ACh HPC tone, in SDV and WD rats relative to controls. Collectively, our findings identify ACh signaling as a neural substrate for gut-originating VAN potentiation of HPC function, and that impairments in this signaling pathway may underlie WD-induced HPC dysfunction.

Disclosures: L. Tierno Lauer: None. **S.E. Kanoski:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.070/LBA66

Topic: F.08. Food and Water Intake and Energy Balance

Support: Department of Defense Grant, HT94252310156

Title: A neural basis for anorexia nervosa

Authors: *C. SU[1], Y. XU[2], Q. TONG[3];
[1]UTHealth at Houston, Houston, TX; [2]IMM, Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [3]IMM, Univ. of Texas Hlth. Sci. Center, Houston, Houston, TX

Abstract: Anorexia nervosa (AN) is an eating disorder characterized by voluntarily restricted food intake, low body weight, fear of gaining weight, distorted body image, increased anxiety and physical activity. AN normally occurs in juveniles and teenagers and has a very high mortality rate in girls. However, the underlying neural basis of AN remains largely unknown. Here, we provide evidences that aberrant hyperactivity of steroidogenic factor 1 (SF1) and estrogen receptor-a (ERα) neurons in VMH, a satiety center within the brain, contributes for AN and its sexual dimorphism. We delivered Cre-dependent AAV-Flex-NaChBac and AAV-Flex-Kir2.1 virus into VMH to activate or inhibit SF1 and ERα neurons respectively. We measured the body weight and blood glucose. We tested the anxiety-related behaviors using open field test, elevated plus maze test. We found chronic activation of entire VMH neurons led to severe hypophagia, self-starvation, and ultimately death, whereas chronic inhibition led to hyperphagia and weight gain. Chronic activation of VMH^{SF1} led to a dramatic voluntary hypophagia, weight loss, anxiety and hyperactivity in both females and males. Interestingly, chronic inhibition of VMH^{SF1} neurons caused obesity on HFD in males but not females. We found that the expression of SF1 and ERα in neurons within VMH mainly located in VMHdm and VMHvl respectively, and showed nonoverlapping expression. Interestingly, the VMHvl harbored more ERα neurons in females than in males. Chronic inhibition of VMH^{SF1} neurons in ovariectomized mice caused obesity. We further found that glutamate release was not required for weight loss and anxiety-like behaviors resulting from VMHSF1 hyperactivity. Together, these findings support that hyperactivity of neurons within VMH is the neural basis for AN, and the different distribution of ERα neurons in VMH may contribute for the sexual dimorphism of AN.

Disclosures: C. Su: None. **Y. Xu:** None. **Q. Tong:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.071/LBA67

Topic: F.08. Food and Water Intake and Energy Balance

Support: Start-up Funds

Title: Weight-loss effects of loxapine in mc4r-deficiency based obesity via hypothalamic bdnf/trkb signaling

Authors: *C. KINNEY[1], A. ZHAO[1], E. TSAO[1], J. HAN[2];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Mount Sinai Hosp., New York, NY

Abstract: Obesity driven by genetic deficiencies in the melanocortin 4 receptor (MC4R) remains difficult to treat since this receptor is a point of convergence for many peripheral satiety signals. Genetic variants that result in a reduction in its expression or activity cannot be significantly overcome by increasing upstream signaling drive. However, downstream elements, such as the anorexigenic protein brain-derived neurotrophic factor (BDNF), in the hypothalamus could theoretically rescue weight gain due to MC4R deficiency. We report here that loxapine induces significant weight-loss in both diet-induced obese and MC4R-deficient mice. This weight loss is due to reduced food intake and is preferentially lost from the fat compartment. Loxapine also increases anorexigenic BDNF expression and activation of its receptor TrkB in the hypothalamus, contributing to signaling drive within the leptin-melanocortin system downstream of MC4R. These findings suggest the feasibility of drug targeting downstream of MC4R to rescue deficiencies not only in MC4R, but also of upstream elements such as leptin.

Disclosures: C. Kinney: None. **A. Zhao:** None. **E. Tsao:** None. **J. Han:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.072/LBA68

Topic: F.08. Food and Water Intake and Energy Balance

Support: ADA Award 4-23-PDFWH-01
BRAIN & BEHAVIOR RESEARCH FOUNDATION Sponsor Award 31485

Title: Endocannabinoid signaling to astrocytes in the hypothalamus modulates feeding behavior and energy metabolism

Authors: *D. HERRERA MORO[1], C. PEREZ DE NANCLARES[3], P. KOFUJI[2], A. ARAQUE[4];
[2]Neurosci., [1]UMN, Minneapolis, MN; [3]Univ. of Minnesota, Twin Cities, Minneapolis, MN; [4]Neurosci., Univ. of Minnesota Twin Cities Campus, Minneapolis, MN

Abstract: The brain controls energy homeostasis by fine tuning feeding and energy expenditure to nutrient availability. Disruption of this regulation results in obesity and associated metabolic pathologies. In particular, the lateral hypothalamus (LH) mediates autonomic metabolic regulation and motivational processes underlying feeding behavior. Over the last decades, evidence has shown that hypothalamic circuits are highly vulnerable to obesogenic diets and that diet-induced obesity (DIO) modifies astrocyte physiology, which contributes to local hypothalamic inflammation. The endocannabinoid (eCB) system participates in the pathophysiology of obesity, partly through the activation of type 1 eCB receptors (CB1Rs) in the brain and peripheral organs. Importantly, eCBs modulate synaptic function through the activation of astrocytic CB1Rs. By combining Ca^{2+} imaging selectively in astrocytes and in vivo metabolic profiling, we explored the contribution of astrocyte eCB signaling in the LH in the development of DIO. We show that astrocytic CB1R contributes to DIO-induced astrocyte hyperactivity and reactivity in the hypothalamus. Additionally, in vivo phenotyping after astrocyte CB1R KO in the LH shows increased food intake and body weight and decreased insulin sensitivity in lean and obese mice. In conclusion, our findings suggest that astrocyte eCB signalling plays a crucial role in obesity-associated functional changes in hypothalamic astrocytes and contributes to disbalances in systemic glucose metabolism and energy homeostasis associated with the development of DIO.

Disclosures: D. Herrera Moro: None. **C. Perez de Nanclares:** None. **P. Kofuji:** None. **A. Araque:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.073/LBA69

Topic: F.08. Food and Water Intake and Energy Balance

Support: K. Lisa Yang Brain-Body Center Postdoctoral Fellowship
NIH (NS131457, GM135413)
McKnight Foundation
Alfred P. Sloan Foundation
The Picower Institute for Learning and Memory

JPB Foundation

Title: Pathogen infection induces sickness behaviors by recruiting neuromodulatory systems linked to stress and satiety in C. elegans

Authors: S. PRADHAN[1], G. MADAN[1], D. KANG[1], E. BUENO[1], A. ATANAS[1], T. KRAMER[1], U. DAG[1], ***J. LAGE**[2], M. GOMES[1], A. K. LU[1], J. PARK[1], S. W. FLAVELL[1]; [1]Picower Inst. for Learning & Memory, Dept. of Brain & Cognitive Sci., [2]MIT, Cambridge, MA

Abstract: When animals are infected by a pathogen, peripheral sensors of infection signal to the brain to coordinate a set of adaptive behavioral changes known as sickness behaviors. While the pathways that signal from the periphery to the brain have been intensively studied in recent years, how central circuits are reconfigured to elicit sickness behaviors is not well understood. Here we find that neuromodulatory systems linked to stress and satiety are recruited upon infection to drive sickness behaviors in C. elegans. Upon chronic infection by the bacterium Pseudomonas aeruginosa PA14, C. elegans decrease their feeding behavior, then display reversible bouts of quiescence, and eventually die. The ALA neuron and its neuropeptides FLP-7, FLP-24, and NLP-8, which control stress-induced sleep in uninfected animals, promote the PA14-induced feeding reduction. However, the ALA neuropeptide FLP-13 instead acts to delay quiescence and death in infected animals. This accelerated behavioral response to infection in flp-13 mutant animals is not caused by overaccumulation of PA14 due to defective pharyngeal grinding of bacteria or increased exposure time on pathogenic lawns. Cell-specific genetic perturbations show that the neurons that release FLP-13 to delay quiescence in infected animals are distinct from ALA. A brain-wide imaging screen reveals that infection-induced quiescence involves ASI and DAF-7/TGF-beta, which control satiety-induced quiescence in uninfected animals. Our results suggest that a common set of neuromodulators are recruited across different physiological states, acting from distinct neural sources and in distinct combinations to drive state-dependent behaviors.

Disclosures: **S. Pradhan:** Other; *Equal contribution. **G. Madan:** Other; *Equal contribution. **D. Kang:** None. **E. Bueno:** None. **A. Atanas:** None. **T. Kramer:** None. **U. Dag:** None. **J. Lage:** None. **M. Gomes:** None. **A.K. Lu:** None. **J. Park:** None. **S.W. Flavell:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.074/LBA70

Topic: F.08. Food and Water Intake and Energy Balance

Support: NRSA 1F31DK138767-01

Title: Functional and behavioral dynamics of GLP-1 receptors in the central amygdala

Authors: *M. DURAN[1], J. A. HARDAWAY, III[2];
[1]Psychiatry and Behavioral Neurobio., [2]Psychiatry, Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Glucagon-like peptide-1 receptor (GLP-1R) activation reduces food intake via multiple brain sites, i.e., hypothalamus, hindbrain, and limbic systems. Peripheral and central administration of GLP-1R agonists activate the central nucleus of the amygdala (CeA), yet the mechanisms mediating this action are understudied. In the present study, *in vivo* fiber photometry and GCaMP in the CeA in freely behaving mice was used to determine the role of GLP-1Rs in modulating neural activity in response to peripheral administration of a GLP-1R agonist. In addition, chemogenic inhibition of the CeA with an inhibitory DREADD was performed where feeding behavior was assessed in the presence of a GLP-1R agonist. Freely-behaving mice with fiber optic cannulas implanted in CeA were attached to a fiber photometry system and neural activity recorded in response to intraperitoneal administration of saline, Exendin-4 (Ex4, agonist), or Exendin-9 (Ex9, antagonist). Home caged mice with inhibitory DREADD were given its chemogenetic actuator deschloroclozapine (DCZ) in the presence of Ex4. We found that Ex4 activates CeA neurons, and this effect is blocked by prior administration of Ex9. When the CeA is chemogentically inhibited, food-seeking behaviors remain intact despite the presence of Ex4. These measurements from freely behaving mice suggest that CeA GLP-1Rs are potentially mediating changes in neuronal activity when activated by a GLP-1R agonist and influence feeding behaviors.

Disclosures: M. Duran: None. **J.A. Hardaway:** None.

Late-Breaking Poster

LBA006: Theme F Late-Breaking Posters

Location: MCP Hall A

Time: Monday, October 7, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA006.075/LBA71

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH F31 Grant F31DK137484

Title: Oxytocin neurons in the paraventricular hypothalamus and supraoptic nucleus bidirectionally influence food intake

Authors: *J. REA, S. E. KANOSKI;
USC, Los Angeles, CA

Abstract: Oxytocin (OT) is a neuropeptide produced in the paraventricular (PVH) and supraoptic (SON) nuclei of the hypothalamus that acts in the brain to influence food intake. While numerous studies have investigated OT's role in food intake control using a pharmacological approach, such approaches do not model the physiological conditions of

endogenous OT release, nor can they differentiate whether observed effects are mediated by OT neurons originating in the PVH vs. SON subpopulations. To address these gaps, we targeted excitatory OT-specific designer receptors exclusively activated by designer drugs (DREADDs) to distinct regions in Sprague Dawley rats, allowing for selective activation of OT neurons in either the PVH or SON at the beginning of the nocturnal feeding period. Animals were tested for each standard chow, an 11% sucrose solution, and a highly palatable 45% by kcal high fat diet (HFD). Results revealed that while DREADDs-mediated excitation of PVH OT neurons significantly reduced the size of the first meal of standard chow following dark onset, surprisingly, SON OT neuron activation had the opposite effect by increasing the first nocturnal meal size. Similarly, SON OT neuron activation increased the size of the 1st drinking burst for sucrose and the number of drinking bursts resulting in a significant increase in sucrose intake. Activation of PVH OT neurons significantly reduced HFD intake with a trend towards decreasing average meal size while activation on SON OT neurons saw an increase in average meal size on HFD. To further examine the physiological role of OT neurons in eating behavior, we irreversibly silenced synaptic transmission of OT neurons in either the PVH or SON by expressing a tetanus toxin light chain under the control of the OT-specific promoter, which cleaves the vesicle associated membrane protein synaptobrevin that is necessary for vesicular release of neuropeptide. While silencing of OT neurons in the PVH and SON had no effect on average 24 hr food intake, silencing of OT neurons in the SON resulted in a significant reduction in average 1st nocturnal meal size. This effect is even more pronounced during a refeeding following a fast, where SON OT neuron silencing significantly decreases average meal size which is coupled to a significant increase in meal frequency, thus yielding no change in cumulative intake. PVH OT synaptic silencing had no impact on standard chow intake, but led to an increase in meal size along with a trending compensatory decrease in meal frequency when animals were maintained on a HFD. Collectively these data reveal that PVH and SON OT neurons function to reduce and increase meal size, respectively.

Disclosures: J. Rea: None. **S.E. Kanoski:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.001/LBA1

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIH Grant 1R15MH134219-01A1

Title: Evidence for a specific role of inhibitory intolerance of uncertainty during threat-safety discrimnation learning

Authors: *D. C. JOHNSON[1,2], M. KINNEY-PETRUCHA[2];
[1]York College, CUNY, Queens, NY; [2]The Grad. Center, CUNY, New York, NY

Abstract: Uncertainty is a core component of threat and associated learning processes. One factor impacting uncertainty in threat learning paradigms is the threat reinforcement rate, which refers to the proportion of times a cue is reinforced with an aversive stimulus. Here, we tested the effect of partial vs continuous threat reinforcement on threat discrimination learning, as indexed by skin conductance response (SCR) and self-reported US expectancy and evaluative responses. Participants (n = 102) completed a task in which three colored shapes were paired with electric shock at reinforcement schedules of 100% (CSP_{100}), 50% (CSP_{50}) and 0% (CSM). The data show enhanced SCR for the CSP_{100}, consistent with previous findings. While participants differentiated between the threat and safety cues in their self-report data, they did not differentiate between the CSP_{100} and $CSP_{50.}$ Additionally, the study examined associations between trait measures and threat-safety discrimination. Previous exploratory research from our lab showed distinct roles for the inhibitory and prospective subscales of intolerance of uncertainty (I-IU and P-IU) on fear acquisition, where high I-IU and P-IU were associated with diminished and heightened threat-safety learning, respectively. Here, we tested this finding using a confirmatory approach. Similar to our previous research, no association was observed between total IU score or trait anxiety and learning. However, a two-factor model of IU showed high inhibitory IU was associated with diminished threat discrimination, consistent with our previous work, but only for the uncertain but not the certain cue, an interaction not previously observed. We found no association between prospective IU and learning, contrary to previous findings. Finally, we show that participants with higher scores in total IU reported higher levels of dislike for the uncertain vs certain cue. We think this work makes three valuable contributions. One, it highlights the importance of following up exploratory findings with confirmatory tests. Two, the results contribute to a growing literature exploring how the uncertainty inherent to predictors of threat, individual differences in sensitivity to uncertainty, and interactions between these two factors, can shape the acquisition of threat memories. Three, in accordance with dimensional views of psychopathology, the work suggests that studying fear-relevant traits can be valuable for better understanding variability in the acquisition of threat memories and, in parallel with research in clinical populations, could help elucidate the role of threat learning in clinical anxiety.

Disclosures: D.C. Johnson: None. **M. Kinney-Petrucha:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.002/LBA2

Topic: G.01. Fear and Aversive Learning and Memory

Support: MH123260-01

Title: Role of auditory cortex and its long-range GABAergic projections to lateral amygdala in recent and remote recall

Authors: *T. G. HENNEGHAN[1], S. WASBERG[2], L. WATKINS[1], I. MUZZIO[1];
[1]Psychological and Brain Sci., [2]Univ. of Iowa, Iowa City, IA

Abstract: Emotional memory is the lens through which we interpret the world and is essential for our behavioral and emotional balance. The auditory cortex (AC) and lateral amygdala (LA) are critical regions for processing auditory signals and emotional information, respectively. Reciprocal connectivity between the AC and LA is fundamental to understanding how emotional memories are formed and retrieved. While previous research has identified plastic changes in these regions due to learning and shown that excitatory projections from LA to AC are necessary for fear associations, gaps remain in understanding the specific role of somatostatin (SST) inhibitory neurons within this pathway. Recent research by the Apicella lab revealed a long-range SST projection from AC to LA, which synapses on the same excitatory neurons that project to AC (Bertero et al., 2019; Bertero and Apicella, 2024), but its functional role and impact on memory persistence are unclear. To address this, we developed a sound discrimination task. Mice were bilaterally injected with an inhibitory DREADD under the CAMKII promoter in AC. Four weeks after surgery, mice were fear-conditioned with a tone associated with shock (CS+, 15 kHz) and another tone never paired with shock (CS-, 3 kHz). The animals were then tested with the CS+, CS-, and two intermediate tones (11 and 7 kHz) presented randomly on days 2, 15, and 30 following conditioning. Experimental mice received clozapine oxide (CNO), the ligand that activates DREADDs, on either day 2 or day 15, while control mice received either saline or CNO. Our findings reveal that chemogenetic inhibition of AC principal cells during early retrieval significantly affects early and remote discrimination of the CS-. However, the same manipulation on day 15 only has subtle effects. Our data also suggest that inhibiting the long-range GABAergic projections from AC to LA on day 2 also impairs the ability of mice to discriminate between fearful and safe sounds. We are currently investigating if inhibition of this projection has similar effects at later time points during retrieval. This study provides insights into the functional role of SST long-range projections on emotional processing and clarifies the intricate involvement of both LA and AC in remote memory. These findings hold significant implications for the development of targeted therapies for anxiety-related disorders by modulating specific neural pathways involved in emotional regulation, highlighting the potential for innovative therapeutic approaches.

Disclosures: T.G. Henneghan: None. **S. Wasberg:** None. **L. Watkins:** None. **I. Muzzio:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.003/LBA3

Topic: G.01. Fear and Aversive Learning and Memory

Support: NIGMS R35GM142566

Title: Neural basis for individual differences in fear memory in zebrafish

Authors: B. D. FONTANA[1], N. RAJPUT[1], D. KANANI[1], ***J. W. KENNEY**[2];
[1]Biol. Sci., [2]Wayne State Univ., Detroit, MI

Abstract: Fear is a fundamental emotional state that is highly conserved across the animal kingdom. Despite the intrinsic importance of fear for survival, its behavioral manifestation varies between individuals where the choice of response can be the difference between life and death. However, we know little about the biological basis for these individual differences in fear behavior. To plumb the depths of this behavioral variation, we used adult zebrafish as a model organism. Fish were trained to associate a new environment with fear by exposing them to conspecific alarm substance (CAS), an ethologically relevant chemical stimulus released from the epithelial cells of injured fish to alert nearby animals to danger. After tracking with DeepLabCut, we trained a random forest machine learning model to identify different behaviors (e.g., freezing, bursting, and erratic movements) to greater than 95% accuracy. We collected data from over 400 animals from four different inbred strains (AB, TU, TL, and WIK) and both sexes. We used an unsupervised machine learning approach to identify four distinct behavioral clusters: (1) low fear responsivity, (2) increased erratic behavior, (3) high freezing interspersed with increased erratic behavior, and (4) high freezing interspersed with normal swimming behavior. We found that both background strain and sex had an influence on the type of fear behavior exhibited. Finally, we performed whole-brain activity mapping to identify the neural basis individual differences in fear behavior. To do this, we used a combination of *in situ* hybridization chain reaction for *c-fos*, tissue clearing, light-sheet microscopy, and image registration to the adult zebrafish brain atlas. We used partial least squares to identify brain regions that covary with different behaviors. We found that freezing engages the dorsal and ventral telencephalon whereas erratic movement is primarily characterized by elevated activity in the spinal cord and hindbrain. We discuss the implications of these findings with respect to how higher brain regions, like the telencephalon, modulate brain activity to give rise to different behavioral outputs.

Disclosures: B.D. Fontana: None. **N. Rajput:** None. **D. Kanani:** None. **J.W. Kenney:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.004/LBA4

Topic: G.01. Fear and Aversive Learning and Memory

Support: Israel Science Foundation Grant ISF 946/17
Israel Science Foundation Grant ISF 258/20
Israel Science Foundation Grant ISF 1207/22
DFG Grant 48998

Title: An intra-insula circuit differentially regulates associative aversive and immune conditioning

Authors: *F. CRUCIANI[1], H. KAYYAL[2], S. KOLATT CHANDRAN[2], E. EDRY[2,3], S. SCHIF-ZUCK[4], T. KOREN[5,6], A. YIANNAKAS[2,7], A. ROLLS[5,6], A. ARIEL[4], K. ROSENBLUM[2];
[2]SAGOL DEPARTMENT OF NEUROBIOLOGY, [3]Ctr. for Gene Manipulation in the Brain, [4]Departments of Biol. and Human Biol., [1]Univ. of Haifa, Haifa, Israel; [5]Dept. of Neuroscience, Rappaport Fac. of Med., [6]Dept. of Immunology, Rappaport Fac. of Med., Technion - Israel Inst. of Technol., Haifa, Israel; [7]Inst. of Biochem. and Mol. Med., Univ. of Bern, Bern, Switzerland

Abstract: Conditioned immune response (CIR), a Pavlovian conditioning procedure, is an example of for a non -declarative brain-body interaction. In CIR, a sensory stimulus is paired with an immunomodulatory agent. A subsequent re-exposure to the conditioned stimulus leads to both aversion toward the stimulus and an anticipatory immune response. The insular cortex (IC) computes and integrates internal and external information, with distinct functions among the antero-posterior axis. Among the other functions, the anterior IC encodes taste and its valence and the posterior IC stores an accurate representation of the immune responses. Although the underlying mechanisms were not investigated, lesion studies suggest that an intact IC is necessary for conditioned immune responses. In our research, we hypothesized that a bi-directional circuit connecting the anterior and posterior IC mediates the CIR. To test this hypothesis, we subjected adult male mice (n>7) to CIR, by pairing novel saccharin with a single injection of lipopolysaccharide (LPS); saccharin re-exposure triggered behavioral aversion and an increased cellular immune response similar but not identical to LPS exposure (i.e. the UCS alone). Following correlative studies, indicating a predominant role of the anterior to posterior IC pathway, we chemogenetically inhibited the reciprocal anterior to posterior connectivity during retrieval of the behavioral aversion and the anticipatory immune response. Our results showed that retrieval of CIR requires the activity of the neurons projecting from the anterior to the posterior IC, whereas modulating the anticipatory immunological dimension involves bi-directional projections. Our study proved our hypothesis and uncovered that intra-insular circuit contributes to immune homeostasis. In addition, it paves the way for a personal, behavioral and drug-independent brain stimulation treatment, when fine-tuning of the immune system is needed. Our current efforts are directed towards understanding the dynamics and the coding of CIR by looking at the correlation between activity of specific neurons in the insula and behavioral readout by combining licking microstructure analysis and fiber photometry.

Disclosures: F. Cruciani: None. **H. Kayyal:** None. **S. Kolatt chandran:** None. **E. Edry:** None. **S. Schif-Zuck:** None. **T. Koren:** None. **A. Yiannakas:** None. **A. Rolls:** None. **A. Ariel:** None. **K. Rosenblum:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.005/LBA5

Topic: G.02. Reward and Appetitive Learning and Memory

Support: DGAPA PAPIIT IN209122
DGAPA PAPIIT IN203124

Title: Differential effects of dopaminergic activation in the nucleus accumbens shell on latent inhibition of conditioned taste aversion depending on the degree of sugar familiarity

Authors: *M.-I. I. MIRANDA[1], N. Y. ATAUCUSI VARGAS[2];
[1]Inst. Neurobiologia-UNAM, Queretaro, Qro., Mexico; [2]Inst. de Neurobiología, UNAM, Queretaro, Mexico

Abstract: The reward system is crucial for appetitive behavior, being significantly activated by dopaminergic transmission during sweet food consumption that mediates the integration of sweet taste with positive post-ingestion consequences. Thus, the reward system interacts with the memory system during rewarding experiences, facilitating behaviors like ingestion scalation of caloric and hedonic foods, such as sugar. In this regard, the nucleus accumbens shell (NACsh) is a vital structure of the reward circuit, functioning as a sensory sentinel that promotes hedonic feeding and may modulate flavor memory. Therefore, the dopaminergic function in the NaCsh during appetitive learning and aversive taste memory formation needs to be studied in more detail. Accordingly, this research aimed to evaluate the effects of dopaminergic activation in the NACsh during conditioned taste aversion (CTA) of novel sugar or the latent inhibition of CTA (LI-CTA) of familiar or highly familiar sugar. Thus, male adult Wistar rats received bilateral injections of dimethyl sulfoxide-10% in physiological saline (control group; 0.05ul/0.5ul side) or the dopamine agonism, apomorphine (9 ul/0.5 ul side) 30 min before CTA-acquisition of novel 10 % sugar solution, familiar sugar (20 min access over three days), or high-familiar sugar solution (continuous access for 21 days). The results show increased appetitive response and sugar preference since the first consumption. During CTA acquisition, apomorphine treatment decreased appetitive response only for novel sugar, significantly impacting CTA and aversive memory extinction. On the contrary, dopamine receptor activation did not affect sugar preference for familiar or highly familiar sugar and did not impact the LI-CTA; nonetheless, dopamine receptor activation increased the appetitive relearning of highly familiar sugar. Likewise, long-term sugar consumption (21 days) induces minor variability in sugar preference over water, which was enhanced by apomorphine treatment. These findings indicate that dopaminergic activity balance in the NACsh is related to a decrease in aversive memory formation of novel stimuli and an increase in appetitive response for highly familiar stimuli, suggesting changes in

NACsh dopamine receptor sensitivity during appetitive or aversive memory formation, as well as during memory updating, depending on the degree of stimulus familiarity.

Disclosures: M.I. Miranda: None. **N.Y. Ataucusi Vargas:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.006/LBA6

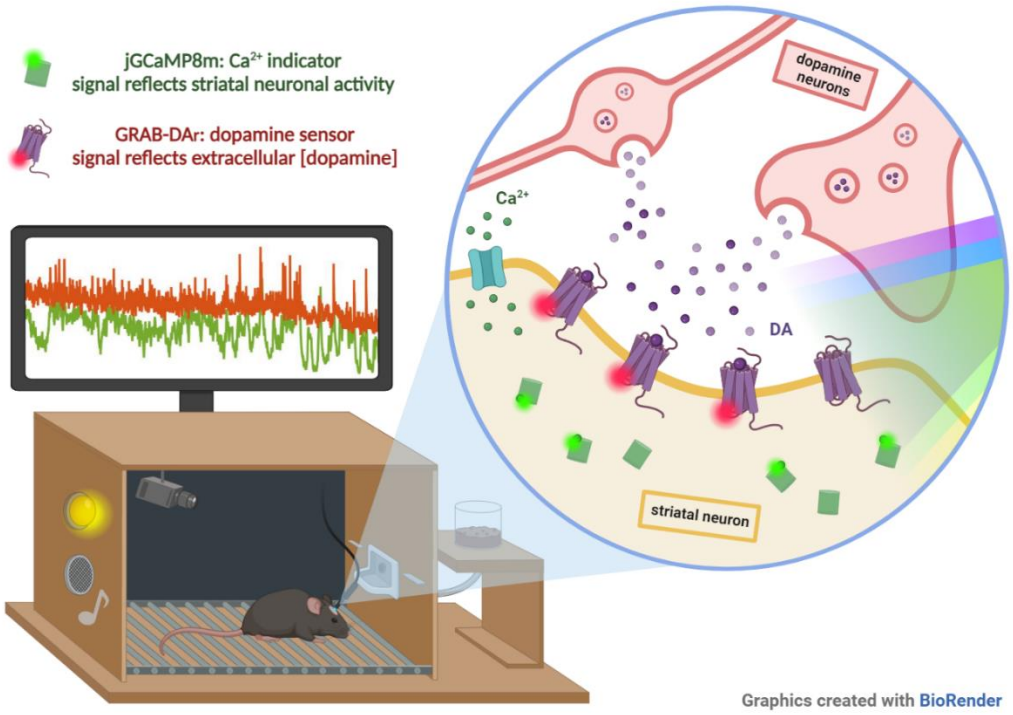
Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Grant 1R15MH122729-01

Title: Characterizing striatal patch-dopamine interactions in freely moving mice

Authors: *H. GAO[1], Y. LEE[1], S. KRIKAWA[1], S. CHANG[1], Z. GREER[1], H. FELLER[1], J. A. NADEL[2], C. D. HOWARD[1];
[1]Dept. of Neurosci., Oberlin Col., Oberlin, OH; [2]Dept. of Neurosci., Northwestern Univ., Chicago, IL

Abstract: Selecting appropriate actions and updating behaviors based on outcomes is a crucial process for all animals. Striatal patches (also known as ‘striosomes’) are specialized regions in the striatum, characterized by unique cellular markers and inputs relative to the surrounding ‘matrix’ tissue. Additionally, patches act as the sole striatal output to substantia nigra pars compacta (SNc), suppressing dopamine release. Accordingly, previous studies have outlined the important role of striatal patches in action selection and decision-making. While patches are well-poised to inhibit dopamine release, no studies have fully characterized patch-dopamine interactions in freely moving mice during behavior. To examine this, we utilized fiber photometry to detect subsecond fluctuations in striatal activity and dopamine signaling via genetically encoded calcium indicators (jGCaMP8m/FLEX-jGCaMP8m) and GPCR-activation-based dopamine sensors (GRAB-DAr) in C57BL6/J wild-type, Sepw1 NP67 (patch-Cre), and Plxnd1 OG1 (matrix-Cre) mice. During locomotion and operant conditioning, freely behaving mice demonstrated synchronous dopamine spikes with both patch and matrix activity. Moreover, during Pavlovian conditioning and in a more complex behavioral task with mixed stimulus-response and action-outcome trials, we observed covariance between dopamine signaling and striatal activity that largely, but not perfectly, fit the reward prediction error model. Overall, patch and matrix signaling was predominantly consistent in these behavioral contexts, suggesting complementary, rather than antagonistic, activity between patches and nigrostriatal dopamine release. This work provides foundational insight into the interplay between the striatum and dopaminergic system in freely moving mice.



Disclosures: H. Gao: None. **Y. Lee:** None. **S. Krikawa:** None. **S. Chang:** None. **Z. Greer:** None. **H. Feller:** None. **J.A. Nadel:** None. **C.D. Howard:** None.
Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.007/LBA7

Topic: G.02. Reward and Appetitive Learning and Memory

Support: HHMI Gilliam Fellowship
NIH Grant R01MH130755

Title: The basolateral amygdala differentially encodes social and nonsocial reward

Authors: *J. L. JAVIER[1], J. ISAAC[2], H. BALASUBRAMANIAN[2], M. MALAVIKA[3];
[1]Biol. Dept., Emory Univ. Neurosci. Grad. Program, Atlanta, GA; [3]Dept. of Biol., [2]Emory Univ., Atlanta, GA

Abstract: As animals navigate their environment, they must make decisions on whether to engage with different reinforcing stimuli. While several studies have explored the neural substrates that underlie decisions between positive and negative stimuli, less research has focused on how different brain regions encode choice and reward when given two different

competing, appetitive stimuli. Recently, we explored how the mPFC encoded social and nonsocial reward using a novel two choice operant assay (Isaac et al, 2023). This study revealed largely non-overlapping representations of sucrose and social reward that was modulated by internal state and sex. However, it is unclear if social and food reward representations remain largely distinct in other nodes of the reward circuitry, specifically the basolateral amygdala. To address this question, I focused on the role of the basolateral amygdala, a region known to encode positive and negative valence of food rewards, in encoding social and nonsocial reward-related behaviors. Using in vivo cellular resolution calcium imaging while mice performed an operant assay in which they can choose between food and social rewards, I found that the BLA differentially encodes social and nonsocial reward choice and consumption (n=7 adult male mice, 1801 neurons). Additionally, it seems that rather than remain stable, reward representations are modulated by changes in internal state, such as thirst. Additionally, the BLA representations are distinct from those found in the mPFC. For example, compared to representations in the mPFC where social reward excite neurons where the majority group, in the BLA, sucrose reward excite neurons outnumbered those inhibited by sucrose reward or modulated by social reward. The unique representations in these two connected nodes of the social reward circuit points to a possible difference in the information being encoded in either region. This adds valuable insight into how the brain may differentially weigh competing reward options in one setting and support decisions to interact with one over another.

Disclosures: J.L. Javier: None. **J. Isaac:** None. **H. Balasubramanian:** None. **M. Malavika:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.008/LBA8

Topic: G.02. Reward and Appetitive Learning and Memory

Support: NIH Grant R01AA013983
NIH Grant R01DA031734

Title: Rewarding aggression in male and female mice

Authors: *B. BLASETTI[1], H. COVINGTON, III[3], M. Z. LEONARD[4], E. L. NEWMAN[5], K. SCHAEFER[6], T. SYDNOR[2], M. FRIER[1], K. A. MICZEK[2], M. M. WEERA[2];
[2]Psychology, [1]Tufts Univ., Medford, MA; [3]SUNY Empire State Univ., Saratoga Springs, NY; [4]Pharmacol., Vanderbilt Univ., Nashville, TN; [5]Psychiatry, McLean Hosp., Belmont, MA; [6]Massachusetts Gen. Hosp., Somerville, MA

Abstract: Rewarding Aggression in Male and Female Mice
Brittany M. Blasetti, Herbert E. Covington III, Michael Z. Leonard, Emily L. Newman, Kira Schaefer, Teghan Sydnor, Micah Frier, Klaus A. Miczek, Marcus M. Weera
Aggression is a powerful reinforcer in social and territorial species. Female mice, like males, will readily attack same-sex intruders following cohabitation with a partner. Thus, the current series of experiments systematically examined if female mice will also work for the opportunity to fight. Measures of stereotypical 'scalloped' patterns of fixed interval (i.e., FI) operant responding - a rapid acceleration of responding as the end of the interval approaches - were used to operationally define 'motivational states' while anticipating an opportunity to physically confront same-sex conspecifics. We found that both male and female Swiss Webster mice respond here for the opportunity to fight. Specifically, both males and females acquire rates and scalloped patterns of operant responding for the opportunity to fight that are stable and persistent across sessions. At the completion of each fixed interval operant session, the performance of aggressive behavior in both males and females consists of short latencies to attack and considerably escalated patterns of fighting, consistent with historical measures of schedule-induced aggression across many species investigating males. No significant changes in motivational or performance measures of rewarding aggression were observed across the entire estrous cycle in females. Using fixed interval operant responding procedures, we are currently investigating the neurobiological mechanisms that contribute to aggression seeking and performance (i.e., fighting) in male and female mice, and how these systems are dysregulated by chronic consumption of alcohol and other misused substances.
This study is supported by NIH grants R01AA013983 and R01DA031734.

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Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.009/LBA9

Topic: G.02. Reward and Appetitive Learning and Memory

Support: McKnight Brain Research Foundation

Title: Assessing Effects Of The GLP-1 Receptor Agonist Exendin-4 On Risk-Taking Behavior

Authors: *Z. KRUMM[1], W. PYON[2], B. SETLOW[3], J. L. BIZON[4];
[1]Neurosci., [2]Univ. of Florida, [3]Dept. of Psychiatry, Univ. of Florida, Gainesville, FL; [4]Neurosci., Univ. of Florida Dept. of Neurosci., Gainesville, FL

Abstract: Balancing perceptions of expected reward vs. expected costs is instrumental in several types of behaviors, including risk-taking. Extreme preference for one over the other is a feature of multiple neuropsychiatric conditions, including substance use disorders (risk seeking) and anorexia nervosa (risk avoidance). Dopamine signaling in mesostriatal circuits plays a fundamental role in mediating both expected and experienced behavioral costs and rewards, making it a compelling target for therapeutic modulation in the treatment of conditions characterized by risk-taking behaviors. Fortunately, pre-clinical evidence has suggested that the glucagon-like peptide 1 (GLP-1) receptor agonist family of medications modulate mesostriatal dopamine signaling , and initial clinical studies indicate that they may reduce the frequency of behaviors ranging from gambling to alcohol consumption. In order to determine if GLP-1 receptor agonism can directly influence risk-taking behaviors, we evaluated the effects of acute administration of the intermediate-acting GLP-1 agonist exendin-4 on performance of a risky decision-making task in 7-month-old Sprague-Dawley rats (n=8 male, 7 female). In this task, rats make discrete choices between two response levers, one that yields a small reward (1 food pellet) with no risk of punishment and another that yields a large reward (2 food pellets) accompanied by a mild footshock that ranges in probability from 0 to 100%. Different doses of exendin-4 (0, 0.1, 0.3, 1.0, 3.0 µg/kg in 0.9% saline vehicle) were administered subcutaneously at a volume of 1.0 ml/kg, 1 hour prior to test sessions in the task, using a randomized, within-subjects design such that each rat received each dose of the drug, with at least a 48-hour washout period between successive injections. Data in male rats show that exendin-4 reduces choice of the large, risky reward (reduces risk taking) in a dose-dependent manner (two-way ANOVA, dose x risk, main effect of dose, $F_{(4,24)}=15.66$, $p<.001$). Even when excluding the highest dose (3.0 µg/kg), which is the only dose of those chosen that is reportedly sufficient to suppress food intake, this finding remained significant (main effect of dose, $p=0.004$). In addition, exendin-4 did not reduce rats' preference for the large reward in the absence of punishment. Replication of these findings in females is ongoing, as are experiments to evaluate effects of exendin-4 on task-related dopamine signals in the nucleus accumbens. Collectively, these data will begin to inform the mechanism(s) by which the incretin family of medications influence risky decision making, and reward-directed behaviors more broadly.

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Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.010/LBA10

Topic: G.03. Motivation

Support: NIMH IRP 1ZIAMH002950

Title: The midline thalamus shapes the motivational aspect of instrumental actions via the ventral striatum

Authors: *E. E. MACDONALD[1], J. MA[2], B. B. AVERBECK[3], M. A. PENZO[4];
[1]NIMH, Bethesda, MD; [2]XuZhou Med. Univ., Beijing, China; [3]NIMH/NIH, Bethesda, MD;
[4]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Changes to motivation are pervasive among neuropsychiatric disorders such as depression and addiction. Understanding the neural mechanisms that underlie motivational processes is thus critical for the development of effective therapies. While changes in local dopamine (DA) concentration within the ventral striatum (VS) have been recently identified as a feature of motivational drive, the neural circuit mechanisms that account for this process are unknown. The paraventricular thalamus (PVT) is heavily implicated in motivated behaviors including reward seeking and threat avoidance, and stimulation of PVT can evoke local VS DA release. To investigate the mechanisms by which the PVT shapes motivational processes, we trained mice in a two-way active avoidance task. The PVT-VS pathway shows increased activity during the safety outcomes following a successful avoidance, and these outcomes are thought to play a role in avoidance reinforcement. Furthermore, these safety outcome periods in avoidance tasks have increased VS DA concentration. Thus, increased activity in PVT-VS during safety is potentially driving avoidance through the motivational effects of VS DA. To examine the role of PVT-VS DA in avoidance motivation in mice, we utilized in vivo fiber photometric recordings and optogenetic manipulation of PVT-VS and VS DA activity during avoidance. Inhibition of PVT-VS activity immediately after avoidance responses significantly impaired safety outcome-evoked DA, indicating that PVT is driving DA during this period. Analysis PVT-VS activity recordings using functional linear mixed modeling revealed PVT-VS activity during safety was positively related to avoidance velocity, a proxy for motivational drive, signifying that PVT is contributing motivational signals to VS. In addition, optogenetic perturbation of PVT-VS activity during safety decreased avoidance behavior, and a Rescorla-Wagner learning model fit to this data estimated value of avoidance to decrease with inhibition at safety, further suggesting that PVT-VS is conveying motivational value of avoidance. Whereas perturbation of VS DA release during safety had similar effects on avoidance rate, recordings of VS DA activity had a positive relationship with avoidance latency and not velocity, indicating that these inputs might be contributing to different aspects of avoidance motivation. Collectively, our findings suggest that safety period activity from both PVT and DA in VS are critical to avoidance behavior, and the role of PVT-VS input is related to avoidance motivation. Ongoing work will investigate the circuit mechanisms by which PVT-VS shapes motivational VS DA release.

Disclosures: E.E. Macdonald: None. **J. Ma:** None. **B.B. Averbeck:** None. **M.A. Penzo:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.011/LBA11

Topic: G.03. Motivation

Support: NIH Grant R00AA029726
NIH Grant R01AA013983
NIH Grant R01AA023305
VA Grant BX003451

Title: Avoider rats show blunted sensitivity to alcohol's aversive effects: The role of lateral hypothalamic projections to the lateral habenula

Authors: *S. BONAUTO[1,2], O. R. BRUNKE[2], N. W. GILPIN[3,4,5], M. M. WEERA[1,2];
[1]Tufts Univ., Boston, MA; [2]Tufts Univ., Medford, MA; [3]Dept. of Physiol., [4]Alcohol and Drug Abuse Ctr. of Excellence, LSU Hlth. Sci. Ctr., New Orleans, LA; [5]Southeast Louisiana VA Healthcare Syst., New Orleans, LA

Abstract: Traumatic stress leads to avoidance behaviors and alcohol misuse in some people. Similarly, in rats, predator odor ("traumatic") stress produces avoidance behavior in some animals (termed Avoiders), but not others (termed Non-Avoiders). In this model, Avoiders show persistent increases in alcohol drinking after stress exposure. Using multiple approaches, we tested the hypothesis that Avoider rats show lower sensitivity to the inherent aversive effects of moderate to high doses of alcohol, which may be one reason these animals consume more alcohol. First, we found that adult male Avoider rats exhibit less alcohol (1.5 g/kg)-induced conditioned place aversion (CPA) compared to Non-Avoiders and stress-naïve Controls. Then, we found that both male and female Avoiders also have less alcohol conditioned taste aversion (CTA) to saccharine when paired with a 1.5 g/kg alcohol injection. Together these results suggest that Avoider rats are less sensitive to the aversive effects of alcohol following stress. To elucidate the neurobiological mechanisms behind this phenomenon, we are currently testing the hypothesis that the lateral hypothalamus (LH) to lateral habenula (LHb) circuit is important for mediating the aversive effects of alcohol, and that dysregulation of this circuit contributes to blunted alcohol aversion in Avoiders after stress. Using a combination of retrograde tracing and cFos immunohistochemistry in male rats, we found that recruitment of LH-LHb neurons following alcohol injection was blunted in Avoiders compared to Non-Avoiders and Controls. Collectively, these data suggest that the stress-induced escalation of alcohol drinking seen in Avoider rats may be facilitated by lower sensitivity to the aversive effects of alcohol. This work was supported by NIH grants R00AA029726, R01AA013983 (Weera), R01AA023305 (Gilpin) and by VA grant BX003451 (Gilpin).

Disclosures: S. Bonauto: None. **O.R. Brunke:** None. **N.W. Gilpin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Glauser Life Sciences. **M.M. Weera:** None.

Late-Breaking Poster

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Program #/Poster #: LBA007.012/LBA12

Topic: G.03. Motivation

Support: NIH R21 MH 129809 (to PLB)

Title: Analysis of estrogen's role in habenula-induced inhibition of dopamine neurons in rats

Authors: V. J. WALDRON[1], M. SUTTAWIREESAN[1], S. FATIMAH[1], I. J. MERCHENTHALER[2], ***P. L. BROWN**[1];
[1]Psychiatry, Univ. of Maryland Sch. of Med., Catonsville, MD; [2]Epidemiology & Publ. Hlth., Univ. of Maryland, Baltimore, MD

Abstract: Clinically relevant sex differences have been noted in a number of affective, behavioral, cognitive, and neurological health disorders. Midbrain dopamine (DA) neurons are implicated in several of these same disorders and consequently are under investigation for their potential role in the manifestation of these sex differences. The lateral habenula (LHb) exerts significant inhibitory control over DA neuronal firing, and we previously found that this control is both qualitatively and quantitatively different in female and male rats. However, the degree to which circulating gonadal hormones regulate this difference is not known. We hypothesized that circulating estrogen is responsible for the reduced DA inhibition previously demonstrated in female rats and predicted that estrogen removal would block this reduction. Fifty-three female Sprague-Dawley rats (200-225g; Charles River) were randomly assigned to one of three surgical groups: Sham, ovariectomized (OVX), or ovariectomized with estrogen replacement (+ EB). After 14-21 days single unit, extracellular recordings of substantia nigra DA neurons were performed in anesthetized animals; both spontaneous and LHb evoked activity were obtained. Recording and stimulation locations were histologically confirmed. In the OVX group, successful surgeries were confirmed by the lack of cornified epithelial cells in vaginal lavage samples and by weight gain exceeding that seen with Sham rats. These outcomes were reversed in the + EB group. For all measures of spontaneous activity (firing rate, firing pattern, coefficient of variation, percent spikes in burst) there were no significant differences amongst groups. In all three groups, LHb stimulation (0.5 Hz, 100 us, 1.0 mA) inhibited most DA cells. However, there were no significant differences in the prevalence, duration, or magnitude of inhibition amongst the three groups. Rebound excitation, an LHb evoked response phenotype that is more prevalent in male rats, did not differ amongst the Sham, OVX, or + EB groups. Although the DA neuronal response to LHb stimulation differs by sex, this difference does not appear to be driven by circulating estrogen in female rats. It is possible that circulating androgens are responsible for this sex difference, or that the difference results from an organizational effect of hormones during development. Determining the neuroanatomical and/or neurophysiological source of this sex difference will aid in understanding the contribution of the LHb-DA inhibitory circuit to mental health disorders.

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Late-Breaking Poster

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Program #/Poster #: LBA007.013/LBA13

Topic: G.03. Motivation

Support: Nu Rho Psi Undergraduate Research Grant
CNU Summer Scholars Funding

Title: Can Fluoxetine counteract L-dopa-induced impulsivity and restore behavioral self-control in male Betta splendens?

Authors: *K. S. WATSON[1], D. DURANTE[1], E. HOFFMAN[2], J. MARTIN[1], P. E. HARRIS[1], M. FLORES-VACCARI[3], A. J. VELKEY[1];
[1]Neurosci., [2]Cell. and Mol. Biol., [3]Psychology, Christopher Newport Univ., Newport News, VA

Abstract: Previous research in our lab has demonstrated that male *B. splendens* responding for food reward in a discrete-choice instrumental-response task can exhibit behavioral self control, defined as a stable preference for larger-later (LL) over smaller-sooner (SS) food rewards. More recently, we reported that oral administration of the dopamine precursor L-DOPA to male *B. splendens* substantially reduces self-control and increases impulsive preference for the SS option. Previous literature on both humans and non-human animals indicates that the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine can be effective in decreasing aggression and impulsivity. The purpose of the present study is to determine if oral administration of fluoxetine can rescue the behavioral self-control diminished by L-DOPA in male *B. splendens*. Subjects were randomly assigned across 2 groups: fluoxetine only (F) or fluoxetine/L-DOPA combo (FD). Subjects in both groups were given a single oral dose of fluoxetine (2 mg/kg) at 9 am for one week prior to the beginning of trials and continuing throughout the duration of the trials. Additionally, subjects in the FD group were given an oral dose of L-DOPA (60 mg/kg) prior to each daily trial. Using a submerged T-maze, thrice-daily instrumental-choice trials were conducted in which subjects were presented with a choice between an SS reward (1 food pellet delivered immediately) and an LL reward (3 pellets delivered after a 15-s delay). Across the two groups, over half of all subjects were removed prior to completion of the study due to abnormal feeding or swimming patterns. Attrition was differential; nearly twice as many of the removed subjects were in the FD group as the F group. All of the remaining subjects in the FD group stabilized on the SS option, while results in the F group were mixed, with twice as many subjects stabilizing on the SS option than the LL option. Based on the stabilization rates in the FD group, it does not appear that the tested dosage of fluoxetine restores behavioral self-control when it is

disrupted by L-DOPA. Furthermore, fluoxetine-only dosing also potentially disrupts behavioral self-control in this model.

Disclosures: K.S. Watson: None. **D. Durante:** None. **E. Hoffman:** None. **J. Martin:** None. **P.E. Harris:** None. **M. Flores-Vaccari:** None. **A.J. Velkey:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Program #/Poster #: LBA007.014/LBA14

Topic: G.03. Motivation

Title: Investigating the Link Between Social Reward Sensitivity and Social Media Addiction

Authors: *K. TYSON[1], D.-M. MIREA[2], Y. NIV[1];
[2]Psychology, [1]Princeton Univ., Princeton, NJ

Abstract: With over 5 billion people using social media, it is clear that social media is becoming an important part of daily life around the world. Although social media can have a positive effect on someone's ability to connect socially through various online platforms, there is also evidence that social media can have a serious impact on (and be impacted by) mental health in ways that are unclear. The very feature of social media that signals social support, praise or validation - the social media rewards, such as likes, shares or comments - could itself be potentially harmful through reward processing mechanisms that lead to addiction. Prior research has found that looking at social media posts with more likes results in increased activity in neural regions associated with reward processing, reinforcement, and addiction. Other studies have shown that heightened activity of these regions in response to task-based social reward in early adolescence predicts social media addiction and depression in late adolescence. In order to test this connection directly from social media behavior in adults, here we use participants' whole history of Twitter data to examine how their social media addiction relates to their "behavioral reward sensitivity", i.e. how participants' posting is reinforced by how many likes they receive . We predict that people with higher symptoms of social media addiction had higher levels of reward sensitivity upon starting their account, which then decreased with the number of years of social media use. Overall, this finding would suggest that initial high reward sensitivity is a potential cause of social media addiction later on, and would corroborate neural findings in adults using participants' real-world social media data.

Disclosures: K. Tyson: None. **D. Mirea:** None. **Y. Niv:** A. Employment/Salary (full or part-time):; Princeton University.

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Topic: G.03. Motivation

Support: NIDA Grant R00 DA048119

Title: Investigating the effects of 2,5-Dimethoxy-4-iodoamphetamine on habitual behavior

Authors: *A. TSYRULNIKOV, T. AJIBADE, M. FRANCIS, A. SMITH;
Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Maladaptive habitual and compulsive behaviors are characteristic of various neuropsychiatric disorders, such as substance use disorder (SUD) and obsessive-compulsive disorder (OCD). Current pharmacotherapeutics fail to address the habitual nature of maladaptive learning and potent associations that drive compulsive behaviors. Psychedelic drugs like psilocybin increase cognitive flexibility and are currently being investigated as therapeutics for disorders like SUD and OCD. However, there have been no investigations into the effects of psychedelics on habitual behavior or the neural circuitry involved. Preliminary data from our lab shows that acute administration of the 5HT2A receptor agonist 2,5-Dimethoxy-4-iodoamphetamine (DOI) in mice leads to significant activation of cells within the parafasicular nucleus of the thalamus, a brain region known to be involved in regulating behavioral flexibility and guiding goal-directed actions. We hypothesized that psychedelics may promote cognitive flexibility by reducing habitual behavior. To test this, we used an operant model of goal-directed and habitual behavior in mice (C57BL/6, n=24). All mice were food restricted and began 5 days of operant self-administration of food pellets on a fixed ratio 1 (FR1) reinforcement schedule to induce goal-directed responding. To test whether mice were responding in a goal-directed manner, we used a satiety-induced devaluation test, in which mice were pre-fed either regular chow or food pellets to induce a valued or devalued state, respectively. Mice were then put through an extinction session where no pellets were received. Half the mice remained goal-directed and underwent devaluation after 5 days of FR1 self-administration. To induce habitual responding, the other half of the mice underwent 7 days of random interval training before undergoing the same devaluation test. 24 hours before each devaluation session, mice received an i.p. injection of either 1 mg/kg DOI or saline. DOI decreased devalued responding specifically after random interval training, suggesting that it reduces habitual responding and restores goal-directed behavior. Ongoing experiments are being performed to replicate this behavioral data, test the effect of DOI on reversal learning as a measure of behavioral flexibility, and use whole-brain c-Fos mapping to identify structures differentially activated by goal-directed vs. habitual behavior. This work addresses a critical gap in our understanding of the effect of psychedelics on behavioral flexibility and may aid in the development of novel therapeutics for psychiatric disorders rooted in habitual behaviors.

Disclosures: A. Tsyrulnikov: None. **T. Ajibade:** None. **M. Francis:** None. **A. Smith:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.016/LBA16

Topic: G.03. Motivation

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NIH grant K99DA056573
Stanford Vice Provost for Undergraduate Education Major Grant

Title: Molecular mapping of serotonin receptor expression across the mouse striatum

Authors: *M. GUO, D. F. CARDOZO PINTO, M. B. POMRENZE, N. ESHEL, R. C. MALENKA;
Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA

Abstract: The neuromodulators dopamine (DA) and serotonin (5-hydroxytryptamine; 5HT) are key regulators of motivated behaviors. In the striatum, DA drives reinforcement at least in part by differentially modulating the activity of the canonical striatal output pathways. There, DA is thought to increase the excitability of direct pathway medium spiny neurons defined by expression of Gs-coupled D1 receptors (D1-MSNs) while decreasing the excitability of indirect pathway neurons expressing Gi-coupled D2 receptors (D2-MSNs). Recently, 5HT signaling in the striatum has been shown to exert an opponent effect on reinforcement driven by DA release (Cardozo Pinto et al., 2023 BioRxiv). However, the cellular and circuit mechanisms underlying this activity remain unclear largely because we lack a comprehensive understanding of 5HT receptor organization across the striatal subregions and cell-types. Here, we used fluorescence *in situ* RNA hybridization to quantify the expression of the eight most abundant serotonin receptors across D1- and D2-MSNs in the lateral and medial compartments of the dorsal striatum as well as the ventral striatal nucleus accumbens core, lateral shell, and medial shell (dmStr, dlStr, NAcC, NAcMedSh, and NAcLatSh; respectively). We find that members of the Gi-coupled 5HT receptor 1 family are differentially organized across striatal subregions and cell-types, with one receptor exhibiting a consistent preference for D1-MSNs (*htr1f*), another exhibiting a consistent preference for D2-MSNs (*htr1d*), and yet another exhibiting a varied preference for D1- or D2-MSNs across subregions (*htr1b*). By contrast, the Gq-coupled receptors *htr2a* and *htr2c* shared a preference for D2-MSNs, but with differential expression across subregions with *htr2a* enriched

in lateral and *htr2c* in medial subregions. Finally, Gs-coupled receptors *htr4*, *htr6*, and *htr7* showed a cell-type bias favoring D2-MSNs, with the exception of a D1-MSN preference by *htr4* in the NAcMedSh and NAcLatSh regions where it was most highly expressed. Focusing on the NAcMedSh where we show 5HT inputs are densest, we find that most excitatory (i.e., Gs- or Gq-coupled) receptors are preferentially expressed in D2-MSNs, while most inhibitory (i.e., Gi-coupled) receptors are preferentially expressed on D1-MSNs. These results suggest that the same striatal neurons that are excited by DA are likely inhibited by 5HT, and vice-versa. Our work thus provides a comprehensive molecular map of serotonin receptor expression across the mouse striatum and uncovers new receptor expression motifs that may contribute to the opponent actions of DA and 5HT signaling in this part of the brain.

Disclosures: M. Guo: None. **D.F. Cardozo Pinto:** None. **M.B. Pomrenze:** None. **N. Eshel:** F. Consulting Fees (e.g., advisory boards); Boehringer Ingelheim. **R.C. Malenka:** A. Employment/Salary (full or part-time):; Bayshore Global Management. F. Consulting Fees (e.g., advisory boards); MapLight Therapeutics, MindMed, BrightMinds Biosciences.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.017/LBA17

Topic: G.03. Motivation

Support: R01 DA048280
E. JRM is a co-founder of and stakeholder in Promentis Pharmaceuticals

Title: Gender-specific mechanisms in stress-induced approach motivation deficits: the role of rtp801/redd1 and mtorc1 pathway.

Authors: *D. OLIVEIRA[1], M. K. ESTES[2], B. KURTOGLU[3], E. THOMPSON[4], A. RAMANUJAM[5], B. M. WINDSOR[6], R. A. WHEELER[7], J. R. MANTSCH[3];
[1]Phamacology and Toxicology, [2]Pharmacol. & Toxicology, [3]Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI; [4]Med. Col. of Wisconsin, Wauwatosa, WI; [5]Loyola Univ. Chicago, Chicago, IL; [7]Biomed. Sci., [6]Marquette Univ., Milwaukee, WI

Abstract: Deficits in reward processing and motivation are key symptoms of major depressive disorder (MDD). These deficits are linked to structural and synaptic neuroplastic changes in the prefrontal cortex induced by stress. Chronic stress, often present at the onset of depressive disorders, exacerbates these changes. This further impairs reward processing and contributes to the severity of MDD symptoms. The RTP801/REDD1(DNA damage-inducible transcript 4) protein, a stress-sensitive negative regulator of mTORC1 (mammalian target of rapamycin complex-1), plays a crucial role in these processes. Increased expression of RTP801/REDD1,

driven by chronic stress, produces structural alterations in dendritic spines and synaptic transmission leading to deficits in reward processing. However, activation of Rheb (Ras homolog enriched in brain), a GTP-binding protein that directly activates mTORC1, has been shown to counteract the effects of REDD1. By activating mTORC1, Rheb can rescue the structural and functional impairments caused by increased REDD1 expression. To better characterize the disruptive effects of stress on reward processing, we will examine the contribution of oral corticosterone (CORT) exposure via drinking water and chronic unpredictable stress (CUS) in the acquisition of conditioned approach behavior, using Pavlovian autoshaping in adult male and female Sprague Dawley rats (3-4 months old). CUS (twice daily stress exposure over 14 days) or oral exposure to 50 µg/mL of CORT over 14 days in the drinking water selectively reduced cue-directed behavior ($P < 0.001$) in males, but not in females as assessed in the autoshaping task. CUS and oral CORT exposure increased PrL REDD1 expression and CUS decreased phosphorylation of Raptor ($P < 0.001$), a key regulatory protein for the stability and function of mTORC1, measured 4 hours post-CUS. Preliminary study suggests a sex difference. Ongoing studies are examining effects in oral CORT exposure on phospho-raptor. RTP801/REDD1 overexpression in the PrL disrupted approach motivation in males but had no effect in females. Similarly, to assess the impact of Rheb overexpression on conditioned approach and PrL regulation, we injected AAV9-CaMKII-caRheb-mCherry or control AAV into the PrL four weeks before the autoshaping tests. Notably, Rheb overexpression significantly mitigated the effects of CUS on approach motivation in males ($p<0.001$). We are currently expanding our studies to further investigate these effects and incorporate additional controls. These findings have implications for our understanding of stress-related disorders such as MDD and have the potential to guide novel therapeutic approaches.

Disclosures: D. Oliveira: None. **M.K. Estes:** None. **B. Kurtoglu:** None. **E. Thompson:** None. **A. Ramanujam:** None. **B.M. Windsor:** None. **R.A. Wheeler:** None. **J.R. Mantsch:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Program #/Poster #: LBA007.018/LBA18

Topic: G.03. Motivation

Support: NIH Grant1 R03 DA057563-01

Title: Oxytocin receptor activation in the nucleus accumbens differentially mediates phasic and tonic dopamine release

Authors: *R. C. CRENSHAW[1], M. SYEDA[2], L. J. YOUNG[4], D. B. LESTER[3];
[1]Univ. of Memphis, Cordova, TN; [2]Univ. of Memphis, Collierville, TN; [3]Psychology Dept.,

Univ. of Memphis, Memphis, TN; [4]Ctr. for Translational Social Neurosci., Emory Univ., Decatur, GA

Abstract: Oxytocin Receptor Activation in the Nucleus Accumbens Differentially Mediates Phasic and Tonic Dopamine Release
Rebecca C. Crenshaw, Madiha Syeda, Larry J. Young, and Deranda B. Lester
Oxytocin is being researched as a new treatment option for substance use disorder. Oxytocin likely alters the rewarding properties of stimuli by altering their effects on mesolimbic dopamine release. Our lab has previously shown that oxytocin infused directly into the nucleus accumbens (NAc) reduces stimulation-evoked phasic dopamine release. The current study expands on these findings using in vivo fixed potential amperometry with carbon fiber recording electrodes in the NAc of anesthetized C57Bl/6J mice. Given that oxytocin can act on multiple types of receptors, we infused the selective oxytocin receptor agonist [Thr4, Gly7]-oxytocin (TGOT) (25 ng in 1 µl volume over 1 min) into the NAc during dopamine recordings. Dopamine release was elicited with electrical stimulations in parameters set to mimic phasic (20 pulses at 50Hz) and tonic (4 pulses at 5 Hz) activity patterns. We found that intra-NAc TGOT reduced dopamine release elicited by phasic stimulations (-22.5%) with no significant differences observed between males and females; however, intra-NAc TGOT infusions did not significantly alter dopamine release elicited by tonic stimulations (-3.5%). Phasic dopamine release in the NAc is classically thought to drive drug-related reward and learning, with phasic firing highlighting salient environmental stimuli. Oxytocin has previously shown to reduce the rewarding effects of drugs but promote the salience of social stimuli. Although more research is needed, the present findings lend support to the hypothesis that oxytocin's opposing influence on drug vs social reward may be related to its differential mediation of phasic vs tonic dopamine release.

Disclosures: R.C. Crenshaw: None. **M. Syeda:** None. **L.J. Young:** None. **D.B. Lester:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.019/LBA19

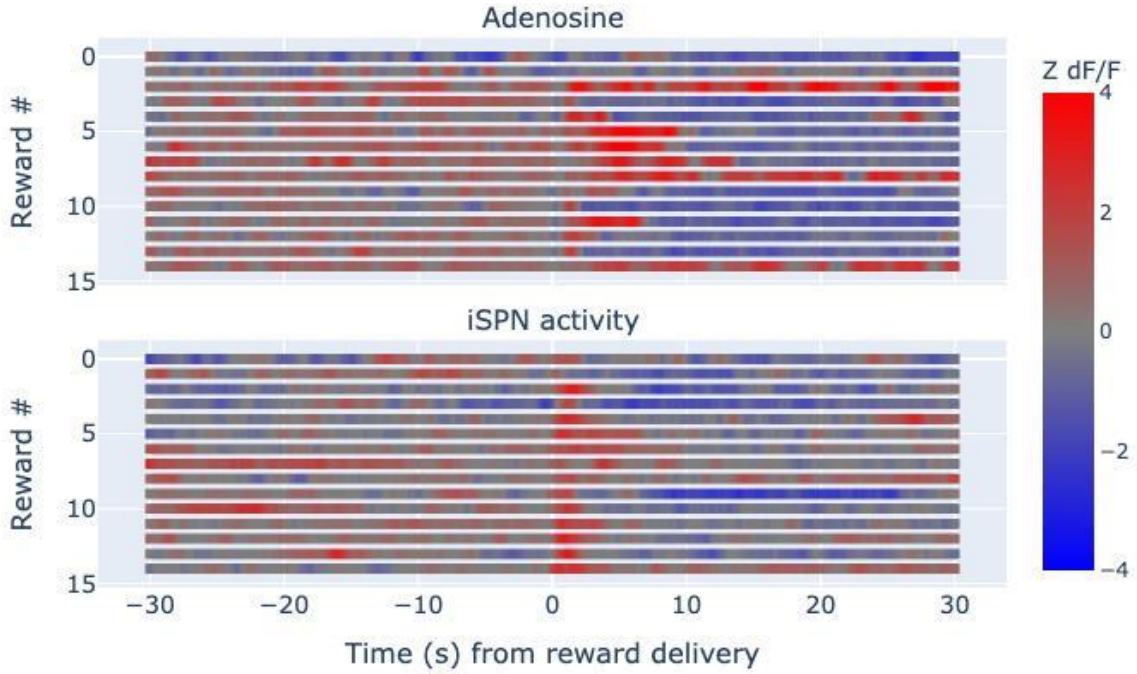
Topic: G.03. Motivation

Title: Adenosine, dopamine, and indirect pathway signaling during escalating effort to obtain reward

Authors: *R. P. FAUST[1], J. A. BEELER[2];
[1]Psychology, Queens Col., Flushing, NY; [2]Psychology, Queens Col. CUNY, Flushing, NY

Abstract: The motivational functions of striatal adenosine remain poorly understood despite high expression of adenosine 2A receptors (A2ARs) on indirect pathway striatal projection

neurons (iSPNs). Genetic and pharmacological manipulation of A2ARs in medial striatum alters motivation to work for reward in a manner indicating that adenosine opposes the activating effects of dopamine. However, in contrast to dopamine, fast adenosine dynamics during effort exertion have not been characterized. To explore the relationship between adenosine, iSPN dynamics and effort, we employed fiber fluorometry to monitor dopamine, adenosine, and iSPN activity in the nucleus accumbens core of mice in a progressive ratio (PR) paradigm (n=4 adult WT mice transduced with GRAB-rAdo1.3 + GRAB-gDA3m; n=4 adult A2A-Cre mice transduced with GRAB rAdo1.3 + Cre-dependent GCaMP8m). Complete videos of each progressive ratio session were recorded with an overhead infrared camera. The accompanying figure displays heatmaps of Z-scored changes (dF/F) in adenosine levels and iSPN activity aligned to reward delivery for each reward earned by a representative A2A-Cre mouse on a PR5 schedule. Adenosine levels fluctuated or increased while mice lever pressed for reward; sustained decreases were rarely observed during lever pressing. Cues signaling reward delivery evoked phasic increases in dopamine release and iSPN activity. Adenosine levels during reward retrieval positively correlated with apparent effort exerted to retrieve each reward. After successful reward retrieval, adenosine levels decreased rapidly, and this decrease persisted until reward consumption was complete. Similar dips in adenosine also occurred during grooming bouts. These results are consistent with previous findings that striatal adenosine accumulates during locomotion (Ma et al., Nature 2022) and suggest that it may signal physical effort.



Disclosures: R.P. Faust: None. **J.A. Beeler:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.020/LBA20

Topic: G.03. Motivation

Support: NIH R01MH122622

Title: Contributions of Dopamine Receptor Subtypes in the Nucleus Accumbens to Social Reward

Authors: *E. A. CROSS[1], H. ALBERS[2];
[1]Georgia State Univ., Atlanta, GA; [2]Georgia State Univ. Neurosci. Inst., Atlanta, GA

Abstract: The Nucleus Accumbens (NAc) is a key component of the mesolimbic dopamine system (MDS), which plays an important role in the expression of many motivated behaviors. Here, we investigated the role of dopamine (DA) receptors in the NAc in the rewarding properties of social interactions. The NAc contains multiple subpopulations of medium spiny neurons (MSNs) with one population expressing D1-type dopamine receptors (D1Rs), another expressing D2-type receptors (D2Rs), and a third expressing both. D1Rs are excitatory G_s coupled G-protein coupled receptors (GPCRs), whereas D2Rs are inhibitory and G_i coupled. For decades, it has been proposed that these two receptor populations work in opposition to produce balanced motor output, and more recently, the same dichotomy has been proposed for valanced behaviors. The canonical view is that D1Rs mediate reward and approach while D2Rs mediate aversion and avoidance. There is a significant gap in our knowledge, however, in the roles of these receptor subtypes in the context of the rewarding properties of social behavior. In this study, we tested the hypothesis that DA receptors in the NAc modulate the rewarding properties of social interactions with D1R activation increasing social reward and D2R activation decreasing social reward. This was evaluated by utilizing the selective D1R antagonist, SCH23390, and the D2R antagonist, eticlopride, injected into the NAc prior to an operant social preference (OSP) task. The results support the hypothesis that D1Rs are critical for social reward, because D1R antagonism by SCH23390 in the NAc decreased social entries, social preference score (SPS), and increased the latency to enter a chamber with a social stimulus. Post hoc analyses revealed that this effect was driven primarily by the data obtained in females, however the same relationship existed in males. Additionally, we tested the hypothesis that antagonism of D2Rs in the NAc increases social reward. The results, however, do not support this hypothesis. D2R antagonism by eticlopride had no statistically significant effect on entries, SPS, or latency in OSP. Therefore, the role of D2Rs in social reward remains unclear and requires further investigation.

Disclosures: E.A. Cross: None. **H. Albers:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.021/LBA21

Topic: G.03. Motivation

Title: Educational motivation to acquire knowledge, attitudes and practices in the diagnosis of pulmonary tuberculosis (PT) in nursing students.

Authors: *J. ARIAS-RICO[1], A. DURAN VALERIO[2], E. RAMÍREZ MORENO[3], R. BALTAZAR TELLEZ[4], I. MORENO-VITE[4], Z. CALDERÓN-RAMOS[6], Z. OLGUÍN[5], J. HERNÁNDEZ-HERNÁNDEZ[7];
[1]Univ. Autonoma Del Estado De Hidalgo, Pachuca, Mexico; [2]Univ. Autónoma del Estado de Hidalgo, México., Metztitlán, Mexico; [3]Univ. Autónoma del Estado de Hidalgo, Pachuca, Hidalgo, Mexico; [4]Univ. Autónoma del Estado de Hidalgo, Pachuca de Soto, Mexico; [5]Univ. Autónoma del Estado de Hidalgo, Minerald e la Reforma, Mexico; [6]Univ. Autonoma del Estado de Hidalgo, SAN AGUSTIN TLAXIACA, Mexico; [7]Univ. Autónoma del Estado de Hidalgo, México, México, Mexico

Abstract: Nursing professionals often underestimate the importance of learning habits and the efficacy of instructional strategies for their development. It is therefore recommended that teaching training be provided which allows for the use of successful teaching methods and strategies and facilitates self-regulated learning in clinical practice students. The objective of this study was to evaluate the association between an educational intervention designed to motivate nursing students to acquire knowledge, attitudes, and practices in the diagnosis of pulmonary tuberculosis. Methods: The study design is analytical, comparative, and quasi-experimental, with the sample size corresponding to the population of a nursing school with a technical level, which is 100% of the enrolled nursing students. From this sample and in accordance with the criteria of elimination and exclusion, a population of 75 subjects signed the informed consent form and the participants' privacy form, according to the ethical standards. The database was structured based on a survey that included three distinct steps: the administration of a pre-test, an educational intervention, and a post-test. The statistical analysis was conducted using the Stata 16 program, which calculated mean, standard deviation, percentages, univariate analysis, and the Student's t-test. The statistical significance was determined using a p-value ≤ 0.05. Results: In the initial evaluation of the students (pretest), it was found that 53.3% had low knowledge, attitudes, and practices. After the intervention, another evaluation was carried out and found values of 79% in the three variables (posttest). Comparing the initial and final diagnosis of the population's knowledge, practices, and attitudes, the average initial diagnosis was 4.9 (CI 4.63 - 5.26), while the average final diagnosis increased significantly to 7.2 (CI 7.00 - 7.41, $p \leq 0.05$). Conclusion: These results suggest a positive impact of the intervention, reflected in a significant improvement

in knowledge, attitudes, and practices in the diagnosis of tuberculosis among the surveyed population.

Disclosures: J. Arias-Rico: None. **A. Duran Valerio:** None. **E. Ramírez Moreno:** None. **R. Baltazar Tellez:** None. **I. Moreno-Vite:** None. **Z. Calderón-Ramos:** None. **Z. Olguín:** None. **J. Hernández-Hernández:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.022/LBA22

Topic: G.04. Emotion

Title: An electrophysiological investigation of fight-flight defense responses in humans using 3d virtual reality environment

Authors: *V. MAITHANI[1], K. FAUJDAR[2], M. K. ASTHANA[3];
[1]Humanities and Social Sci., Indian Inst. of Technology, Roorkee, Roorkee, India; [2]Dept. of Cognitive and Brain Sci., Indian Inst. of Technology, Gandhinagar, Gandhinagar, India; [3]Dept. of Humanities & Social Sci., Indian Inst. of Technol. Roorkee, Roorkee, India

Abstract: Fear is an intense emotion in response to an imminent threat resulting in fight-or-flight defense responses, integrating it as an essential part of the survival mechanism. In the predatory imminence continuum, with one end denoting complete safety and the other depicting the chances of being consumed by a predator, the defense response changes as the psychological perception of the threat imminence increases. The current study investigated the fight/flight responses in humans and underlying neural correlates using EEG in a 3D virtual reality (VR) simulation. Sixteen participants (Mean age (SD)=23.94 (3.45)) participated in the study. The participants were presented with a desktop VR environment from a first-person perspective in an urban street view. The experiment consisted of 2 phases: The training (familiarisation with the task and controls) and the experimental phases. The experimental phase consisted of 5 conditions. Conditions 1 to 4 included a threat avatar, presented pseudo-randomly in 1 of the streets. The conditions differed based on the proximity of threat (distal versus proximal) and the escapability of the participant's avatar (escape versus no escape). Condition 5 included no threat. A total of 20 trials were presented, with each condition presented 4 times. At the appearance of the threat, participants responded with Fight/Flight response followed by a rest scene of 10s and a fixation of 5s. An 8-channel EEG was recorded for the Frontal regions to analyse the power of different frequency bands across conditions. A chi-square test indicated no significant difference between fight/flight responses across 4 conditions. A Wilcoxon signed rank test indicated significant difference between Fight/Flight responses only in 'Proximal Threat No Escape' condition, z=-2.20, p=0.03. A Friedman test for reaction time indicated significant difference

across 4 conditions, X2 (3, N=16) =10.725, p=0.01. A time-frequency analysis of EEG data (N=9) showed peaks in delta power at certain points for all conditions, however an overall low power was assessed for all the frequency bands across conditions. The findings indicate a heightened fight over flight response for all conditions. A reason for an increase in fight responses is because in the VR environment there were no consequences to their action in contrast to real life scenarios. Further, a significant difference in reaction time shows a distinct mechanism for proximity of the threat and possibility of escape. In addition, the delta power observed across conditions may indicate not only the involvement of emotional (threat) and cognitive (fight/flight) component, but different neural signatures.

Disclosures: V. Maithani: None. **K. Faujdar:** None. **M.K. Asthana:** None.

Late-Breaking Poster

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Topic: G.04. Emotion

Support: NIH Grant R01MH134972-01A1
NIH Grant K12GM000680-19

Title: The human auditory pathway encodes looming sound intensity

Authors: *M. K. THIEU[1], P. A. KRAGEL[2];
[2]Psychology, [1]Emory Univ., Atlanta, GA

Abstract: The ability to detect and avoid looming threats is critical for survival, a feat accomplished by brain pathways linking the cortex and multiple midbrain nuclei. Looming sounds evoke stronger firing in the primary auditory cortex of rodents and nonhuman primates. Primate neuroimaging studies have revealed that looming evokes stronger BOLD responses in the auditory cortex, superior temporal gyrus, and amygdala. Cortical projections convey information about looming objects to the superior colliculus, a midbrain structure that responds to salient, aversive events to coordinate defensive behavior. However, it remains unclear whether these regions represent looming *per se* or reflect more general qualities of aversive sounds. Here we evaluated these accounts by comparing encoding models trained to predict brain responses to naturalistic aversive sounds along stages of the auditory pathway. First, we trained a shallow convolutional network to classify cochleagrams of simulated moving sounds that collide with or miss the listener. We used representations of looming from the convolutional network to predict BOLD response patterns elicited by two varieties of aversive sounds: an environmental sound with sharp intensity ramping (a knife scraping on a bottle), and complex vocalizations (e.g., yelling, crying). We trained models for the inferior colliculus, superior colliculus, primary

auditory cortex, and amygdala. To assess the distinctiveness of looming compared to other auditory features, we contrasted looming encoding models with models constructed using overall sound intensity, acoustic roughness and features from deep neural networks for speech recognition. We used leave-one-subject-out cross validation to quantify model performance and prediction across stimulus types to assess generalizability. We found evidence that looming is encoded in the auditory pathway and better predicts responses to basic compared to complex sounds. Looming models trained on knife-scraping generalized better than those trained on vocalizations in primary auditory cortex (Cohen's d = 1.30), amygdala (d = 0.63), and superior colliculus (d = .29). Conversely, the models trained using speech recognition and roughness features showed better generalization when trained on vocalizations in amygdala (speech: d = -0.56, roughness: d = -0.88), and superior colliculus (speech: d = -0.82, roughness: d = -1.03). Together, these findings demonstrate that looming is encoded in the human auditory pathway, and simple representations of ramping stimulus intensity generalize to predict brain responses to complex, naturalistic sounds across stimulus types and individuals.

Disclosures: M.K. Thieu: None. **P.A. Kragel:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Program #/Poster #: LBA007.024/LBA24

Topic: G.04. Emotion

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Hope for Depression Research Foundation
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NIH Grant 1R01EB026937
NIH Grant 1R01MH125430

Title: Awidespread oscillatory network to selectively target aggressive behavior in real-time

Authors: *Y. GROSSMAN[1], A. TALBOT[1], N. M. GALLAGHER[1], G. E. THOMAS[1], A. FINK[3], K. WALDER[1], S. J. RUSSO[4], D. E. CARLSON[2], K. DZIRASA[5];
[2]Electrical and Computer Engin., [1]Duke Univ., Durham, NC; [3]Neurosci., Icahn Sch. of Med. At Mount Sinai Grad. Training Program In Neurosci., New York, NY; [4]Neurosci., Icahn school of medicine at mount sinai, New York, NY; [5]Duke Univ. Med. Ctr., Durham, NC

Abstract: Aggression is a prevalent, necessary, social behavior. However, agonistic social behavior can be detrimental to individuals and social groups under conditions of behavioral pathology. While several brain regions have been identified as loci for aggression encoding, none of these neural structures are uniquely responsive during aggression. Therefore, targeting

any of these structures for treatment impacts many other aspects of behavior. Better understanding of brain-wide encoding of aggressive behavior could facilitate development of treatments to selectively mitigate aggression without impacting other behavior aspects. We proposed using machine learning to identify a widespread network incorporating multiple brain regions capable of distinguishing attack from social behavior. We hypothesized that this network, which would be causally linked to aggressive state, could sync optogenetic stimulation events to specifically target aggressive behavior. To accomplish these goals, we implanted male CD1 mice with multiwire recording electrodes in the ventromedial hypothalamus, lateral septum, medial amygdala, nucleus accumbens, lateral habenula, mediodorsal thalamus, ventral hippocampus, infralimbic cortex, prelimbic cortex, lateral orbitofrontal cortex, and the primary visual cortex. We then recorded from the implanted CD1 mice as they engaged in attack and non-attack social behavior. Using machine learning algorithms, we generated a network (*EN-AggINH*) capable of discriminating attack behavior from non-attack behavior (n=20 for training network, n=9 for testing network). We further validated that this novel network using chemogenetics (n=8) and aggression-inducing stimuli (n=8). We then used this network to deliver closed-loop optogenetic stimulation to the prefrontal cortex (PFC; n=9). Closed-loop stimulation was sufficient to decrease aggressive behavior in CD1 mice as well as shift *EN-AggINH* activity, with no significant effects on locomotion or social behavior. Using mediation analysis for the closed-loop and chemoenetic experiments, we demonstrated that shifts in attack behavior were largely mediated by *EN-AggINH* activity. Furthermore, we used the network to identify novel circuits for aggression mitigation (PFC->NAc, n=8; PFC->MeA, n=8; PFC->LHb, n=8). By targeting circuits identified by the network, we demonstrated mechanistic relevance of *EN-AggINH*. This research identifies a network robustly and causally associated with aggression that can be used to selectively target aggressive state while maintaining other social and locomotor behaviors.

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Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.025/LBA25

Topic: G.04. Emotion

Support: R01DA053581
R01MH105592
F32MH135620

Title: Transcriptomic diversity of basolateral amygdala cell types across humans and non-human primates

Authors: *M. TOTTY[1], S. V. BACH[2], M. R. VALENTINE[3], M. STOCKER[5], J. E. KLEINMAN[6], S. C. PAGE[7], T. M. HYDE[8], K. MARTINOWICH[4], V. D. COSTA[9];
[1]Johns Hopkins Bloomberg Sch. of Publ. Hlth., Baltimore, MD; [2]LIBD, [3]Lieber Inst. for Brain Develop., Baltimore, MD; [4]Lieber Inst. for Brain Develop., Pasadena, MD; [5]Oregon Hlth. and Sci. Univ., Portland, OR; [6]Clin. Sci., Lieber Inst. For Brain Develop., Washington, DC; [8]Genet. Neuropathology, [7]Lieber Inst. For Brain Develop., Baltimore, MD; [9]Dept. of Behavioral Neurosci., Oregon Natl. Primate Res. Ctr., Beaverton, OR

Abstract: The amygdala is a limbic brain region whose dysfunction has been implicated in numerous psychiatric disorders including post-traumatic stress disorder, substance use disorder, and major depression. In primates, the basolateral complex of the amygdala (BLA) is a cortical-like structure that is composed of various anatomical subregions, including the lateral (LA), basal (BA), accessory basal (aBA), and central nuclei (CeA), which have divergent connectivity with downstream target regions and are linked to specific cognitive and behavioral functions in preclinical models. The ability to differentially target cell-types within these subregions is of great interest for the potential development of novel therapeutics. However, the molecular identities of cell-types that differentiate the BLA in humans, and how well conserved they are across species, remain entirely unknown. To address this, we performed single-nucleus RNA sequencing (10X Genomics Chromium v3) of the BLA in humans (n=5) and two non-human primate (NHP) species (macaque, n=5; baboon, n=3). Due to difficulties in accurately identifying BLA subnuclei in postmortem human brains, the entire BLA was carefully dissected and sequenced in humans. In NHPs, however, precise punches of either the LA, BA, aBA, or CeA were performed. Following standard pre-processing and data integration procedures we found 12 distinct excitatory cell-type clusters and 18 inhibitory cell-type clusters that were well-mixed across species. Using the anatomical locations from dissected NHP samples, we found a number of excitatory cell-types that were specific to either the LA (2 clusters), BA (2 clusters), and aBA (1 cluster) subregions. Using pseudobulk differential expression analysis, we discovered novel marker genes for the LA (GULP1) and BA (COL25A1) subregions which were further validated using fluorescent in situ hybridization in both NHP and humans. We additionally found four inhibitory cell-types that were enriched in CeA punches, including one intercalated cell-type, while all other 14 inhibitory cell-types were well-mixed across subregions. All cell-types showed relatively strong conservation as determined by cross-species cell-type classification (mean AUROC > 0.7). Collectively, we have confirmed the first subregion-specific marker genes for excitatory neurons in humans and NHPs. This data will be made available publicly following publication; and thus, will be a valuable resource for developing targeted therapeutics in the amygdala.

Disclosures: M. Totty: None. **S.V. Bach:** None. **M.R. Valentine:** None. **M. Stocker:** None. **J.E. Kleinman:** None. **S.C. Page:** None. **T.M. Hyde:** None. **K. Martinowich:** None. **V.D. Costa:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.026/LBA26

Topic: G.04. Emotion

Support: NINDS Grant 5R01NS114405

Title: Identifying the neural correlates of rumination: A lesion-symptom mapping approach

Authors: *E. BRANDT[1], J. E. BRUSS[4], A. D. BOES[2], D. TRANEL[3];
[2]Pediatrics, Neurol. & Psychiatry, [3]Dept Neurol, [1]Univ. of Iowa, Iowa City, IA; [4]Neurol., UIHC, Iowa City, IA

Abstract: Background. Rumination may be defined as obsessional thinking involving excessive, repetitive thoughts that interfere with other forms of mental activity. It is thought to be a transdiagnostic symptom of mood and anxiety disorders. Previous work using fMRI suggests that the default mode, frontoparietal, and salience networks may all be involved in rumination. However, previous work has focused on state rumination in which individuals are actively engaging in rumination. Less attention has been given to trait rumination, or one's general tendency to engage in ruminative thinking, which may be more closely associated with psychopathology. The present study leverages a lesion-symptom mapping approach to examine the neural correlates of trait rumination. We hypothesized that lesions to the default mode network will be associated with lower levels of trait rumination, while lesions to the frontoparietal and salience networks will be associated with higher levels of trait rumination. **Methods.** We included 169 adults from the Iowa Lesion Patient Registry, who were in the chronic epoch (> 3 months) following focal brain lesion. All participants completed the Minnesota Multiphasic Personality Inventory (MMPI), a comprehensive self-report measure of personality traits. The Stress and Worry subscale from the MMPI was used as a measure of trait rumination with higher scores indicating higher-than-average levels of trait rumination and lower scores indicating lower-than-average levels of trait rumination. Lesion-symptom mapping was used to identify lesion locations associated with higher and lower levels of trait rumination. **Results.** We found that lesions to the default mode network, in particular the right ventromedial prefrontal cortex and left inferior parietal lobule, were associated with lower levels of trait rumination. In other words, decreased functioning in these regions was associated with a decreased tendency to ruminate. We did not find a significant association between rumination and lesions to the frontoparietal or salience networks. **Conclusion.** These findings suggest that hyperactivity in areas of the default mode network may be involved in excessive rumination associated with mood and anxiety disorders. This provides further evidence for the role of the default mode network in internalizing disorders.

Disclosures: E. Brandt: None. **J.E. Bruss:** None. **A.D. Boes:** None. **D. Tranel:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.027/LBA27

Topic: G.04. Emotion

Support: STI2030-Major Projects 2021ZD0202803

Title: A Brainstem Circuit Amplifies Aversion

Authors: *Y. ZHOU;
Chinese Inst. for Brain Res., Beijing, China

Abstract: Dynamic gain control of aversive signals enables adaptive behavioral responses. While the role of amygdalar circuits in aversive processing is well established, the neural pathway for amplifying aversion remains elusive. Here, we show that the brainstem circuit linking the interpeduncular nucleus (IPN) with the nucleus incertus (NI) amplifies aversion and promotes avoidant behaviors. IPN GABA neurons are activated by aversive stimuli and their predicting cues, with their response intensity closely tracking aversive values. Activating these neurons does not trigger aversive behavior on its own but rather amplifies responses to aversive stimuli, whereas their ablation or inhibition suppresses such responses. Detailed circuit dissection revealed anatomically distinct subgroups within the IPN GABA neuron population, highlighting the NI-projecting subgroup as the modulator of aversiveness related to fear and opioid withdrawal. These findings unveil the IPN-NI circuit as an aversion amplifier and suggest potential targets for interventions against affective disorders and opioid relapse.

Disclosures: Y. Zhou: None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.028/LBA28

Topic: G.04. Emotion

Support: NIH Grant R01
Autism Science Foundation

Title: Aberrant affective empathic responses in SHANK3 autism mouse model

Authors: *S. QIAO, Y.-H. JIANG;
Yale Univ., New Haven, CT

Abstract: Affective empathy is defined as that an individual can percept and respond to other's emotion. Abnormal empathy is considered as one of the hallmarks for autism spectrum disorder (ASD) and other psychiatric disorders. Studies from both human and rodents have suggested that anterior cingulate cortex (ACC) and basomedial amygdala (BLA) associated ensembles are implicated in empathy. However, how empathy behavior changes and its underlying mechanisms in ASD remain poorly understood. *SHANK3* is one of the most replicated causative ASD genes from human ASD genomics studies. We hypothesize that *SHANK3* deficits in ACC-BLA circuit leads to abnormal affective empathy in ASD. Using the *Shank3* exon 4-22 deletion (*Shank3*$^{\Delta e4\text{-}22}$) mouse model (*Shank3*-KO), we investigated affective empathy behavior in ASD through social fear transfer behavior assay. A wild-type (WT) demonstrator mouse experiences a series of foot shocks while a *Shank3*-KO or WT observer mouse freeze behavior is scored during the process and then compared. Unexpectedly, we found that *Shank3*-KO mice significantly freeze longer than WT, suggesting that *Shank3* deficiency results in exaggerated affective empathy responses. Moreover, conditional inactivation of *Shank3* in ACC decreased freezing duration, suggesting a role of *Shank3* of ACC in mediating normal fear transfer process. Whereas conditional deletion of *Shank3* in BLA increased freeze time, recapitulating the phenotype from *Shank3*-KO mice. Further optogenetic inhibition on ACC-BLA circuit restored the elevated fear transfer responses in *Shank3*-KO mice. These results imply that *Shank3* in ACC-BLA circuit is pivotal in modulating affective empathy behaviors. To explore the cellular mechanism, *in vivo* Ca^{2+} signals of neuronal activity were recorded in WT and *Shank3*-KO BLA excitatory neurons with fiber photometry. WT mice neurons activity increased as expected after shocks began, but *Shank3*-KO mice neuron activity is inhibited after shocks began. When compared to WT, *Shank3*-KO neurons Ca^{2+} signals are bigger in habituation period while the signals are smaller in fear transfer stage. It suggested that *Shank3* deficiency causes BLA neurons overactivation, which impairs neuron responses to emotion transfer stimuli and results in aberrant empathy behavior. Our results support a critical role of *Shank3* in ACC-BLA circuit in aberrant fear transfer behavior in ASD model. This study offers valuable insights into the empathy behaviors in ASD, presents a unique opportunity to dissect the underlying cellular mechanisms, and lays the groundwork for the circuit based behavioral treatment for ASD.

Disclosures: S. Qiao: None. **Y. Jiang:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.029/LBA29

Topic: G.04. Emotion

Support: NIMH R01MH118441

Title: Infralimbic projections to the ventral pallidum/ substantia innominata constrain freezing during fear extinction learning

Authors: *M. G. SCLAR[1], C. FERNANDES HENRIQUES[2,4], Y. GUETTA[3], Y. MIURA[2,4], R. ZHANG[2], E. LIKHTIK[2,4], A. K. FRIEDMAN[2,4];
[2]Biol., [3]Psychology, [1]Hunter College, CUNY, New York, NY; [4]Biol. Program, The Grad. Center, City Univ. of New York, New York, NY

Abstract: Fear extinction learning and retrieval are essential for overcoming fear, allowing an organism to decrease defensive responses to previously threatening stimuli. The infralimbic cortex (IL) is known to facilitate extinction memory retrieval via its projections to the basolateral amygdala (BLA), but the circuits that facilitate its role in extinction learning remain less clear. Given the robust connections of the IL with the attention- and action- modulating nuclei of the basal forebrain, we investigated the involvement of this pathway in extinction, and compared it to the IL-BLA circuit. More specifically, we were interested in the ventral pallidum/substantia innominata (VP/SI) subnuclei of the basal forebrain, given their previously demonstrated role in modulating behavior in aversive and appetitive tasks. First, using retrograde tracing combined with immunohistochemistry labeling for the immediate early gene cFos, our results show distinct neuronal populations within the IL that differentially project to the BLA and VP/SI. Whereas superficial (L2/3) IL neurons primarily target the BLA and are most active during extinction retrieval, both L2/3 and deeper (L5) IL layers project to the VP/SI, with only the L5 VP/SI projectors becoming preferentially active during extinction learning. Next, using *in vitro* patch clamp recordings of IL-VP/SI projectors, we show that they have increased excitability during extinction learning, followed by decreased excitability during retrieval, as well as lower rheobase at the end of extinction learning compared to retrieval. Lastly, to evaluate the functional significance of this pathway, we used the inhibitory opsin *enhanced Archaerhodopsin* (eArch3.0) to inhibit IL terminals in the VP/SI during extinction learning. Our findings show that inhibiting IL input to the VP/SI kept defensive freezing high compared to controls, thereby slowing extinction learning without affecting next-day extinction retrieval. These results suggest that IL projections to the VP/SI become more active and excitable during extinction learning. Further, IL inputs to the VP/SI constrain defensive freezing during learning. Taken together with previous work, we propose that IL communication with downstream targets during extinction functions as a switchboard, with IL-VP/SI communication increasing during extinction learning and IL-BLA communication increasing during retrieval.

Disclosures: M.G. Sclar: None. **C. Fernandes Henriques:** None. **Y. Guetta:** None. **Y. Miura:** None. **R. Zhang:** None. **E. Likhtik:** None. **A.K. Friedman:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.030/LBA30

Topic: G.04. Emotion

Support: Whitehall Foundation
T. Denny Sanford Institute for Empathy and Compassion, UCSD

Title: Food deprivation suppresses the social transfer of pain in mice

Authors: *A. V. NGUYEN[1], J. ZHANG[2], P. REZAIE BOROON[2], K. CONWAY[2], M. L. SMITH[1,2];
[1]Neurosciences, [2]Neurobio., Univ. of California San Diego, La Jolla, CA

Abstract: Prioritizing competing needs is essential for survival. Dr. Abraham Maslow conceptualized this as a ‘Hierarchy of Needs’ which posits that physiological needs like hunger are prioritized over psychological needs like social interaction. However, the underlying neural circuits that prioritize feeding over social needs remain largely unexplored. We developed a "social transfer of pain" model to study empathy-like behavior in mice where 'bystander' mice exhibit pain and negative affective states after interacting with a partner experiencing inflammatory pain. To understand how competing physiological and psychological need states affect behavior, we sought to determine how food deprivation of bystander mice impacted their acquisition of socially transferred pain. Given the strong evidence that food deprivation suppresses both social behaviors such as maternal care and pain related behaviors in mice, we hypothesized that food deprived bystanders would not develop mechanical hypersensitivity. To test this, bystander mice were food deprived for 8-24 hours immediately preceding social interaction with a mouse given an inflammatory pain stimulus. We found that 24-hour food deprived bystanders did not acquire mechanical hypersensitivity following this social interaction indicating that food deprivation impairs the social transfer of pain in mice. Future experiments will explore whether food deprivation also attenuates other pain and affective phenotypes in bystanders following the social transfer of pain. Further exploration of the neural circuits underlying this behavior could reveal the endogenous mechanisms by which social information about pain is inhibited, offering critical insights into the neurobiology underlying prioritization of competing needs and the interaction between feeding and pain circuitry.

Disclosures: A.V. Nguyen: None. **J. Zhang:** None. **P. Rezaie Boroon:** None. **K. Conway:** None. **M.L. Smith:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.031/LBA31

Topic: G.04. Emotion

Support: NIH R01MH110483
NIH R21MH125277-01A1

Title: Covid-19 pandemic related loneliness associated with ptsd symptoms and amygdala and subnuclei volumes in trauma survivors.

Authors: *M. GUENTHER[1], S. CHANDRA[1], A. AMER[1], C.-H. SHIH[2], X. WANG[1], H. XIE[1]; [1]Neurosciences and Psychiatry, [2]Emergency Med., The Univ. of Toledo Col. of Med. and Life Sci., Toledo, OH

Abstract: Background: The COVID-19 pandemic caused significant mental problems globally due to fear of infection and social isolation. However, how trauma survivors respond to the pandemic and if the amygdala plays a neuropathological role remains unknown. This study tested perceived pandemic loneliness, PTSD severity, and amygdala volume in previous trauma survivors. Methods: Fifty-seven life-threatening trauma survivors from an acute PTSD study (2016-2020) were recruited. The participants completed COVID-related interpersonal needs questionnaire (INQ), social interaction (CSI), and PTSD checklist (PCL) online surveys, the virtual PTSD diagnosis interview, and structural MRI (sMRI) scans to measure amygdala and subnuclei volumes. Pre-pandemic PTSD history and COVID infection information were collected. The relationships between the psychological assessments and amygdala volumes were tested using partial correlations. The effects of PTSD history, COVID infection, and pandemic PTSD diagnosis on amygdala and subnuclei volumes were tested using univariate ANOVA analyses. Results: A total of 55 subjects were diagnosed pandemic PTSD (N=22) or nonPTSD (N=33). 14 out of 18 PTSD (77.8%) and 10 out of 29 nonPTSD subjects (34.5%) had pre-pandemic PTSD ($\chi 2 = 0.004$). There were 19 subjects with a COVID infection distributed in both the PTSD and nonPTSD groups ($\chi 2 = 0.517$). The results showed that INQ and CSI scores in the pandemic PTSD group were higher than in the nonPTSD group (*ps* = 0.015 and 0.046). INQ scores were significantly positively correlated with PCL scores ($p = 0.003$). INQ and PCL scores were negatively associated with left amygdala volume (*ps* = 0.044 and 0.048) and INQ scores correlated with right amygdala volume at trend level ($p = 0.053$). The effect of pre-pandemic PTSD history, but not pandemic PTSD diagnosis or COVID infection, was significant on right amygdala medial nucleus volume ($p = 0.02$, FDR corrected), which was smaller in the subjects with pre-pandemic PTSD than the subjects without PTSD history. Conclusion: These results suggest that pandemic PTSD subjects had more severe loneliness which was negatively associated with amygdala volumes. Further results suggest that reduced right amygdala medial nucleus volume related to previous PTSD history may contribute to stress maladaptation during the pandemic.

Disclosures: M. Guenther: None. **S. Chandra:** None. **A. Amer:** None. **C. Shih:** None. **X. Wang:** None. **H. Xie:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.032/LBA32

Topic: G.04. Emotion

Title: Impact of 2-AG inhibition on fear and stress responses in mice

Authors: *S. M. CHARLES;
Northwestern Univ., Chicago, IL

Abstract: Impact of 2-AG Inhibition on Fear and Stress Responses in Mice
Maladaptive fear responses are a hallmark of stress-related psychiatric disorders, such as anxiety and PTSD. The endocannabinoid (eCB) system is a retrograde inhibitory signaling pathway. It includes the cannabinoid receptors, endogenous ligands (2-AG and AEA), and their respective enzymes responsible for maintaining homeostasis and regulating stress responses. Growing preclinical evidence implicates 2-AG as a key player in modulating stress adaptation and anxiety-like behaviors in rodents. Thus, the current study examined how altered 2-AG levels modulates stress and fear responses. Adult mice (C57BL/6J) underwent serial compound stimulus (SCS) fear conditioning paradigm to observe shifts in passive to active state defensive responses to imminent threat (Fadok, 2021). Briefly, a 7.5 kHz pure tone is played for 10 seconds, immediately followed by white noise for 10s, and then ends with a 1s shock at 0.9 mA. We utilized DO34, an inhibitor of the 2-AG synthesis enzyme, to lower 2-AG levels globally. DO34 was delivered via intraperitoneal injection on conditioning days to assess the effect of 2-AG levels on types of defensive responses and acquired fear learning. Increased flight responses among DO34 treated animals during white noise was observed as well as increased freezing during pure tone when compared to vehicle mice. Additionally, we examined differences in innate fear responses by subjecting mice to a looming shadow that mimics an aerial predator approaching. Here, we found decreased exploratory behavior in DO34-treated mice as well as an increase in avoidant behavior after first exposure to shadow. While differences between vehicle and DO34 mice were observed in both behavioral paradigms, further studies observing both conditioned and innate defensive behaviors in response to various threatening stimuli are necessary to further understand stress-related pathology in humans.

Disclosures: S.M. Charles: None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

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Program #/Poster #: LBA007.033/LBA33

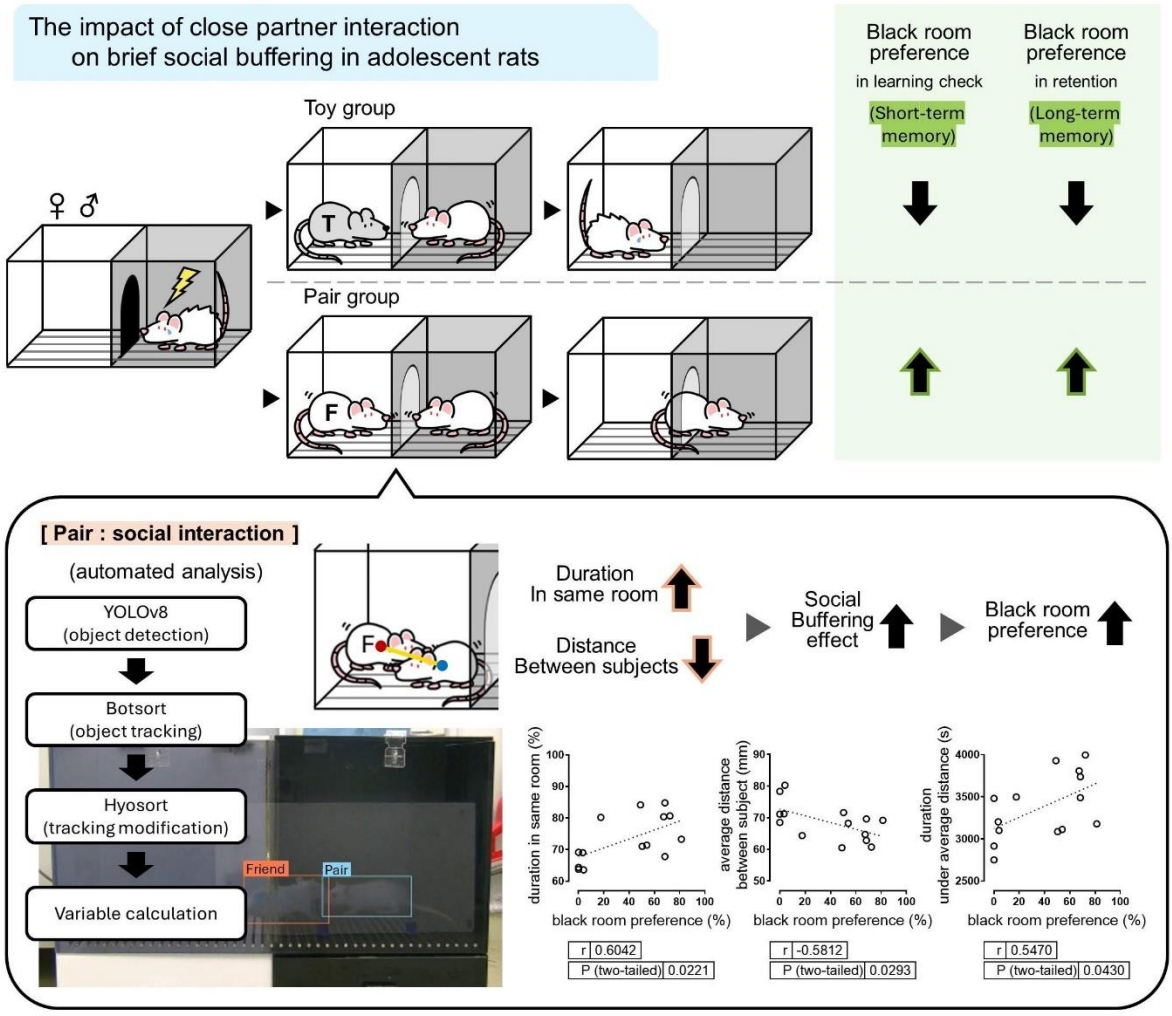
Topic: G.04. Emotion

Support: NRF-2023R1A2C2005346

Title: The impact of close partner interaction on brief social buffering in adolescent rats

Authors: *M. SEO, S.-G. BAE, J. NOH;
Dankook university, Yongin-si, Korea, Republic of

Abstract: Social buffering is a phenomenon where stress is alleviated by the presence of conspecifics while a subject is exposed to a distressing stimulus. Most previous studies have focused on social buffering in adults and used long periods, such as a day, despite evidence that social interactions during adolescence are important and that immediate short treatments are as effective as longer treatments. In this study, we aimed to determine whether brief buffering (only 3 minutes) with conspecifics immediately after fear conditioning can produce a social buffering effect in adolescent Sprague-Dawley rats (4-5 weeks, male and female). We analyzed the data using YOLOv8, a deep learning-based object detection algorithm, to reduce human bias and analyze variables that humans cannot, such as the distance between subjects. This method also solves the problem of computer vision-based methods that cannot analyze in a shuttle box with black and white rooms. The groups were set up as follows: Control(non-shock, non-interaction); Toy(interaction with toy resembling a rat for 3 minutes after an electric shock); Pair(interaction with a conspecific for 3 minutes after an electric shock). In the behavioral test using the passive avoidance test, toy group showed a significant decrease in black room preference regardless of sex. pair group showed a significant increase in black room preference in both the learning check (confirming short-term memory) and retention (verifying long-term memory). In pair group, the more time the pair and their partner spent in the same room, the higher the black room preference, with a significant correlation found between these variables. Additionally, the shorter the average distance between individuals and the longer they stayed in close proximity, the higher the black room preference, with a significant correlation observed. Therefore, we demonstrated that social buffering occurred in both females and males in the short-term and long-term and that the more individuals interact in close proximity in the same room, the greater the effect of social buffering.



Disclosures: M. seo: None. **S. Bae:** None. **J. noh:** None.
Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.034/LBA34

Topic: G.04. Emotion

Support: R01MH121009-02

Title: Interoceptive Signals Modulate Baseline Firing Rates in Multiple Brain Areas

Authors: *M. CARDENAS[1], R. LE[1], G. NEAL[1], A. PAL[1], N. N. MAGNUSSON[4], A. B. MARTIN[2], A. J. FUGLEVAND[3], K. M. GOTHARD[5];

[2]Physiol., [3]Dept. of Physiol., [1]Univ. of Arizona, Tucson, AZ; [4]Neurosci. Grad. program, Emory Univ., Atlanta, GA; [5]Physiol., Univ. Arizona, Col. Med., Tucson, AZ

Abstract: Influential theories proposed that interoceptive signals (internal signals from the body) contribute to emotional and behavioral states. We found that the spontaneous firing rates of a large proportion of neurons in the somatosensory cortex (72%), secondary somatosensory cortex (64%), nucleus basalis of Meynert (50%), and amygdala (46%) of rhesus macaques correlate with heart rate. To determine if these correlations are driven by interoceptive afferents or reflect descending autonomic signals sent from the brain to the heart, we used a non-specific muscarinic antagonist (glycopyrrolate) to increase heart rate. Because glycopyrrolate does not cross the blood brain barrier, interoception is the most likely mechanism by which tachycardia induced by the drug can change neural activity in the brain. We found that glycopyrrolate modulated the baseline firing rates of 61% and 47% of heart rate-correlated neurons in the primary somatosensory cortex and the amygdala, respectively. Furthermore, the baseline firing rate of 13% of amygdala neurons became correlated with heart rate only after glycopyrrolate administration, whereas this effect was not present in the somatosensory cortex. These results suggest that interoceptive afferents drive small but significant changes in spontaneous firing rates across the brain

Disclosures: M. Cardenas: None. **R. Le:** None. **G. Neal:** None. **A. Pal:** None. **N.N. Magnusson:** None. **A.B. Martin:** None. **A.J. Fuglevand:** None. **K.M. Gothard:** None.

Late-Breaking Poster

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Program #/Poster #: LBA007.035/LBA35

Topic: G.04. Emotion

Support: ISF Individual Research Grant 1485/18
1462/23 to S.G.-D

Title: Support for the valence-specific hypothesis in parafoveal facial emotional perception across two studies

Authors: *V. AKSELEVICH[1,2], S. GILAIE-DOTAN[3,2];
[1]Fac. of Life Sci. Sch. of Optometry and Vision Scienc, [2]Gonda Multidisciplinary Brain Res. Ctr., [3]Fac. of Life Sci. Sch. of Optometry and Vision Sci., Bar-Ilan Univ., Ramat Gan, Israel

Abstract: There is still no consensus today about the brain mechanisms that afford perception of facial emotions. The Right-Hemisphere Hypothesis (RHH) and the Valence-Specific Hypothesis (VSH) are two leading theories hypothesizing about the brain mechanisms supporting emotion perception which disagree with respect to hemispheric dominance. A critical disagreement

between them relates to the neural mechanisms supporting facial emotions of positive valence (pleasantness). The RHH suggests they are supported by right hemisphere dominant regions while the VSH posits they are supported by left hemisphere dominant regions. The divided visual field (DVF) paradigm takes advantage of the architecture of the human visual system to reveal potential hemispheric specialization in processing of emotional faces. The paradigm relies on unilateral stimulus presentation for maximizing its effectiveness in examining the processing of stimuli by each hemisphere. Here in two separate studies (one with KDEF and one with NimStim stimuli, each study with 37 different participants) we relied on the DVF paradigm while monitoring eye movements and briefly (200ms) presenting faces with positive, negative or neutral emotional expressions in different locations in the visual field (up to 4°) that allowed us to estimate perceptual valence judgments by location. Across the two studies we found (i) visual field modulations were evident at 4° but not at 2°, (ii) support for the VSH but no support for the RHH (higher positive valence accuracy for right- relative to left- visual field presentation), and (iii) right-left visual field valence-specific performance was correlated within (but not across) valence. These results support the VHS and suggest that visual field and potentially hemispheric differences may be evident for stimuli at eccentricities >2°. Additionally, our results indicate that the mechanisms supporting valence-specific perception may not be uniform and are associated across the visual field.

Disclosures: V. Akselevich: None. **S. Gilaie-Dotan:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.036/LBA36

Topic: G.04. Emotion

Title: Valence Specific Pupillary Correlate of Emotion Perception

Authors: *S. RAY[1], S. MAITY[2];
[2]Social Sci. and Humanities, [1]Indraprastha Inst. of Information Technol., New Delhi, India

Abstract: Emotion perception constitutes one of the fundamental aspects of human interaction, and is dependent upon accurately processing facial expressions. Pupil diameter typically regulates the amount of light entering the eye via pupillary light reflex (PLR), a reflexive constriction or dilation of the pupil in response to bright and dark light, respectively. It has been suggested that LC (Locus Coeruleus), a brain stem region intricately linked to emotion perception, also contributes to the regulation of pupil diameter. LC also plays a significant role in attention via the neurotransmitter norepinephrine (NE), represented as LC-NE system. However, an underexplored aspect is the potential relationship between pupil diameter, attention, and emotion perception. This study systematically investigates the relationship between emotion

perception and pupil diameter through an emotion detection task of face stimuli for three expressions: Happy, Angry, and Neutral. For the control experiment, the stimuli and time course of a trial were precisely the same as the experimental task, only that attention was not directed to the face stimuli but to a red dot overlaid on face stimuli. Participants were supposed to report if the red dot appeared on the right or left side of the face stimuli. The control experiment was designed to compare pupil responses when attention is directed to face stimuli (emotion detection) as opposed to when attention is directed away from face stimuli onto the red dot (Control) overlaid on it. Out of 40 participants recorded, 35 participants qualified the criteria of inclusion (70% and above performance in detection task). A distinct PLR in the form of constriction from baseline (pre-stimulus pupil response) and recovery to baseline was observed 450 ms and 750 ms respectively post stimulus onset for both emotion detection and control task. We compared pupil features like constriction onset, peak minimum amplitude of constriction, constriction and dilation rate between emotion detection and control task. Significant differences were observed between emotion detection and control tasks in all analyzed pupil features. Specifically, the peak minimum amplitude was larger and dilation rate was slower for the emotion detection as compared to the control task. These differences could be attributed to disparity in attentional demands between the two tasks. Within the emotion detection task, significant valence-specific effects in two features: peak minimum amplitude and the dilation rate of pupil was observed, representing pupillary correlates of emotion perception. Our study highlights attention and emotion specific responses in pupil dynamics.

Disclosures: S. Ray: None. **S. Maity:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.037/LBA37

Topic: G.05. Mood Disorders

Support: CONAHCYT CF-2023-G-112

Title: Physical activity is related to GABA and glutamate concentrations in the anterior-cingulate, in depressed patients.

Authors: *M. FLORES-RAMOS[1], S. ALCAUTER[2], R. A. EDDEN[3];
[1]Inst. Nacional de Psiquiatría Ramón de la Fuente, Ciudad de México, Mexico; [2]Neurobiología Conductual y Cognitiva, Inst. De Neurobiologia. Univ. Nacional A, Queretaro, Mexico; [3]Dept. of Radiology, The Johns Hopkins Univ., Baltimore, MD

Abstract: Physical activity is related to GABA and glutamate concentrations in the anterior-cingulate, in depressed patients. A relationship between GABA levels and physical activity has

been observed in several studies in animal models. This association is less studied in humans with depressive disorder. GABA serum levels have been proposed as an indicator of physical performance. In this study, we aimed to evaluate the relationship between GABA and glutamate concentrations and physical activity, in unmedicated depressed patients. Methods: We evaluated 9 depressed patients without treatment; who were evaluated with the International Physical Activity Questionnaire (IPAQ). Magnetic Resonance Imaging experiments were performed with a 3.0 Tesla scanner (Phillips Medical Systems). We evaluated GABA+ and glutamate levels in the ACC, using the Hadamard Encoding and Reconstruction of MEGA-Edited Spectroscopy (HERMES) sequence. Pearson correlations were used to evaluate the association between GABA+ concentrations, glutamate and total metabolic equivalents (METS). Results: A positive association was observed between METS and GABA levels in the ACC, conversely, glutamate showed an inverse relation with the METS. Associations were controlled by age, and BMI. Conclusion: Physical activity is associated with cerebral metabolites in depressed patients; this finding could explain, in part, the effects of exercise in well-being.

Disclosures: M. Flores-Ramos: None. **S. Alcauter:** None. **R.A. Edden:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.038/LBA38

Topic: G.05. Mood Disorders

Support: Wellcome Leap Multichannel Psych program

Title: Oscillatory synchronization networks reflect heterogenous MDD symptoms

Authors: *S. PALVA;
Univ. of Helsinki, Helsinki, Finland

Abstract: Major depressive disorder (MDD) is heterogeneous disorder characterized by a broad spectrum of symptoms. fMRI functional connectivity (FC) research has established brain-symptom associations between fronto-striatal FC and mood regulation, sustained negative affect, and rumination, and fronto-parietal-control network-hypoactivity with cognitive-control deficits. New machine learning (ML)-based approaches have used these data for identifying depression subtypes spanning diagnostic categories. In contrast, there is scarce prior research using magnetoencephalography (MEG) to study depression or identification of depression subtypes. In MEG, activity is characterized by neuronal oscillations and their network synchronization providing temporal clocking mechanisms for dynamic routing of information thus constituting central building blocks of cognitive subfunctions. We here hypothesized that oscillation-based networks would accurate reflect MDD symptoms and their heterogeneity and allow precise

identification of MDD subtypes. We collected resting-state magnetoencephalography (MEG) data from 271 patients (146 Females) diagnosed with depression and used 10 symptom scales to allow identification of transdiagnostic subtypes. The study was performed according to the Declaration of Helsinki, and with approval of local ethical agency. MEG data was source reconstructed and collapsed into cortical parcellations. We then computed inter-areal phase synchronization from source reconstructed MEG data across all parcels and frequencies and estimated their correlations with 10 different symptom scales. This approach revealed significant correlations specifically in alpha- and beta frequency band synchronization with multiple symptom scores. Using these data as a basis for phenotyping with unsupervised machine learning, we identified 4-5 stable depression subtypes, with different symptom and spatio-temporal profiles. These data demonstrate that oscillation-based functional connectivity is highly correlated with heterogeneous depression symptoms and further that these MEG-based oscillatory synchronization connectomes can be used to identify unique MDD subtypes that may complement those identified previously with fMRI.

Disclosures: S. Palva: None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.039/LBA39

Topic: G.05. Mood Disorders

Title: Prevalence and Risk Factors of Prenatal Depression in Mongolian Women

Authors: *G. TUMUR-OCHIR[1], E.-U. PERENLEISAMBUU[2], T. AMARTUVSHIN[3], B. LKHAGVASUREN[4], N. LKHAGVASUREN[5];
[1]Natl. Ctr. of Mental Hlth. Mongolia, Ulaanbaatar, Mongolia; [2]Mongolian Natl. Ctr. for Mental health, Ulaanbaatar, Mongolia; [3]Mongolian Natl. Univ. of Med. Sci., ulaanbaatar, Mongolia; [4]Kyushu Univ., Fukuoka, Japan; [5]SodMed Mental Hlth. Ctr., Ulaanbaatar, Mongolia

Abstract: Background: Prenatal depression is a significant public health concern affecting women globally. Despite its prevalence, research on prenatal depression in Mongolia is limited. This study aimed to determine the prevalence of depression during pregnancy and identify associated factors in the Mongolian population. **Methods:** A cross-sectional study was conducted among 1482 pregnant women aged 18-46 years in urban and rural Mongolia. Participants completed the Edinburgh Postnatal Depression Scale (EPDS) and a structured psychiatric interview. Sociodemographic, obstetric, and psychosocial factors were assessed. Depression was defined as an EPDS score > 13. **Results:** The prevalence of prenatal depression was 15.9% (n=235). Depression was associated with younger age, lower monthly income, nulliparity, rural residence, unplanned pregnancy, and exposure to violence. Compared to urban

women, rural women were 1.9 times more likely to experience depression. Second-trimester pregnancies were associated with a lower likelihood of depression compared to third-trimester pregnancies. Women who planned their pregnancies were 0.6 times less likely to experience depression than those with unplanned pregnancies. Furthermore, compared to non-violated women, currently violated women were 2.3 times more likely to be depressed. Emotionally violated women were 0.3 times more likely to be depressed than those not violated. Finally, women experiencing family discord were 3.1 times more likely to be depressed than those with peaceful family relationships.**Conclusion:** Prenatal depression is a significant public health concern in Mongolia, with a prevalence of 15.9% identified in this study. Risk factors for prenatal depression included young maternal age, rural residence, unplanned pregnancy, exposure to violence, and family discord. These findings emphasize the urgency of developing and implementing prevention and treatment programs for prenatal depression in Mongolia.

Disclosures: G. Tumur-Ochir: None. **E. Perenleisambuu:** None. **T. Amartuvshin:** None. **B. Lkhagvasuren:** None. **N. Lkhagvasuren:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.040/LBA40

Topic: G.05. Mood Disorders

Support: DARPA N660012324006

Title: Novel Measure for Predicting Depression and Suicidal Ideation: The Death Association-Reaction Score from a Sentence Classification Task

Authors: *S. KADIRI[1], B. CAHN[1], D. BYRD[2], I. BLANK[8], A. HABIBI[3], K. LERMAN[4], R. LEAHY[5], T. MEDANI[6], C. MCDANIEL[1], S. NARAYANAN[7];
[1]USC, Los Angeles, CA; [2]Linguistics, USC, los angeles, CA; [3]Psychology, USC, Los Angeles, CA; [4]USC, Marina del Rey, CA; [5]USC, LA, CA; [6]USC, los angeles, CA; [7]Electrical and Computer Engin., USC, Los Angeles, CA; [8]UCLA, UCLA, CA

Abstract: Objective:This study proposes a Death Association-Reaction (DAR)-score to distinguish associations among control, depressed, and suicidal participants using reaction times in a sentence classification task, similar to the Death-Implicit Association Task (D-IAT). Participants classify (agree/disagree) a series of stimuli, and their reaction times are measured to infer associations. Methods: 112 young adults were recruited and categorized into control (42), depressed (35), and suicidal (35) groups based on scores from the PHQ-9 and the Suicidal Ideation Scale (SIS). Participants completed a sentence classification task while their reaction times (RT) were recorded. The task consisted of sentences drawn from four Topic of Interests

(TOIs) (Biographical, Action, Reflection, and Intention) presented in first-person sentence forms predicted to be either congruent or incongruent for individuals within the three mental health groups (20 pairs of statement sentences for each TOI). The DAR-score for each participant was calculated by subtracting the mean RT for congruent from the mean RT for incongruent sentences, then dividing by the standard deviation of all RTs. Congruency was defined both by individual subject responses and by expectations driven by the experimental design. Results were analyzed using DAR-scores, RTs for congruent and incongruent sentences, and Receiver Operating Characteristic (ROC) curves across TOIs and combinations of TOIs.
Results: Congruency based on apriori experimental design predictions generally provided better discriminability than individual subject response-based congruency. Among the four TOIs, 'Intention' TOI had high discriminability for Control vs. Suicidal (AUC=0.94) and Depressed vs. Suicidal (AUC=0.90), but lower for Control vs. Depressed (AUC=0.52). Combining TOIs improved discriminability, with the best results for Intention, Action, and Reflection TOIs combined (Control vs. Suicidal AUC=0.97, Depressed vs. Suicidal AUC=0.88, Control vs. Depressed AUC=0.77).
Summary: The proposed DAR-score from a congruency-based sentence task shows promise as a sensitive measure for detecting and discriminating associations with depression- and suicide-related stimuli among individuals with depressive and suicidal tendencies. The study suggests the potential effectiveness for providing discriminability among depressed, suicidal, and healthy young adults through the use of experimental design-based congruency using first-person sentences to elicit agreement and RTs. We speculate that this method may remain robust even in the face of task response variability extant across individual subjects.

Disclosures: S. Kadiri: None. **B. Cahn:** None. **D. Byrd:** None. **I. Blank:** None. **A. Habibi:** None. **K. Lerman:** None. **R. Leahy:** None. **T. Medani:** None. **C. McDaniel:** None. **S. Narayanan:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.041/LBA41

Topic: G.05. Mood Disorders

Title: The effects of open-class online mindfulness intervention on depression and anxiety: a randomized controlled trial

Authors: *T. TAKAHASHI[1], D. HASHIMOTO[2], S. SHIGARAKI[2], S. KATAGIRI[2], H. CHIBA[3], X. YAN[3], R. SATO[5], N. TANAKA[5], R. OSU[4];
[1]Laureate Inst. for Brain Res., Tulsa, OK; [2]MELON, Tokyo, Japan; [4]Fac. of Human Sci., [3]Waseda Univ., Tokorozawa, Japan; [5]Besli clinic, Tokyo, Japan

Abstract: This study evaluates the efficacy of open-class online mindfulness interventions for mental health, particularly focusing on depression and anxiety. Mindfulness interventions are believed to improve depression and anxiety by training individuals to pay attention to their bodies and enhancing prefrontal function. For future mechanistic studies, it is important to verify whether these easily administered online interventions improve depression and anxiety. We conducted a randomized controlled trial involving 140 adults (mean age: 37.4 years, SD: 10.9; 100 females, 39 males, 1 other) exhibiting symptoms of depression and/or anxiety. Participants were randomly allocated to either an 8-week mindfulness intervention group or a wait-list control group. The intervention was delivered in an open-class style where participants freely chose and joined mindfulness-related meditation classes, although they were instructed to attend at least five days a week. After eight weeks, the groups switched conditions, allowing both groups to experience the intervention and control periods. Outcome measures included the Patient Health Questionnaire-9 for depression, Generalized Anxiety Disorder-7 for anxiety, World Health Organization-Five Well-Being Index, Five Facet Mindfulness Questionnaire-24, and Short-form Self-Compassion Scale. These were assessed pre- and post-intervention/waiting period, three times in total. Results from linear mixed-effects models demonstrated significant interactions for depression, anxiety, and well-being ($p < .05$), with improvements observed post-intervention in each group (adj $p < .05$). After the initial eight-week period, the intervention group showed significantly lower depression and anxiety levels and higher well-being compared to the control group (adj $p < .01$). Regarding mindfulness and self-compassion measures, significant interactions were noted in the nonjudging facet of mindfulness and the negative factor of self-compassion ($p < .01$), with improvements observed post-intervention in each group (adj $p < .05$). After the initial eight-week period, the intervention group showed significantly higher nonjudging skill and lower negative factor of self-compassion compared to the control group (adj $p < .01$). In conclusion, the open-class online mindfulness intervention effectively ameliorates symptoms of depression and anxiety and enhances well-being and specific aspects of mindfulness and self-compassion. Given that the nonjudging facet of mindfulness has been associated with the superior prefrontal cortex in a previous study, future research exploring the neural mechanisms is needed.

Disclosures: T. Takahashi: None. **D. Hashimoto:** A. Employment/Salary (full or part-time):; MELON. **S. Shigaraki:** A. Employment/Salary (full or part-time):; MELON. **S. Katagiri:** A. Employment/Salary (full or part-time):; MELON. **H. Chiba:** None. **X. Yan:** None. **R. Sato:** None. **N. Tanaka:** None. **R. Osu:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.042/Web Only

Topic: G.05. Mood Disorders

Support: JSPS KAKENHI Grant Numbers 22K21150

Title: The comparison of transcriptome data in plasma brain-enriched extracellular vesicles among major depression, bipolar disorder, and healthy control

Authors: *Y. KAGEYAMA[1], S. OKURA[2], Y. DEGUCHI[3], K. INOUE[4], C. M. LISTON[5]; [1]Osaka Metropolitan Univ. Grad. Sch. of Med. Dept. of Neuropsychiatry, Osaka, Japan; [2]Osaka Metropolitan Univ., Osaka, Japan; [3]Osaka metropolitan university, Osaka, Japan; [4]Neuropsychiatry, Osaka City Univ. Med. Sch, Neuropsychiatry, Osaka-City, Japan; [5]Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Background: Extracellular vesicles (EVs) are known to be involved in the pathogenesis of neuropsychiatric disorders. EVs are released from the brain into the bloodstream and carry markers that allow them to be traced back to their originating cells. This makes EVs a promising candidate for biomarker research. However, there is currently no established method for this purpose. In this study, we developed a new liquid biopsy method that focuses on plasma NCAM1-positive EVs. These vesicles are thought to originate partly from the brain but may also come from other sources. Using this method, we analyzed the gene expression levels of patients with major depressive disorder (MDD), bipolar disorder (BD), and healthy individuals to investigate whether the gene expression levels in plasma brain-enriched EVs could serve as diagnostic biomarkers. **Methods:** Total circulating EVs were isolated from 500 μL of plasma samples using two rounds of ultracentrifugation. The purified EVs were confirmed using electron microscopy, a nanoparticle tracking analyzer, and EV antibody array analysis. NCAM1-positive EVs were isolated using immunoprecipitation with anti-NCAM1 antibody beads solution and confirmed by western blotting. Subsequently, RNA-seq and Enrichr analysis were conducted on human plasma samples from 39 MDD patients, 13 BD patients, and 15 healthy controls.**Results:** Using support vector machine analysis, we were able to differentiate between MDD and BD with a 77.9% accuracy rate using 195 gene expression data, wherein gene expression levels are significantly different between MDD and BD. The highest odds ratio from gene ontology analysis was 14.37 (Translation Initiation Factor Activity, adjusted p-value, 0.003). Five genes (EIF3M, EIF5, EIF6, MTIF2, and EIF3D) were found to be related to this gene ontology. The highest odds ratio from pathway analysis was 22.47 (Sumoylation by RanBP2 regulates transcriptional repression, adjusted p-value, 0.03). Two genes (HDAC1 and RAN) were found to be related to this pathway. **Conclusions:** This study demonstrates that the developed method has the potential to be used as a diagnostic biomarker to differentiate between MDD and BD. The method could be applicable to biomarker research in neuropsychiatric disorders.

Disclosures: Y. Kageyama: None. **S. Okura:** None. **Y. Deguchi:** None. **K. Inoue:** None. **C.M. Liston:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

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Program #/Poster #: LBA007.043/LBA42

Topic: G.05. Mood Disorders

Support: AI164769
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We thank Stefano Marenco and the Human Brain Collection Core at the National Institute of Mental Health for providing some of the postmortem human brain tissue samples.
We thank the families for donating the brain tissue used in this study.

Title: Proteomic Profiling of the Hippocampus Reveals Differential Protein Expression in Antidepressant-Treated and Untreated Major Depressive Disorder

Authors: A. M. WAMALWA[1], M. MARIANI[2], R. RAMKUMAR[2], C. SISSOKO[3,2], Y.-Y. HUANG[4], Y. LIU[2,5], A. J. DWORK[6,2], G. ROSOKLIJA[2,7], V. ARANGO[8,2], L. BROWN[2], J. MANN[2,5], H. GALFALVY[2], *M. BOLDRINI[2,5];
[1]Psychiatry, [2]Columbia Univ., New York, NY; [3]Biomed. engineering, Univ. of Cincinnati | Cincinnati Children's, New York, NY; [4]New York State Psychiatric Inst., New York, NY; [5]New York State Psychiatric Inst., New Yrok, NY; [6]Neuropathology, New York State Psychiatric Inst., New York, NY; [7]Macedonia Acad. of Sci., Skopje, North Macedonia, The Republic of; [8]NIMH, NIH, Natl. Inst. of Mental Hlth., SHRUB OAK, NY

Abstract: Major Depressive Disorder (MDD) is a prevalent and complex condition with significant social and economic burdens, characterized by disrupted memory and emotional regulation due to hippocampal dysfunction. The efficacy of antidepressants in treating MDD is limited, with only 20-40% of patients responding, and among those who do show improvement, approximately half continue to experience residual symptoms. Thus, new molecular treatment targets need to be identified. This study presents the first proteomic profiling of the human hippocampus in antidepressant treated (MDDT) and untreated MDD (uMDD) patients, and non-psychiatric controls (CONT). Using shotgun proteomics, hippocampus tissue from 12 uMDD, 12 MDDT, and 12 CONT subjects was analyzed, focusing on the dentate gyrus-hilus region. The analysis identified 1,811 proteins, of which 1,131 were matching quality criteria to be retained. We identified 465 differentially expressed proteins (DEPs) in MDDT and 308 in uMDD compared to CONT, along with 228 DEPs between MDDT and uMDD. DEPs involved in synaptic plasticity and inflammatory response were altered in both MDDT and uMDD compared to controls. Apoptosis related proteins were differentially expressed in uMDD compared to MDDT. Correlations between DEPs expression levels and numbers of neural progenitor cells (NPCs), intermediate neural progenitors (INPs), and granule neurons (GNs) were identified. Three of the 308 DEPs in uMDD compared to control, were also altered at the RNA level in our single nucleus RNA sequencing analysis. CPNE8, which regulates cell adhesion, showed decreased expression at the RNA level but increased expression at the protein level in uMDD

compared to CONT. HSDL2, a critical factor in fatty acid regulation and lipid metabolism, was elevated at both the RNA and protein levels in uMDD. NCEH, which protects against α-synuclein neurotoxicity, was reduced at the RNA level but increased at the protein level in uMDD. Additionally, the long non-coding RNA *AC079793.2*, expressed in immature granule neurons (ImGN) in the snRNAseq dataset, was downregulated in uMDD. The genomic sequence of *AC079793.1* overlaps with ARHGAP15, a RAC1-specific GTPase-activating protein (GAP) present in migrating cortical neurons during development and in most adult cortical neurons. RAC1, essential for neurogenesis, synaptogenesis, and plasticity, was downregulated at the protein level in uMDD compared to CONT. These findings highlight potential new molecular targets for therapeutic intervention in MDD for improving inflammation, synaptic plasticity, apoptosis and neurogenesis, as these pathways appear altered in the hippocampus in the disorder.

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Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.044/LBA43

Topic: G.05. Mood Disorders

Support: IOER Award 03-22-08

Title: Chronic kidney disease is accompanied by behavioral deficits in rodents

Authors: F. DI SOLE[1], V. BABICH[2], A. KORNSTAD[1], K. TEFFT[1], ***V. DURIC**[1];
[1]Des Moines Univ., West Des Moines, IA; [2]Mercy Col. of Hlth. Sci., Des Moines, IA

Abstract: Clinical reports indicate a bidirectional relationship between mental illness and chronic systemic disease. Kidney injury and inflammation have been linked to brain dysfunction and alterations in learning and memory, as well as development of anxiety and depression, however, the underlying neurophysiological mechanisms remain elusive. In the current study, we investigated whether a chronic kidney disease (CKD) state is sufficient to produce deficits in rodent stress behaviors using a mild or severe model of CKD. Male rats were exposed to either

21 days of 0.75% adenine diet (AD) (model of mild CKD), or a combination of AD with unilateral nephrectomy (AD/Unx), prior to the start of AD (model of severe CKD). Control rats received sham surgery and remained on normal diet/chow throughout the experimental paradigm. CKD development in the rat models was determined by a significant increase in serum creatinine used as index for kidney function. Behavioral testing results demonstrate that mild CKD model, especially in combination with unilateral nephrectomy (severe CKD model), is accompanied by anhedonia (i.e., decreased sucrose preference) and increased anxiety-like behaviors in the novelty-suppressed feeding, open field and elevated plus maze tests. These findings suggest that impairment of kidney functionality is sufficient to increase behavioral emotionality in rodents consistent with development of depressive-like and anxiogenic phenotype. Ongoing studies are focused on identifying neurophysiological mechanisms linking renal disease with neurological abnormalities. Furthering our understanding of these mechanisms may aid in the development of improved treatments and prevention strategies for management of mental health comorbidities associated with kidney disease.

Disclosures: F. Di Sole: None. **V. Babich:** None. **A. Kornstad:** None. **K. Tefft:** None. **V. Duric:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.045/LBA44

Topic: G.05. Mood Disorders

Support: KAKENHI 22K17788

Title: Effect of timing of fish oil intake on social avoidance behavior induced by social defeat stress.

Authors: *A. OTSUKA;
Dept. of Life Sci., Kindai Univ., Higashiosaka, Japan

Abstract: Exposure to a psycho-social stress is one of risk factors for human diseases such as depression. Social-defeat stress (SDS) is a well-known rodent model of human's psycho-social stress. In SDS paradigm, rodents show a variety of behavioral changes, including depressive-like behavior and social avoidance. Recently, epidemiological studies reported that higher dietary intake of omega -3 polyunsaturated essential fatty acids including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) decreases the risk of depressive disorders. Fish oil includes high concentrations of DHA and EPA. In a previous study, we found that fish oil intake during the SDS exposure period suppressed social avoidance behavior. In this study, we determined whether the timing of fish oil intake affect social avoidance behavior induced by SDS.

Additionally, we measured serotonin level and expression of genes related to serotonin synthesis in hippocampus. In our SDS protocol, a male C57BL/6J (experimental) mouse was attacked by an aggressive male ICR (aggressor) mouse for 5 min once daily. After the physical interaction, these mice were divided using an acryl plate permitting sensory contact until next day. This procedure was repeated for eight days, and an experimental mouse was subjected to social defeat by an aggressor mouse. For fish oil treatment, experimental mice were fed a diet containing fish oil at middle (M-FO), and high (H-FO) concentrations. The daily dosage of DHA/EPA in M-FO and H-FO groups was approximately 120 mg and 240 mg, respectively. Control group supplemented equivalent canola oil. These diets were fed to experimental animals for 2 weeks before or after SDS exposure. After SDS protocol, we performed social interaction test and compared social behaviors between FO and control groups. In control group, SDS-exposure mice showed social avoidance behavior compared to non-stressed mice. However, M-FO and H-FO groups that had consumed fish oil for 2 weeks before SDS exposure did not exhibit negative social behavior. On the other hand, M-FO and H-FO groups that had consumed fish oil for 2 weeks after SDS exposure showed negative social behavior. Fish oil intake during the 2 weeks before SDS exposure did not affect serotonin level in the hippocampus. In contrast, TPH mRNA expression levels of these groups were higher than control group. In addition, fish oil intake after SDS exposure did not affect serotonin levels or serotonin synthesis in hippocampus. These results suggest that fish oil intake before stress exposure improves psycho-social behavioral disorder caused by SDS. This improvement could be explained by increases in serotonin synthesis in hippocampus.

Disclosures: A. Otsuka: None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

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Program #/Poster #: LBA007.046/LBA45

Topic: G.05. Mood Disorders

Support: National Institutes of Mental Health (1R01MH113986)
Cystic Fibrosis Foundation (002544I221)

Title: Sars-cov-2 neurotropism induces anxiety/depression-like behaviors in mice

Authors: *Q. GE[1], J. DU[2];
[2]Anat. and Neurobio., [1]The Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been associated with a wide range of post-acute sequelae of COVID-19 (PASC) neurological symptoms. However, the mechanisms

governing SARS-CoV-2 neurotropism and its effects on long-term behavioral changes remain poorly understood. Using a highly virulent mouse-adapted SARS-CoV-2 strain, denoted as SARS2-N501Y$_{MA30}$, we achieved the first in vivo investigation of PASC neurological symptoms in mice. We demonstrated that intranasal inoculation of SARS2-N501Y$_{MA30}$ results in viral dissemination to multiple brain regions, including the amygdala and hippocampus. Behavioral assays indicated a marked elevation in anxiety- and depression-like behaviors post infection. A comparative analysis of RNA expression profiles disclosed alterations in the post-infected brains. Additionally, we observed dendritic spine remodeling on neurons within the amygdala after infection. Infection with SARS2-N501Y$_{MA30}$ was associated with microglial activation and a subsequent increase in microglia-dependent neuronal activity in the amygdala. Transcriptomic analysis of infected brains revealed the upregulation of inflammatory and cytokine-related pathways, implicating neuroinflammation in the pathogenesis of neuronal hyperactivity and behavioral abnormality. Overall, these data provide critical insights into the neurological consequences of SARS-CoV-2 infection and underscore microglia as a potential therapeutic target for ameliorating virus-induced neurobehavioral abnormalities.

Disclosures: Q. Ge: None. **J. Du:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Program #/Poster #: LBA007.047/LBA46

Topic: G.05. Mood Disorders

Support: NRF-2021R1I1A1A01045145

Title: Stress, Depression, and Brain Protein Pathology: New Therapeutic Targets from Mouse Studies

Authors: *Y. KWON[1], Y. BANG[2], H. CHOI[3];
[1]CHA university, Seongnam-si, Korea, Republic of; [2]Col. of pharmacy, CHA Univ., Seongnam-si, Korea, Republic of; [3]Col. of Pharm., CHA Univ., Pocheon-si, Korea, Republic of

Abstract: Depression, affecting approximately 350 million people globally, is increasingly recognized for its link to neurodegenerative conditions. The rising prevalence of depression, contributing to an estimated 800,000 suicides annually (1.4% of all deaths worldwide, WHO), emphasizes the need for novel antidepressant treatments, especially as only one new drug class has emerged in the past 30 years. It is well known that stress is a major risk factor not only for depression but also for various neurological disorders. However, the direct pathology of the central nervous system due to stress remains unclear. This study explores the relationship between mild stress-induced behavioral abnormalities and neurobiological pathology in a mouse

model, potentially uncovering new therapeutic targets.Mice were subjected to unpredictable mild stress over six weeks to examine the association between depression-like behaviors and protein aggregation in the brain, focusing on alpha-synuclein, ubiquitin, and p62. Behavioral assessments confirmed significant depressive-like symptoms, including reduced sucrose preference and increased immobility in the forced swim test. Post-mortem analyses revealed marked increases in ubiquitin, p62, and alpha-synuclein accumulation in the cortex and hippocampus regions of UMS-exposed mice.These findings suggest that unpredicted mild stress can induce depressive-like symptoms in mice, which are associated with abnormal protein accumulation in the brain. This supports the hypothesis that protein aggregation may play a role in the pathophysiology of depression, offering a potential mechanistic link between neurodegenerative diseases and depressive disorders. These insights could guide future research into targeted therapies for depression and related neurodegenerative conditions.

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Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.048/LBA47

Topic: G.05. Mood Disorders

Support: NCN Grant 2021/41/B/NZ4/02603

Title: Study of the interactions between 5HT7 and NMDA receptors at the single dendritic spine level

Authors: *Z. BEDROOD[1], M. BIJATA[2], K. B. DORE[3], J. WLODARCZYK[4];
[1]Nencki Inst. of Exptl. Biol., Warsaw, Poland; [2]Nencki Inst. of Exptl. Biol. PAS, Warsaw, Poland; [3]Neurosciences, UCSD Dept. of Neurosciences, La Jolla, CA; [4]Nencki Inst. of experimental Biol., Warsaw, Poland

Abstract: Major depressive disorder (MDD) is a prevalent global condition resulting from impaired synaptic plasticity, often associated with abnormal serotonin and NMDA receptor (NMDAR) signaling. Our recent research uncovered a novel pathway involving the serotonin 5-HT7 receptor (5-HT7R) and matrix metalloproteinase 9 (MMP-9), linking changes in dendritic spine morphology to extracellular matrix (ECM) remodeling. Chronic stress enhances MMP-9-dependent proteolytic cleavage of its substrates in the hippocampal CA1 region through NMDAR engagement, as demonstrated in animal models. Using behavioral, biochemical, and imaging techniques, we investigated 5-HT7R/MMP-9 signaling and dendritic spine plasticity in the hippocampi of mice treated with the selective 5-HT7R agonist LP-211, and in a chronic unpredictable stress (CUS) model of depressive-like behavior. Acute activation of 5-HT7R

induces depressive-like behavior in an MMP-9-dependent manner. Since both 5-HT7R and NMDAR are targets for antidepressant therapy and influence dendritic spine remodeling, and considering the role of MMP-9 in NMDAR diffusion and activity, we hypothesize that these molecules form a unified signaling module. We characterized the physical and functional interactions between 5-HT7R and NMDAR in primary hippocampal culture co-transfected with plasmid vectors encoding GluN1-GFP, GluN2B, and 5-HT7R-mRuby using FRET-based methods and high-resolution confocal microscopy. The use of custom-made COLOCALIZER software allowed for the creation of a co-localization map. Co-localization analysis showed a high degree of overlap between the two channels in the microscopic images (Mander's coefficient was found to be 0.90±0.01). The Fluorescence Recovery After Photobleaching (FRAP) was used to determine the dynamics of the 5-HT7R and NMDAR subunits separately in an individual sample and mixed sample. The results indicate that the fluorescence recovery halftime, $\tau_{1/2}$, in neurons co-expressing GluN1-GFP/GluN2, is shorter ($\tau_{1/2}$ ~ 15.24 s) compared to the group in which neurons co-expressing GluN1-GFP/GluN2/5-HT7R-mRuby ($\tau 1/2$ ~ 19.89 s), indicating that fluorescence recovery is faster in neurons co-expressing GluN1-GFP/GluN2 and showing the presence of interaction between them. Our study advanced the understanding of the interactions between 5-HT7R and NMDAR, indicating their direct interaction.

Disclosures: Z. Bedrood: None. **M. Bijata:** None. **K.B. Dore:** None. **J. Wlodarczyk:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.049/LBA48

Topic: G.05. Mood Disorders

Support: IOER Award 03-22-08

Title: Genetic profiling of the prefrontal cortex during peripheral chronic inflammatory pain

Authors: *A. KORNSTAD[1], K. TEFFT[1], M. GIRGENTI[3], M. BANASR[4], V. DURIC[2]; [2]Physiol. and Pharmacol., [1]Des Moines Univ., West Des Moines, IA; [3]Psychiatry, Yale Sch. of Med., New Haven, CT; [4]Neurobio. of Depression and Aging, Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada

Abstract: Altered mood and psychiatric disorders are commonly associated with chronic pain conditions; however, brain mechanisms linking pain and comorbid clinical depression are still largely unknown. In this study, we aimed to identify limbic biomarkers that underlie susceptibility/resiliency to development of depressive-like behaviors during chronic pain state. Genome-wide RNA-seq analysis was used to examine the transcriptomic profile of the prefrontal cortex (PFC), a brain region that regulates mood and stress responses, from male rats exposed to

chronic inflammatory pain. Pain-exposed animals were further separated into either '*resilient*' or '*susceptible*' to development of enhanced behavioral emotionality based on behavioral testing. RNA-seq bioinformatic analysis, followed by validation using qPCR, revealed dysregulation of PFC genes involved in neuroinflammation, neuroplasticity and oxidative stress. Specifically, *S100a9*, *Fmod* and *Cd74*, genes with functional roles in neuroinflammation and immune-inflammatory responses, and *Fos*, *Lox*, *Gstm2*, *Nupr1* and *Mgst1*, genes associated with oxidative stress/antioxidative pathways, were significantly dysregulated between '*resilient*' or '*susceptible*' pain groups. Moreover, differentially expressed genes (DEGs) were further characterized in the PFC of female animals exposed to chronic pain and in rodents stress models to determine whether their dysregulation is driven by common stress responses vs. affective pain processing. Altogether these results continue to strengthen the connection between dysregulation of PFC genes involved in neuroinflammatory and oxidative stress processes with increased behavioral emotionality often expressed in chronic pain states.

Disclosures: A. Kornstad: None. **K. Tefft:** None. **M. Girgenti:** None. **M. Banasr:** None. **V. Duric:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.050/LBA49

Topic: G.05. Mood Disorders

Title: Antidepressant-like effects of betanin, a phytochemical from the beetroot plant, in the chick social-separation stress test, a dual screening assay of anxiety and depression.

Authors: *S. W. WHITE, **V. A. VILLARREAL**;
Psychology & Philosophy, Sam Houston State Univ., Huntsville, TX

Abstract: Phytochemicals are naturally occurring compounds produced by plants to promote survival and have demonstrated numerous beneficial health effects. Betanin, found in the beetroot plant (*beta vulgaris*), has demonstrated antioxidant, anti-inflammatory, antimicrobial, anticancer, and neuroprotective effects. Preclinical studies and small sample clinical trials suggest betanin may reduce symptoms associated with anxiety and/or depression. The chick social-separation stress test exposes chicks to an isolation stressor which elicits distress vocalizations (DVocs) as a means to re-establish contact with conspecifics. Isolated chicks display a high rate of vocalizations over the first three min which gradually declines over the following 27 min and remains low but stable for the remainder of the isolation period. The initial high rate of DVocs in the first 3 min models a state of panic (i.e., anxiety-like phase) and the low steady rate of DVocs over the last 60 min of isolation models a state of behavioral despair (i.e., depression-like phase). Utilizing male Black Australorp chicks, we conducted a dose-response

study evaluating the potential anxiolytic and/or antidepressant effects of betanin. Starting on day-aged-2, animals were orally-treated with one of three doses of betanin, 10, 30, or 100 mg/kg, or saline twice a day for 8-9 days. Samples sizes for all treatment groups were n = 17-18. On days 9-10, animals were exposed to a 90-minute isolation stressor and DVocs were recorded. Vocalization rates for the two individual phases were analyzed using separate one-way analysis of variance (ANOVA) and post-hoc tests using Fisher's LSD were conducted. Betanin had no effect on DVoc rates during the anxiety-like phase of the model. However, the 30 mg/kg dose of betanin significantly elevated DVoc rates during the depression-like phase of the model compared to saline-treated animals, [$F(3,67)$, $p = .012$], indicative of attenuation of behavioral despair (i.e., antidepressant-like effects). Additional analyses reported a medium to large effect size, $\eta_p^2 = .098$, and suboptimal power with observed power of .578. The results of this exploratory study suggest a prolonged betanin regimen may be useful in reducing symptoms of depression, although further testing is needed before making conclusions. Future studies to evaluate the effects of betanin on biomarkers associated with depression, such as the stress hormone corticosterone and the pro-inflammatory cytokine IL-6, are planned. As market use of phytochemicals become more popular, this avenue of research offers promise in the development of novel approaches to treat mood disorders.

Disclosures: S.W. White: None. **V.A. Villarreal:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.051/LBA50

Topic: G.05. Mood Disorders

Support: NRF-2022M3E5E8081208

Title: Metformin modulates insulin mechanisms to attenuate ROS-induced neuronal damage and alleviate depressive symptoms through a gender-specific mechanism.

Authors: *J.-E. KIM[1,2], J. CHO[3,4], J.-H. KOO[3,4], Y. JANG[3,4], S.-H. JUNG[2,5], T.-K. KIM[3,2,5]; [1]Lab. of Exercise Biochem., Korea Natl. Sport Univ., Seoul, Korea, Korea, Republic of; [2]Sport Sci. Inst., [3]Lab. of Exercise Biochem., [4]Dept. of Training for Hlth. Care and Mgmt., [5]Dept. of Physical Educ., Korea Natl. Sport Univ., Seoul, Korea, Republic of

Abstract: Repetitive stress can cause mood disorders such as depression include weight changes, cognitive impairment, and social withdrawal. Depression is known that women are particularly vulnerable compared to men but the gender-specific mechanisms are not fully understood. Recently, Metformin, as a primary treatment for type 2 diabetes mellitus(T2DM), effects for antidepressant through reverses metabolic dysfunction, neuronal damage and

behavioral changes associated with neurological disorders through neuroimmuological, neuroplastic, and neuro-oxidative modulation. In this study, we aimed to investigate how the mechanisms of depression that affect stress responses in gender are regulated by metformin. To investigate the C57BL/6 mice were treated with 2h x 14d repetitive restraint stress (RST) to induce depression and depressive symptoms were assessed through behavioral tests.RNA-seq was performed to confirm gene and transcript profiling related to the stress response according to gender in ventral hippocampus. And to determine the effect of metformin after repeated stress treatment, 200mg/kg, 10ml/kg metformin was orally administration for 3weeks to RST-susceptible mice. As a result, sociality and desire for life were reduced in RST-susceptible mice through the behavior tests, but this was confirmed to be reversed with metformin treatment. Interestingly, this phenomenon appeared to be more severe in female mice. Additionally, in a previous study, it was confirmed through HT22 cells that reactive oxidative stress(ROS) levels, which had increased due to corticosterone treatment, were alleviated by metformin treatment. Taken together, our findings suggest that female mice are more susceptible to changes in depressive-like behavior as a stress response after repeated stress, and that metformin may alleviate depressive symptoms by increasing insulin signaling in neurons.

Disclosures: J. Kim: None. **J. Cho:** None. **J. Koo:** None. **Y. Jang:** None. **S. Jung:** None. **T. Kim:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.052/LBA51

Topic: G.06. Anxiety Disorders

Support: McNair Foundation

Title: Chronic ambulatory DBS recordings reveal neural patterns during sleep that predict OCD symptom severity

Authors: *T. KUTCHER[1], G. REYES[2], Z. NAQVI[2], V. ALLAM[2], T. B.-L. LIU[3], T. FRACZEK[4], Y. ZHOU[2], A. DENG[2], J. A. HERRON[6], E. STORCH[2], W. K. GOODMAN[5], S. A. SHETH[3], N. R. PROVENZA[3];
[1]Rice Univ., Houston, TX; [3]Neurosurg., [2]Baylor Col. of Med., Houston, TX; [4]Baylor Col. of Med., Seattle, WA; [5]Psychiatry, Baylor Col. of Med., Houston, TX; [6]Dept. of Neurolog. Surgery, Univ. of Washington, Seattle, WA

Abstract: In Obsessive-Compulsive Disorder (OCD), there is emerging evidence of neural circadian rhythms in severely symptomatic patients. However, the relationship between these neural patterns and sleep remains unexplored. Understanding this link could reveal the impact of

neural activity patterns during sleep on disease state and inform improved therapy delivery to treat patients. In this study, we employed a 24/7 ambulatory recording setup using recording-capable deep brain stimulation (DBS) devices for chronic stimulation and local field potential (LFP) recording alongside wearables for tracking sleep metrics. The DBS device was configured to continuously record LFP power in the theta-alpha (9 Hz) frequency band based on our previous work demonstrating its efficacy as a biomarker for OCD symptom state. We tracked neural and behavioral metrics over 30+ days in 4 OCD patients implanted with leads in the ventral capsule/ventral striatum (VC/VS), an effective DBS target for OCD. 2 of the 4 patients in this study were responders to DBS therapy. Despite symptom improvement after DBS, responders still exhibited varying degrees of symptom severity as measured by Yale-Brown Obsessive-Compulsive Scale II (YBOCS II) scores. We developed a sleep-awake classifier using LFP to determine sleep state predictive capability independent of time-of-day information. Results indicate that severely symptomatic patients exhibit significant differences in 9 Hz power not only in sleep vs awake states but also in sleep phases, where NREM phases exhibit higher 9 Hz power than REM sleep and awake states ($p<0.001$). The best classification features for predicting sleep-awake state were rolling amplitude and average of the LFP waveforms, as well as overall spectral power derived from short-term Fourier transforms. We found a strong correlation between classifier accuracy and YBOCS II scores ($R2 = 0.97$), as our classifier could adequately predict sleep states in severe OCD (0.740 to 0.824 AUROC) but failed to adequately predict sleep states in our mildly symptomatic patient (0.559 AUROC). These findings suggest that 9 Hz neural activity in the VC/VS during sleep may be a driving factor in the highly predictable circadian patterns observed in severe OCD and can be used to predict when severely symptomatic patients are asleep. Further research can enforce neural predictability during sleep as an essential aspect of the OCD disease state and lead to new therapeutic strategies.

Disclosures: T. Kutcher: None. **G. Reyes:** None. **Z. Naqvi:** None. **V. Allam:** None. **T.B. Liu:** None. **T. Fraczek:** None. **Y. Zhou:** None. **A. Deng:** None. **J.A. Herron:** None. **E. Storch:** None. **W.K. Goodman:** None. **S.A. Sheth:** None. **N.R. Provenza:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.053/LBA52

Topic: G.08. Other Psychiatric Disorders

Title: Molecular profiling of dorsolateral prefrontal cortex from individuals with bipolar disorder

Authors: *W. JIANG, N. HEINTZ;
Lab. of Mol. Biol., Rockefeller Univ., New York, NY

Abstract: Bipolar disorder (BD) is a psychiatric disorder that patients suffer from fluctuating mood and energy levels, yet the mechanisms by which mood and energy levels are altered remain poorly understood. Several cortical brain areas have been implicated in BD. Form these we focused on the dorsolateral prefrontal cortex (DLPFC) where most changes are predicted to occur based on previous imaging studies. We applied a recently developed strategy called serial fluorescence-activated nuclei sorting (sFANS) (Pressl et al., 2024) that allows to separate multiple neuronal and non-neuronal cell types from human cortical samples. We performed sFANS followed by deep RNA sequencing on DLPFC samples from six clinically diagnosed BD donors. Using this strategy, we profiled the molecular changes in twelve cortical cell-types across different cortical layers in BD patient donors. The nuclear transcriptome data was compared to age, sex matched unaffected control donors (n = 5) for each profiled cell-type using DESeq2. Reelin-positive (RELN+) interneurons possessed the highest number of differentially expressed genes (DEGs) compared to control donors among the twelve profiled cortical cell-types, indicating RELN+ interneurons are significantly affected in DLPFC in BD patients. Using gene set enrichment analysis (GSEA), we identified potential pathways that are perturbed by BD. Ongoing experiments are aimed at developing strategies to isolate subtypes of RELN+ interneurons and study their contribution to the cause and effect of BD. These studies identified a candidate cell-type that is predominantly affected in BD patients, opening the possibility of new therapeutical interventions of BD targeting this cell type.

Disclosures: W. Jiang: None. **N. Heintz:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.054/LBA53

Topic: G.08. Other Psychiatric Disorders

Support: Federal Funds

Title: Glur1, 2/3 expression in the hippocampus of activity-based anorexia (ABA) females.

Authors: A. VANOYE CARLO[1], K. CARVAJAL[2], ***B. V. PHILLIPS-FARFAN**[3];
[1]Inst. Nacional de Pediatría, Mexico City, Mexico; [2]Inst. Nacional de Pediatría, mexico city, Mexico; [3]Inst. Nacional Pediatría, Mexico City, Mexico

Abstract: Anorexia nervosa (AN) is a serious eating disorder. It is defined by abnormally low body weight, excessive and irrational fear of gaining body weight, distorted bodily perception and intense anxiety associated with their body image or weight. AN prevalence is 1-2%, showing many relapses and a low recovery. Although underestimated, mortality from AN is the highest among all mental disorders. Activity-based anorexia (ABA) reproduces the hyperactivity, body

weight loss and low food intake of AN. Morphological alterations and changes in GABAergic receptors have been observed in the hippocampus, associated to ABA. Thus, our objective was to determine if there is an alteration in the expression of different glutamate receptors, associated with ABA in pubertal female rats. Wistar female rats (21-day-old) were housed individually, divided in four groups: 1) ad libitum food and drink, 2) with access to an exercise wheel, 3) with access to food for only 1 hour per day, and 4) subjected to ABA (exercise wheel plus access to food for only 1 hour per day). Glutamate receptor-1 and 2/3 expression was assessed by immunohistochemistry. The usual characteristics were observed: increased activity in the exercise wheel, body weight loss and low food intake. A trend for augmented GluR2/3 and reduced GluR1 expression in ABA females was observed.

Disclosures: A. vanoye carlo: None. **K. Carvajal:** None. **B.V. Phillips-Farfan:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.055/LBA54

Topic: G.08. Other Psychiatric Disorders

Title: Effects of electrical vestibular nerve stimulation (VeNS) for insomnia on mental health related quality of life (HRQoL): a secondary analysis of a randomized, double-blind sham-controlled trial

Authors: *J. MCKEOWN[1,2], G. CURRY[3], J. REEL[2], R. ROBINSON[2], S. WATSON[2], T. CHEUNG[4,5], J. SITTLINGTON[3];
[1]UC San Diego, La Jolla, CA; [2]Neurovalens Ltd., Belfast, United Kingdom; [3]Sch. of Biomed. Sci., Ulster Univ., Coleraine, United Kingdom; [4]The Mental Hlth. Res. Ctr., [5]The Sch. of Nursing, The Hong Kong Polytechnic Univ., Hong Kong SAR, China

Abstract: Insomnia is intrinsically linked to poor mental health. The aim was to explore the impact of an electrical vestibular nerve stimulation (VeNS) treatment for insomnia on mental health-related quality of life (HRQoL). This study was a secondary analysis of a double-blind randomised, sham-controlled trial (RCT) that evaluated the efficacy and safety of VeNS on chronic insomnia. The study was undertaken at two sites in the United Kingdom (UK) and Hong Kong (HK) (ID:NCT04452981) and included adults (18-80 years) with chronic insomnia (Insomnia Severity Index (ISI) score ≥15). Eligible participants who provided written consent, were randomly assigned to either sham or active groups and were instructed to use their device daily at home, for 30 minutes, over a period of 4 weeks (minimum 5 days per week). The primary outcome of the RCT was change in ISI score from baseline to week 4. A secondary outcome was change in the Short Form-36 (SF36) at 4 weeks. To explore the impact of VeNS for insomnia on mental HRQoL, the SF-36 Mental Component Summary score (MCS) was

calculated on a scale from 0 to 100 in accordance with the SF-36 scoring manual with the change from baseline calculated. A higher score represents better mental HRQoL. Data on device usage, including the applied stimulation intensity, session duration (in minutes), and total number of completed sessions, were recorded and uploaded through a dedicated study application. Participants (mean age: 40.8 ± 13.5 years) were mostly female (66.7 %) and of Asian ethnicity (68.0 %). A per-protocol analysis reported that 95% of participants within the active group (n=61) reported an improvement in their ISI score with a mean reduction of 5.80 [95%CI:-6.79, -4.81] points, while 75% of participants within the sham group (n=65) reported an improvement in their ISI score with a mean reduction of 3.52 [-4.74,-2.30] points, with the active group's improvement being significantly greater($p=0.013$). The MCS score for the active group increased by 7.62 points ($p<0.001$), exceeding the minimal clinically important difference. The sham group's increase was not statistically significant (3.51,$p=0.112$). The between-group difference in MCS score was significant ($p=0.016$). There was no significant correlation between stimulation power level used and ISI score improvement ($r=0.142$, $p=0.284$). The findings from this secondary analysis shows that the significant improvement in insomnia severity observed in the active group led to greater improvements in mental HRQoL. Future research should investigate how VeNS, a low risk and non-invasive intervention for chronic insomnia, could also benefit individuals with specific mental health difficulties.

Disclosures: **J. McKeown:** A. Employment/Salary (full or part-time):; Neurovalens Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurovalens Ltd. **G. Curry:** 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.; Ulster University, Coleraine. **J. Reel:** A. Employment/Salary (full or part-time):; Neurovalens Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurovalens Ltd. **R. Robinson:** A. Employment/Salary (full or part-time):; Neurovalens Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurovalens Ltd. **S. Watson:** A. Employment/Salary (full or part-time):; Neurovalens Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurovalens Ltd. **T. Cheung:** 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.; The Hong Kong Polytechnic University. **J. Sittlington:** 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.; Ulster University, Coleraine.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.056/LBA55

Topic: G.08. Other Psychiatric Disorders

Title: Predicting adolescent depression and anxiety using machine learning models

Authors: *Y. AHN;
Yale-NUS Col., Singapore, Singapore

Abstract: Predicting adolescent depression and anxiety using machine learning models
Although early intervention in adolescent depression and anxiety disorders is crucial, they often remain underdiagnosed. This is in part because the presentation of symptoms can differ from that of adults, complicating the diagnostic process. To address this gap, machine learning models may offer novel tools to support early detection.
In this study, we extracted data from the US National Survey of Children's Health (NSCH) - a nationally representative, annual survey of children's health. Each year, guardians of selected children are asked to complete surveys on their child's: (i) mental and physical health, (ii) access to health care, and (iii) family, neighborhood, school, and social environments. We combined data from 2016-2022, restricting analysis to adolescents aged 12-17. After feature selection and engineering, our final sample included data from 78,379 participants and 79 variables. Of the adolescents observed, 9% had depression and 16% had anxiety.
Using the combined dataset, we trained and tested five machine learning models to predict the presence of either depression and anxiety. As predictor variables, we included: 50 variables related to the child's living environment and experiences ('environmental'), 19 related to non-psychiatric health conditions ('health'), and 10 related to the child's behaviors ('behavioral'). Subsequent analyses used the model with maximum sensitivity, selected to minimize false negatives (Random Forest). When all three categories of variables (environmental, health-related, and behavioral) were used to train the model, the model showed 83% overall accuracy (0.77 sensitivity, 0.84 specificity, and an ROC AUC score of 0.88).
An adolescent's: (i) special needs status, (ii) history of being bullied, (iii) limited ability to do things, (iv) ability to make friends, and (v) difficulties with memory emerged as the strongest predictors of depression and anxiety.
Taken together, this study presents a proof of concept for how machine learning models can contribute to the early identification of depression and anxiety amongst adolescents. Our findings suggest that in schools or primary care settings, a screening tool can be developed to flag out at-risk adolescents based on a limited set of environmental, health-related and behavioral questions. More broadly, our findings underscore how a range of adversities and environmental settings may be associated with the presentation of mood-related symptoms. These results are consistent with allostasis and epigenetic models of mental health, and may suggest modifiable risk factors to target.

Disclosures: Y. Ahn: None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

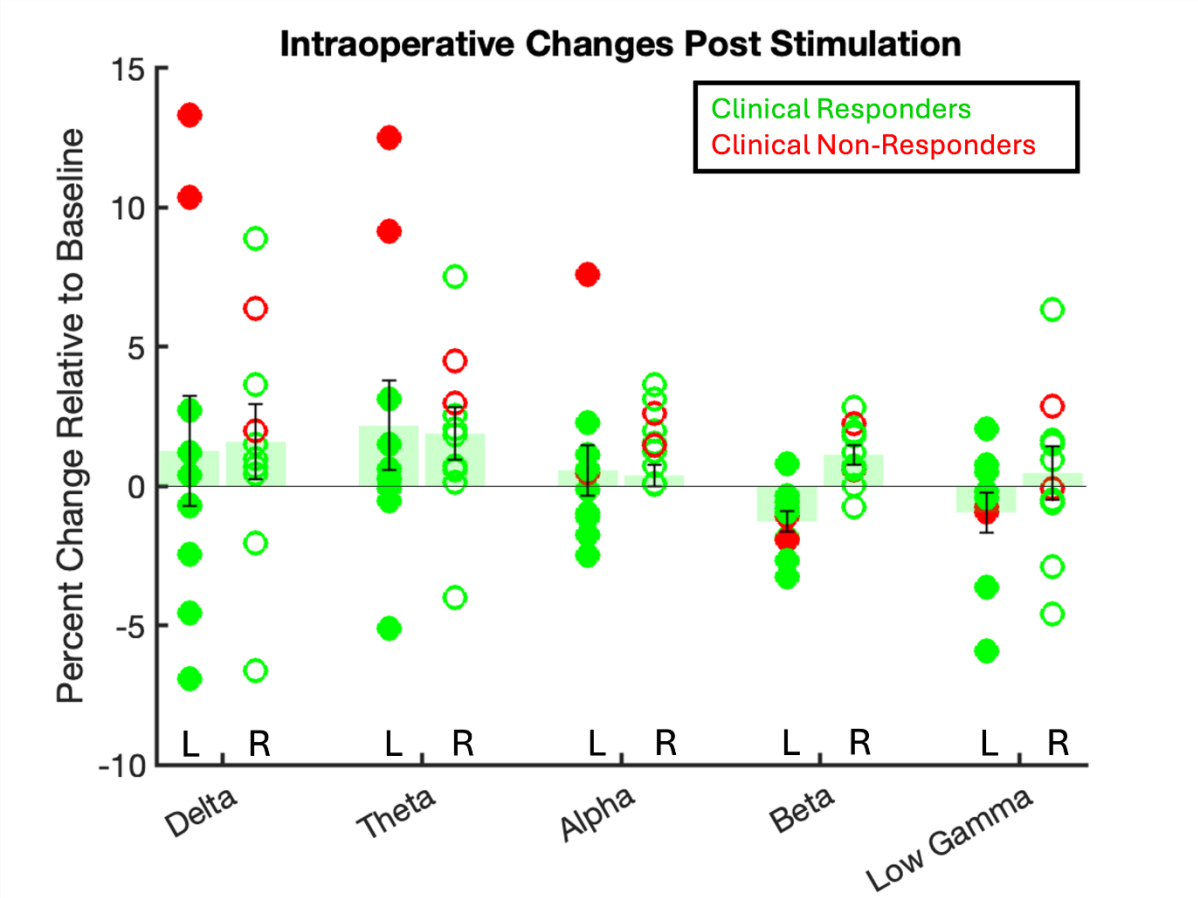
Program #/Poster #: LBA007.057/LBA56

Topic: G.08. Other Psychiatric Disorders

Title: Intraoperative biomarker of non-response in patients with severe obsessive-compulsive disorder undergoing deep brain stimulation

Authors: Z. IMTIAZ[1], S. H. OLSON[1], H. S. MAYBERG[4], K. CHOI[2], B. H. KOPELL[1], M. H. FIGEE[1], *A. H. SMITH[3];
[2]Radiology / Neurosurg., [3]Psychiatry, [1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Ctr. for Advanced Circuit Therapeut., Mount Sinai, New York, NY

Abstract: Biomarkers that determine whether a person will respond to a certain treatment would be clinically valuable, and may also advance understanding of pathophysiological mechanisms. However, to develop robust biomarkers it may be necessary to test how the brain responds to a particular intervention. Here, we examined one such dynamic biomarker: the brain's response to brief stimulation trains prior to permanent implantation of deep brain stimulation (DBS) electrodes in patients with severe obsessive-compulsive disorder (OCD). The macroelectrodes were placed in the ventral anterior limb of the internal capsule (vALIC) for eventual outpatient treatment, but intraoperatively we examined brain activity before and after delivering two minutes of electrical current to the pre-operatively determined white matter therapeutic target. Specifically, pre- and post-stimulation we recorded two minutes of resting-state local field potentials (LFPs) in the globus pallidus externus (GPe), the basal ganglia grey matter nucleus recently implicated by the main animal model of OCD. All patients were then followed for six months post-operatively to track their clinical outcomes. We found that of our cohort of 10 patients (mean age = 35.5 ± 17.7 years; 6 males, 4 females), there was an average decrease of 40.14% in the cohort's Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score, significantly improved from their pre-DBS Y-BOCS score ($p=1.6e-4$, paired t-test; $t(9)=6.22$, 95% CI = [7.82 16.77]). At month six, only two patients (1 male, 1 female) never reached the standard criterion for clinical response, defined as greater than 35% decrease in YBOCS score. Those same two patients were also the only patients to display acute left-sided elevation of GPe low-frequency LFPs (delta: 1-4 Hz, theta: 4-7 Hz) in response to intraoperative stimulation (Figure 1). These preliminary findings may provide a signal that could be used to rapidly gauge the suitability of individuals' circuits for planned treatments, potentially paving the way to noninvasive techniques for predicting response to OCD DBS.



Disclosures: Z. Imtiaz: None. **S.H. Olson:** None. **H.S. Mayberg:** None. **K. Choi:** None. **B.H. Kopell:** F. Consulting Fees (e.g., advisory boards); Medtronic, Abbott, Turing. **M.H. Figee:** None. **A.H. Smith:** None.
Late-Breaking Poster

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Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.058/LBA57

Topic: G.08. Other Psychiatric Disorders

Support: NIH Grant R00MH121355

Title: Investigating the neurophysiological mechanisms of chronic unpredictable stress.

Authors: *D. A. SAN MIGUEL, Jr[1], J. DONEGAN[2];
[1]Col. of Pharm., Univ. of Texas, Austin, Austin, TX; [2]Psychiatry, Dell Med. Sch. at UT Austin, Austin, TX

Abstract: Chronic stress is a risk factor for many psychiatric disorders, including mood and anxiety disorders. The ventral hippocampus (vHipp), analogous to the anterior hippocampus in humans, mediates anxiety-related behaviors and the neuroendocrine response to stress. Additionally, postmortem brain studies have revealed significant reductions in the number of parvalbumin (PV) interneurons within the hippocampus in individuals diagnosed with major depressive disorder and animals exposed to stress. Therefore, the goal of the current experiments was to identify the neural circuit mechanisms by which chronic unpredictable stress (CUS) produces anxiety-like behaviors in C57BL/6J male and female adult mice. In Study 1, we first measured anxiety-like behaviors in mice after CUS. Mice were exposed to CUS, which involved 14 unique stressors per week (two per day) for three weeks. We found that CUS significantly reduced the time spent in the center of the arena on the open field test (OFT) and the time spent in the open arms of the elevated plus maze (EPM). In Study 2, we used opto-electrophysiology to determine the effect of CUS on vHipp cell firing. Mice were briefly administered CUS, then vHipp pyramidal cells projecting to the mPFC were identified by a fluorescent reporter, and extracellular electrophysiology was used to measure the firing rate. We found that the firing rate of vHipp to medial prefrontal cortex (mPFC) projection neurons was significantly increased in mice exposed to CUS which is in alignment with previous research that has shown that the specific projection from vHipp to the mPFC is necessary for anxiety-related behavior. We have shown previously that the firing rate of these cells is regulated by inhibitory PV interneurons. Therefore, to investigate how PV interneuron inhibition is affected by CUS, we used optogenetics to inactivate the vHipp PV and found that inactivating these inhibitory PV cells led to increased firing rates of vHipp◊mPFC projection neurons in control animals but not in CUS animals, suggesting that this dysregulation of inhibition is what is driving the significantly higher firing rates. To further explore whether this deficit in PV modulation is the primary mechanism driving these anxiety-like effects, in Study 3 we plan to investigate whether an excitatory Designer Receptor Exclusively Activated by Designer Drugs (DREADD) targeting PV interneurons in the vHipp is sufficient to alleviate anxiety-like behaviors in mice exposed to CUS. Together, these results will provide insight into the neural circuit mechanisms by which chronic stress leads to anxiety-like behavior and the cell types involved in modulating this.

Disclosures: D.A. San Miguel: None. **J. Donegan:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.059/LBA58

Topic: G.08. Other Psychiatric Disorders

Support: NIH Grant AI164769
NIH Grant AG076949

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NIH Grant AG080790

Title: Hippocampus molecular pathway disruption in major depressive disorder at single-nucleus and spatial resolution

Authors: *M. MARIANI[1,8], C. SISSOKO[2,8], A. RAMNAUTH[2,8], M. REZAEI[2,8], M. B. WAMALWA[2,8], R. RAMKUMAR[2,8], Z. ZHANG[9], L. POLIZZI[11,2], A. TARTT[2,8], C. FULMORE[8,2], Y. LIU[2,3], Y.-Y. HUANG[8], A. J. DWORK[8,2,12,4], G. ROSOKLIJA[2,12,4], V. ARANGO[2,8], R. HEN[2,10,5,6], J. MANN[2,8,7], H. GALFALVY[2,8], M. BOLDRINI[2,8];
[2]Psychiatry, [3]Biostatistics, [4]Pathology and Cell Biol., [5]Neurosci., [6]Pharmacol., [7]Radiology, [1]Columbia Univ., New York, NY; [8]Mol. Imaging and Neuropathology, [9]Mental Hlth. and Data Sci., [10]New York State Psychiatric Inst., New York, NY; [11]Univ. of Trento, Pisa, Italy; [12]Macedonian Acad. of Sci. & Arts, Skopje, North Macedonia, The Republic of

Abstract: Major depressive disorder (MDD) is characterized by recurrent episodes, severe disease burden, and high suicide rates, with brain studies showing smaller hippocampal volume and granule neuron (GN) loss associated with the disorder. This research aims to determine if reduced adult neurogenesis, neuroplasticity and cell survival have a role in hippocampus anatomical and functional disruptions in MDD. To this end, we analyzed over 350,000 nuclei from untreated MDD and neurotypical control subjects using single-nucleus RNA and ATAC sequencing, Visium spatial transcriptomics, and Xenium multiplex ISH (10X Genomics). We included 52 samples from 9 male deeply phenotyped MDD cases and 12 male controls. Using integration and clustering, we identified 31 cell clusters across 12 broad cell types. We validated these clusters against recent studies. Cell types like oligodendrocytes, astrocytes, and granule neurons (GN) mapped well on their expected regions. RNA Velocity on spatial data identified a neurogenic trajectory going from the subgranular zone to the granule cell layer, expressing maturational stage-specific genes. Using machine learning, we identified quiescent progenitors (Type I), proliferating progenitors (Type II), neuroblasts (Type III), and immature GN (ImGN) based on selected gene expression. Pseudotime trajectory analysis supported a differentiation pathway from Type I, to Type II, Type III, ImGN, and GN, aligning with patterns observed in spatial data. In MDD, cell-type specific analyses reveal significant (FDR < 0.05) alterations in gene expression and chromatin accessibility, with GN showing consistent dysregulation across modalities. GN, excitatory neurons, and ependymal cells exhibited the highest numbers of differentially expressed genes and accessible chromatin regions, highlighting their central role in the molecular disruptions associated with MDD. PsyGeNET analysis identified 43 dysregulated genes associated with psychiatric disorders, including 15 linked to depression ($p = 0.033$). Gene set enrichment analysis revealed pathways related to apoptosis and cellular stress upregulated in GN and ImGN in MDD. This study provides the first single-nuclei and spatial multi-omics profiling of the human hippocampus in MDD, revealing detailed neurogenic trajectories that are altered in MDD. Key findings include altered gene expression and chromatin accessibility in GN and progenitors, with pathways controlling inflammation and apoptosis being implicated in MDD. The study highlights potential molecular targets for therapeutic intervention, though the results need replication in larger cohorts.

Disclosures: M. Mariani: None. **C. Sissoko:** None. **A. Ramnauth:** None. **M. Rezaei:** None. **M.B. Wamalwa:** None. **R. Ramkumar:** None. **Z. Zhang:** None. **L. Polizzi:** None. **A. Tartt:** None. **C. Fulmore:** None. **Y. Liu:** None. **Y. Huang:** None. **A.J. Dwork:** None. **G. Rosoklija:** None. **V. Arango:** A. Employment/Salary (full or part-time):; Work by VA related to this abstract was completed when she was employed at Columbia and the New York State Psychiatric Institute; the opinions expressed in this article are the author.. **R. Hen:** None. **J. Mann:** Other; JJM receives royalties for commercial use of the C-SSRS from the Research Foundation of Mental Hygiene. **H. Galfalvy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); HG and her family own stocks in Illumina, Inc.. **M. Boldrini:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.060/LBA59

Topic: G.09. Drugs of Abuse and Addiction

Support: NIAAA F32 AA029866
NIAAA R01 AA028406
NIAAA L40 AA030427

Title: Prenatal alcohol and cannabinoid co-exposure produces persistent changes in cannabinoid receptor 1-associated synaptic gene networks in the dorsal striatum of middle-aged mice.

Authors: *S. K. ROUZER[1], R. C. MIRANDA[2];
[1]Texas A&M Col. of Med., Bryan, TX; [2]Neurosci. and Exptl. Therapeut., Texas A&M Univ., Bryan, TX

Abstract: Background/Purpose: Alcohol and cannabis are two of the most consumed psychoactive substances by pregnant persons today, with young adults of child-bearing age increasingly engaging in simultaneous alcohol and cannabinoid (SAC) use. Although investigations of prenatal SAC are currently limited, ongoing experiments in preclinical models have revealed synergistic effects of SAC compared to single-drug exposure alone, mediated in part through cannabinoid receptor 1 (CNR1) activity. The goal of this investigation was to determine whether SAC imposes distinct, persistent changes in CNR1-associated gene expression in the dorsal striatum, a region associated with regulation of alcohol-seeking behaviors.
Method: Pregnant C57Bl/6J mice were assigned to one of four groups: drug-free control, alcohol-exposed, cannabinoid-exposed or SAC-exposed, and drug exposure occurred daily between Gestational Days 12-15. Dams received an intraperitoneal injection of cannabinoid agonist CP-55940 (750μg/kg) or volume-equivalent saline, and were then placed in vapor

chambers for 30min of inhalation of ethanol or room air (controls). Approximately one year after birth, offspring dorsal striatal tissue was collected for RNA isolation. Quality-verified samples were then processed for bulk RNAsequencing and transcript quantification of preselected genes. **Results**: Prenatal SAC reduces CNR1 receptor-interacting protein (*CNRip1*) expression, with effect sizes larger in female offspring than male siblings, without producing changes in *CNR1* expression. As *CNRip1* negatively regulates presynaptic CNR1 activity, this may indicate that SAC results in hyperactive striatal CNR1 signaling. Furthermore, cannabinoid exposure in male offspring significantly disrupts the relationship between CNR1 and genes associated with cytoskeletal reorganization, including *Rac1, Wasf1, Actr3, BCR, Dlg4,* and *Dlgap 3.* Preliminary within-animal comparisons of gene expression and adulthood behaviors reveal that *CNR1* expression corresponds significantly with self-administration of alcohol in control animals, and this relationship is lost in drug-exposed offspring; instead, *CNRip1* expression better predicts alcohol-seeking behaviors in all drug-exposed offspring.
Conclusions: Prenatal SAC produces distinct changes in CNR1-associated striatal gene expression compared to single-drug and drug-free controls, with effects detectable in middle age. Subsequent analyses of cortical tissue will facilitate network-level analysis of corticostriatal gene expression, to investigate long-term changes in circuitry that regulates alcohol-seeking behaviors.

Disclosures: S.K. Rouzer: None. **R.C. Miranda:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

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Program #/Poster #: LBA007.061/LBA60

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant AA028352
NIH Grant AA029178

Title: Encoding of Memory-like States for Early Alcohol Experience in Drosophila

Authors: C. LARNERD, ***F. WOLF**;
Univ. of California, Merced, Merced, CA

Abstract: Alcohol-naive animals develop tolerance after a single alcohol exposure. It’s unknown how this early behavioral plasticity supports later developing plasticity associated with alcohol use disorder. Drosophila is helpful for identifying the molecular and circuit mechanisms for alcohol-induced plasticity. We discovered that three memory-like states are the basis for alcohol tolerance. Alcohol memory-like states are genetically and behaviorally identical to classically defined memory traces: labile anesthesia-sensitive, consolidated anesthesia-resistant, and

consolidated long-term memory. Thus, alcohol tolerance and classical learning and memory share molecular signaling pathways. Each alcohol memory-like state is encoded by distinct neural circuitry. Tolerance memory circuitry, however, is distinct. For example, alcohol labile memory and classical labile memory require the PACAP-like neuropeptide amnesiac in different lobes of the mushroom body learning and memory centers. Moreover, chronic alcohol long-term memory is encoded completely independently from the mushroom body circuitry that is critical for classical associative long-term memory. We highlight the parallels between Drosophila and mammals for the memory-like encoding mechanisms for alcohol, and how partial overlaps in circuitry might affect memory strength and perdurance.

Disclosures: C. Larnerd: None. **F. Wolf:** None.

Late-Breaking Poster

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Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.062/LBA61

Topic: G.09. Drugs of Abuse and Addiction

Support: TI2030-Major Projects (2021ZD0202100,2021ZD0200801)

Title: Neuroimaging and NeurophysiologyAbnormalities in Etomidate Abusers

Authors: *J. ZHENG[1,2], S.-Z. AI[4], Y. SUN[3], J. SHI[2];
[1]Peking Univ., Beijing, China; [2]Dept. of Pharmacology, Sch. of Basic Med. Sciences, Natl. Inst. on Drug Dependence, Peking Univ., Beijing, China; [3]Dept. of Pharmacology, Sch. of Basic Med. Sciences, Natl. Inst. on Drug Dependence, Peking Univ., Beijing City, China; [4]The Affiliated Brain Hospital, Guangzhou Med. Univ., Guangzhou, China

Abstract: Background: Etomidate, a general anaesthetic and a relatively new psychoactive substance has increasingly been non-medically abused. Its abuse can lead to paranoia and irritability, threatening safety. However, the damage of etomidate exposure on the brain is unknown. Here, we assessed clinical and neurophysiological abnormalities in etomidate abusers. **Methods:** Etomidate, methamphetamine and heroin abusers were recruited from voluntary drug rehabilitation hospital and compulsory drug rehabilitation centers, they were male and meet the diagnostic criteria of substance use disorder in DSM5. Demographic and drug-using characteristics were collected via self-developed questionnaires. We compared the EEG characteristics of etomidate abusers (n=24) with methamphetamine (n=17), heroin abusers (n=26) and healthy controls (n=18). EEG data were collected using a 32-channel system in a resting state with eyes closed, then were preprocessed by Matlab and EEGLAB. The MRI data of the etomidate abusers (n=42) and healthy controls (n=51) were acquired using a Siemens Prisma 3-Tesla MRI scanner and were preprocessed and analyzed using FreeSurfer and fMRIprep.

Results: Resting-state EEG power spectrum analysis revealed significantly higher relative beta power in all drug abusers groups compared to healthy controls. Specifically, the etomidate abusers exhibited significantly higher whole-brain beta power than the heroin and methamphetamine groups. Within the etomidate group, Pz Beta relative power positively correlated with the degree of etomidate addiction (R=0.67, *P*=0.00072), while O2 Delta relative power was negatively correlated with it (R=-0.8, *P*=0.0032). For MRI index, compared to healthy controls, etomidate abusers had a significant increase in the volume of the left and right putamen and reduced cortical thickness in the bilateral orbitofrontal cortex, left pars orbitalis, left pars triangularis, and right rostral middle frontal cortex in etomidate group ($P_{FDR} < 0.05$). Importantly, the thickness of the left medial orbitofrontal cortex was negatively correlated with both the onset age and the initial dose of etomidate abusers. **Conclusion:** Etomidate abusers have similar increased resting-state beta activity with other drug addictions, suggesting its potential as a common biomarker for drug use disorders. Abusing etomidate significantly impacts brain structure, particularly in the orbitofrontal cortex (OFC) and putamen. This study provides the first evidence for the brain damage of etomidate abusers.

Disclosures: J. Zheng: None. **S. Ai:** None. **Y. Sun:** None. **J. Shi:** None.

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Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.063/LBA62

Topic: G.09. Drugs of Abuse and Addiction

Title: Effects of chronic oral kratom on naloxone precipitated opioid withdrawal in male and female rats

Authors: S. LANG[1], A. O'BRIEN[2], E. RENGEL[2], ***M. GADES**[1];
[1]Univ. of St. Thomas Neurosci. Program, Saint Paul, MN; [2]Univ. of St. Thomas, Saint Paul, MN

Abstract: Rationale: Kratom is a drug derived from the leaves of mitragyna speciosa trees, and has been used for centuries in Southeast Asia for its stimulant and opioid-like effects. In the United States, it has been primarily used for recreation and to mitigate opioid withdrawal symptoms. Kratom is currently unregulated on the federal level due to lack of evidence on the drug's risks and/or benefits. Previous studies have focused on individual alkaloids of kratom and have largely ignored female animals. This study, therefore, aimed to determine how repeated oral administration of kratom powder interacts with the brain via opioid receptors to create withdrawal and tolerance in male and female rats. Methods: Following baseline testing in open field test, elevated plus maze, and tail flick paradigms, sixty-six Sprague Dawley rats (33 female) were randomly assigned to receive either 10% sucrose solution or 35mg/kg kratom in 10% sucrose solution for 15 days. On the final day of drug administration, sucrose animals and half of

the kratom animals received subcutaneous injections of saline, while the other half of kratom animals received subcutaneous injections of 3mg/kg naloxone to precipitate opioid withdrawal. Changes from baseline were compared between groups and sexes. Results: Kruskall Wallis tests and ANOVA revealed no significant difference in locomotor activity, anxiety, or pain threshold between control, kratom, and kratom withdrawal groups ($p>0.05$). Additionally, there were no statistically significant sex differences ($p>0.05$). Conclusions: This study found that precipitated opioid withdrawal using naloxone did not significantly impact behavioral measures of withdrawal and dependence. These results suggest that kratom may act as an alternative harm reduction drug for individuals addicted to opioids. Additionally, we found no sex differences in measures of opioid withdrawal and dependence. Further information is needed to compare oral kratom to other opioid harm reduction drugs such as methadone.

Disclosures: S. Lang: None. **A. O'Brien:** None. **E. Rengel:** None. **M. Gades:** None.

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LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.064/LBA63

Topic: G.09. Drugs of Abuse and Addiction

Title: Social modulation of pain in drug-naïve observers of mice administered chronic morphine.

Authors: *H. K. DEOL[1], L. J. MARTIN[2];
[1]Psychology, Univ. of Toronto, Mississauga, Mississauga, ON, Canada; [2]Psychology, Univ. of Toronto, Mississauga, ON, Canada

Abstract: Opioids, known for their effectiveness, affordability, and long-lasting effects, are commonly prescribed for pain management. In the last decade, opioid prescribing and opioid misuse have dramatically increased, partly due to factors such as pharmaceutical marketing practices and medication formulations. Mice undergoing opioid withdrawal exhibit specific behaviours such as excessive teeth chattering, genital grooming, piloerection, etc.. Although physical withdrawal symptoms subside after a short time, emotional symptoms such as anxiety & irritability often persist for months due to lasting changes in neuropeptides, receptors, and molecular changes. Such altered emotional symptoms in individuals undergoing withdrawal can impact caregivers in their immediate environment. Family members often suffer greatly due to the unpredictability associated with having a relative with an opioid use disorder. In humans, this effect has commonly been referred to as the ‘ripple effect’ as numerous family members are often affected to varying degrees. Stressors come in the form of having to deal with the patients’ behavioural disturbances while restricting their own social activities. Hence these studies aimed to investigate the effects of drug-dependent individuals’ behaviour on the pain sensitivity of their drug-naïve cohabitant. All studies were conducted in adult (7-10-week-old) male C57BL/6 mice.

To date our studies have shown a stress-induced decrease in mechanical pain thresholds as a result of cohabitation with a cagemate undergoing natural opioid withdrawal. These results are further supported as the behavioural hypersensitivity observed can be reversed by the administration of metyrapone hence blocking the stress response. Homecage behaviour analysis has revealed an increase in isolated behaviours in the drug-naïve observers as a result of repeated negative interactions taking place with their opioid administered counterparts. The placement of a physical divider or a social buffer tends to reverse these behaviour effects hence suggesting that the alterations in social interactions occurring in the homecage may ultimately be the source of social stress.

Disclosures: H.K. Deol: None. **L.J. Martin:** None.

Late-Breaking Poster

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Program #/Poster #: LBA007.065/LBA64

Topic: G.09. Drugs of Abuse and Addiction

Support: NIGMS Grant GM113131
NIDA/NIGMS joint grant (DA056871)

Title: Individual differences in ethanol seeking: integrating behavioral economics and neurobiological markers of cue-induced reinstatement

Authors: *T. ALLEN, J. HENSLEY, A. KALINOWSKI, G. KOOHKANSAADI, H. MANNING, S. CHARNTIKOV;
Psychology, Univ. of New Hampshire, Durham, NH

Abstract: Alcohol Use Disorder (AUD) affects millions globally, yet current treatments remain largely ineffective. This study investigated the relationship between individual behavioral markers and neurobiological mechanisms linked to ethanol self-administration and cue-induced reinstatement in rats. We employed a long-access ethanol self-administration model to collect behavioral data, including essential value, responding in the face of negative consequences, and anxiety-related behaviors. Following behavioral procedures, we measured c-Fos expression in brain regions implicated in cue-induced reinstatement. Results revealed that higher essential value was associated with increased substance use-related behaviors and c-Fos expression in several brain regions. Multivariate analyses identified significant behavioral predictors of c-Fos expression during cue-induced reinstatement. Principal component analysis and regression further elucidated the relationship between behavioral patterns and neural activation, with the strongest associations observed in the prelimbic cortex, piriform cortex, and lateral hypothalamus. Our findings provide novel insights into the behavioral and neurobiological

factors underlying individual differences in cue-induced reinstatement of ethanol seeking. This study establishes a foundation for future research to refine neurobiological and behavioral markers associated with individual differences in AUD, potentially leading to more personalized and effective treatment strategies.

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Program #/Poster #: LBA007.066/LBA65

Topic: G.09. Drugs of Abuse and Addiction

Title: The Effect of Eye Movement Desensitization and Reprocessing (EMDR) Therapy on Reducing Craving in Populations with Substance Use Disorder: a systematic review and Meta-analysis

Authors: *A. GARZON[1], D. MARTÍNEZ FERNÁNDEZ[2], I. G. AGUILAR GARCIA[4], J. GARCIA[3], M. LUQUIN DE ANDA[5], D. FERNÁNDEZ-QUEZADA[6];
[1]Dept. of Neurosciences, [2]Farmacobiología, Univ. of Guadalajara, Guadalajara, Mexico; [3]Univ. of Guadalajara, Zapopan, Mexico; [4]Neurosci., [6]Neurocience, [5]Univ. de Guadalajara, Guadalajara, Mexico

Abstract: Substance Use Disorder (SUD) significantly impacts public health, economics, and legal systems worldwide. Approximately 270 million people, or 5.5% of the global population aged 15-64, have used psychoactive substances in the past year. Eye Movement Desensitization and Reprocessing (EMDR) was initially developed in the late 1980s as a therapeutic approach for Post-Traumatic Stress Disorder (PTSD), using bilateral stimulation to integrate traumatic memories with calming physiological responses. However, the effectiveness of EMDR in treating SUD remains unclear, particularly in terms of reducing cravings among affected individuals. This study aims to conduct a systematic review and meta-analysis of the impact of EMDR therapy on craving reduction in individuals with SUD. We examined published, peer-reviewed studies that investigated the continuous associations between EMDR and addictive behaviors, including alcohol, tobacco, cannabis, stimulants, opiates, and other substances. The search was conducted using databases such as PubMed and Web of Science, focusing on studies that measured craving and employed EMDR interventions. Publication bias was assessed using a risk of bias assessment tool and funnel plot analysis. Both random and fixed effects models were used to pool effect sizes, utilizing an R software meta-package. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The results indicated a significant reduction in cravings among patients undergoing EMDR

therapy. Specifically, under the fixed effect model, the standardized mean difference (SMD) was -0.7243, with a 95% confidence interval ranging from -0.9960 to -0.4527 ($z= -5.23$, $p < 0.0001$). The random effects model showed a slightly larger effect size (SMD = -0.7985), with a 95% confidence interval from -1.2314 to -0.3656 ($z = -3.62$, $p= 0.0003$). These findings demonstrate the significant efficacy of EMDR therapy in decreasing cravings in people with SUD.

Disclosures: A. Garzon: None. **D. Martínez Fernández:** None. **I.G. Aguilar Garcia:** None. **J. Garcia:** None. **M. Luquin de Anda:** None. **D. Fernández-Quezada:** None.

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Program #/Poster #: LBA007.067/LBA66

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA Grant U01DA050243

Title: Deep spectrotemporal profiling of ultrasonic vocalization profiles during neonatal opioid withdrawal reveals a kappa opioid receptor component in female mice

Authors: *E. J. SANDAGO[1], K. K. WINGFIELD[2,1], T. MISIC[2], K. JAIN[2], N. ABNEY[2], C. MCDERMOTT[2], K. RICHARDSON[2], M. RUBMAN[2], J. A. BEIERLE[2], S. A. MIRACLE[2,1], B. M. BASKIN[1], E. J. YAO[2], C. D. BRYANT[1];
[1]Pharmaceut. Sci., Northeastern Univ., Boston, MA; [2]Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA

Abstract: Opioid use during pregnancy is a growing public health concern and can lead to neonatal opioid withdrawal syndrome (NOWS). NOWS refers to symptoms that emerge spontaneously following cessation of opioid exposure after gestation. Symptoms include low body weight, body temperature dysregulation, hyperirritability, and excessive, high-pitched crying. There is currently no standard care approach due to high variability of symptom severity. We employ a third trimester-approximate model in mice that is both necessary and sufficient to effectively model NOWS-associated traits. Neonatal inbred FVB/NJ pups are injected with morphine (10 mg/kg, s.c.) or saline (20 ul/g, s.c.) twice daily from postnatal day (P) one to P14. We assess several phenotypes including nociception, ultrasonic vocalization (USV) emission, and locomotor activity during spontaneous morphine withdrawal (16 h post-morphine) on multiple postnatal days. Because neonatal rodent USVs are emitted during isolation to communicate distress and promote maternal attention, USVs can serve to model an enhanced negative affective state during opioid withdrawal. However, the relationship between specific syllables and affective states such as morphine withdrawal remains unknown. Mouse USV syllables are identified by their acoustic features, and we implemented a custom supervised

machine learning model to automatically classify syllables. On P14, morphine exposed pups emitted an increased percentage of Complex 3 syllables. Additionally, morphine-treated females vocalized more and emitted a greater percentage of Complex 3 syllables compared to males. Postmortem brainstem transcriptomics revealed upregulation of the kappa (κ)-opioid receptor (*Oprk1*), whose activity is associated with withdrawal-induced dysphoria. Selectively antagonizing the κ-opioid receptor with norBNI (30 mg/kg, s.c.) was sufficient to reduce USV emissions specifically in morphine exposed female pups during spontaneous withdrawal on P15. Kappa opioid receptor activation with the the κ-opioid receptor agonist with U50,488h on P14 was sufficient to increase USV emission on P10 (both sexes) and P14 (females only). Pups on P14 also showed a significant U50,488h-induced reduction in Complex 3 syllable emissions compared to saline exposed pups. These results indicate a female-specific recruitment of the κ-opioid receptor system and impact of specific syllable differences in neonatal opioid withdrawal symptom severity.

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Late-Breaking Poster

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Program #/Poster #: LBA007.068/LBA67

Topic: G.09. Drugs of Abuse and Addiction

Support: AA026685
AA027372
AA006420
AA007456

Title: The role of the mouse parasubthalamic nucleus in alcohol consumption

Authors: *J. L. DUNNING, Jr.[1], M. KREIFELDT[2], A. OKHUAROBO[3], C. LOPEZ[2], C. MOREAU[2], R. J. SMITH[5], C. RAMAKRISHNAN[6], H. C. BECKER[7], K. DEISSEROTH[8], C. CONTET[4];
[1]Mol. Med., Scripps Res., San Diego, CA; [2]Mol. Med., Scripps Res., La Jolla, CA; [3]Dept of Neuorscience, The Scripps Res. Inst., Toronto, ON, Canada; [4]Mol. Med., The Scripps Res. Inst., La Jolla, CA; [5]Dept Psychological and Brain Sci., Texas A&M Univ., College Station, TX; [6]Stanford Univ., Stanford, CA; [7]Charleston Alcohol Resch Ctr., Med. Univ. of South Carolina, Charleston, SC; [8]Stanford, Stanford, CA

Abstract: Alcohol use disorders are characterized by the loss of control over alcohol drinking and our understanding of the neural populations that influence alcohol drinking is still incomplete. A small nucleus located on the lateral edge of the posterior hypothalamus, known as the parasubthalamic nucleus (PSTN), has recently emerged as a highly interconnected node within a network of brain regions mediating interoception and emotions. This study is the first to describe the contribution of PSTN neurons in alcohol drinking behavior. The PSTN is comprised of glutamatergic neurons, some of which express high levels of corticotropin-releasing factor (CRF, encoded by *Crh*) or preprotachykinin-A (encoded by *Tac1*). To address the functional relevance of this cellular heterogeneity, chemogenetic actuators were expressed within the PSTN of male and female mice using the Cre-lox recombination approach. Excitatory (hM3Dq) or inhibitory (hM4Di or KORD) designer receptors were expressed in subsets of PSTN neurons using *Crh*-IRES-Cre and *Tac1*-IRES-Cre mice, retrograde Cre transport from PSTN target regions in C57BL/6J mice, and activity-dependent Cre induction using FosTRAP2 mice, respectively. Using a chronic limited-access 2-bottle choice model, the results of our studies highlight the differential role of PSTN subpopulations in alcohol drinking behavior. Chemogenetic and optogenetic activation of PSTN *Crh* cells significantly increases alcohol consumption. In contrast, their inhibition significantly reduces alcohol consumption, both in mice subjected to chronic intermittent alcohol vapor inhalation and in air-exposed counterparts. Selective activation or inhibition of general PSTN projections to the central amygdala, bed nucleus of the stria terminalis, or paraventricular nucleus of the thalamus, however, was not sufficient to alter alcohol consumption. To address cell-type specific projections from the PSTN, a chemogenetic INTronic Recombinase Sites Enabling Combinatorial Targeting (INTRSECT) approach was used to selectively activate PSTN cells to target regions via retrograde Flp transport in *Crh*-Cre or *Tac1*-Cre mice . Activation of CeA-projecting PSTN *Crh* cells were sufficient to significantly decrease drinking behavior. Alcohol drinking, withdrawal from alcohol or alcohol expectation was used as stimuli to drive hM3Dq, hM4Di, and/or KORD expression in the PSTN of FosTRAP2 mice. Activations of these ensembles all resulted in significant decreases in alcohol consumption. These observations indicate that the PSTN exerts bidirectional control over alcohol consumption in a cell-type, projection specific and experience-dependent manner.

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Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.069/LBA68

Topic: G.09. Drugs of Abuse and Addiction

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Mayo Graduate School

Title: Caspase-dependent ablation of indirect medium spiny neurons projecting to external globus pallidus promotes compulsive alcohol-seeking and drinking behaviors

Authors: *H. HAROON[1], M. BAKER[2], D.-S. CHOI[3];
[1]Mayo Clin. Rochester, Rochester, MN; [3]Mol. Pharmacol. and Exptl. Therapeut., [2]Mayo Clin. Col. of Med. and Sci., Rochester, MN

Abstract: The dorsomedial striatum (DMS) is primarily recognized for regulating goal-directed reward-seeking behaviors, while the dorsolateral striatum (DLS) is predominantly associated with movement and habitual behaviors. Notably, activating striatal direct-pathway medium spiny neurons (dMSN) enhances reinforcement learning, whereas stimulating striatal indirect-pathway MSN (iMSN) induces avoidance behaviors and inhibits reinforcement. While extensive research has compared the functions of DMS versus DLS or iMSN versus dMSN in reward-seeking, it remains unclear whether iMSN may exhibit distinct roles in suppressing compulsive reward-seeking within each specific striatal subregion. In this study, we sought to address this by selectively ablating $iMSN^{DMS◊GPe}$ and $iMSN^{DLS◊GPe}$ and trained mice to exhibit goal-directed and habitual reward-seeking behaviors using random ratio (RR) and random interval (RI) operant conditioning, respectively. To ablate the circuit in a targeted fashion, we employed a genetically engineered caspase 3, in which activation results in apoptosis. Interestingly, caspase 3-mediated ablation of $iMSN^{DMS◊GPe}$ resulted in an insensitivity to satiety-based reward devaluation in RR-trained mice, consistent with a shift towards habitual behavior. The ablation of $iMSN^{DLS◊GPe}$ did not influence locomotor function in the open field test, nor did it affect the expression of habitual or goal-directed seeking behavior during the devaluation of a random interval or random ratio operant schedule. However, when subjected to quinine adulteration, mice with $iMSN^{DLS◊GPe}$ ablation exhibited increased compulsive alcohol-seeking behaviors in habitual and goal-directed operant conditioning paradigms. Consistently, in a separate cohort of mice, we found that the $iMSN^{DLS◊GPe}$ ablated mice show higher preference and consumption of alcohol than control mice in two-bottle choice experiment, with increasing quinine concentration and exhibit more compulsive-like behavior. The $iMSN^{DLS◊GPe}$ ablated mice prefer more alcohol than control mice while still developing an aversion to seeking the reward. Altogether, our findings reveal an essential role of $iMSN^{DLS◊GPe}$ in behavioral flexibility and inhibiting compulsive-like behavior, which may be a potential therapeutic target for alcohol addiction and other compulsive disorders.

Disclosures: H. Haroon: None. **M. baker:** None. **D. Choi:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Program #/Poster #: LBA007.070/LBA69

Topic: G.09. Drugs of Abuse and Addiction

Support: Leon Levy Foundation

Title: Whole-brain two-timepoint analysis of neuronal activity during the progression of voluntary alcohol drinking

Authors: *E. J. KYZAR, R. SETARA, A. RAMIREZ, B. UCEDA-ALVAREZ, E. RODRIGUEZ, L. ROGERSON, C. D. SALZMAN;
Columbia Univ., New York, NY

Abstract: Alcohol consumption patterns often progress over time, beginning with lower levels of consumption and sometimes progressing to heavier use in persons with alcohol use disorder. Animal models used to study the biological basis of alcohol use disorder typically focus on discrete stages of consumption such as initial intoxication and withdrawal. In most studies, the neural circuitry underlying alcohol use is centered on canonical brain regions involved in particular aspects of the addiction cycle, like the nucleus accumbens for intoxication and the central amygdala for withdrawal. However, addiction is a complex process that evolves over time and likely involves interactions across a broader range of brain areas. Here, we apply recently developed methods that allow for the interrogation of brain-wide activity patterns in an unbiased manner at multiple points in the progression of alcohol consumption. We employ a voluntary alcohol consumption paradigm in mice expressing an activity-dependent genetic label (Trap2:Ai14 mice). Male and female mice were exposed to a modified intermittent access two-bottle free choice (2BFC) task. Activity-dependent neuronal labeling was performed at two timepoints in each animal while the mice were actively consuming alcohol. In the first timepoint, mice were injected with 4-hydroxytamoxifen to label active populations (“trapping”), and, for the second timepoint, mice underwent whole-brain c-fos staining. Mice were split into groups depending on when each timepoint occurred: early-early (EE; “trapped” on the first day of 10% EtOH consumption and sacrificed for c-fos staining 1 week later), early-late (EL; “trapped” on the first day of 10% EtOH consumption and sacrificed for c-fos staining 6 weeks later), and late-late groups (LL; “trapped” 5 weeks after starting 10% EtOH consumption and sacrificed for c-fos staining 1 week later). We performed whole-brain imaging and cell counting with automated segmentation followed by statistical analyses, revealing networks of brain regions with significant overlap at the two timepoints in each group. For example, in the EE group, the top two overall targets were the lateral orbital area and the arcuate nucleus of the hypothalamus. Interestingly, many regions involved in emotional regulation, such as the anterior insula, the basolateral amygdala, and the central amygdala, also showed significant overlap. The two-timepoint whole-brain pipeline and statistical analyses promise to identify previously neglected brain areas involved in different stages of alcohol consumption.

Disclosures: E.J. Kyzar: None. **R. Setara:** None. **A. Ramirez:** None. **B. Uceda-Alvarez:** None. **E. Rodriguez:** None. **L. Rogerson:** None. **C.D. Salzman:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Program #/Poster #: LBA007.071/LBA70

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01AA026865.

Title: Sex differences in diet and alcohol related intake behaviors in mice

Authors: *Z. E. MCCULLERS, B. N. KELLER, C. R. COKER, Y. SILBERMAN;
Neural and Behavioral Sci., Penn State Col. of Med., HERSHEY, PA

Abstract: Background: Alcohol use disorder (AUD) and binge eating disorder (BED) frequently display comorbidity. Research shows that high-fat diets (HFD) can increase alcohol intake, both in human and animal models. Our lab's previous work indicates that male mice consuming intermittent HFD exhibit higher alcohol intake than mice on standard diet. However, whether chow diet composition influences EtOH intake or if sex differences occur has not been studies. Purpose: We hypothesize that chow diet composition and sex significantly shape the ability of HFD to promote alcohol intake Methods: We studied the interactions between chow diet type (Bioserv 4031 or "white chow" vs. Teklad 8604, or "brown chow") and sex HFD modulation of alcohol intake in adult C57Bl6/J mice. Mice were randomly assigned to two groups based on chow diet and split by sex: 1) Male + brown chow diet; 2) Male + white chow diet; 3) Female + brown chow diet; 4) Female + white chow diet. Over a 7-week period, all groups underwent a weekly cycle where they receive HFD (Bioserv F3282, fat calories 60%) for a 24-hour duration (Monday-Tuesday) and consumed their respective chow diets for the remainder of the week. On Tuesday-Friday each week, mice received access to alcohol bottles alongside standard water bottles for four hours per day, starting at 10am each day. Throughout the 7-week paradigm, alcohol concentrations increased every other week, while body mass was recorded daily. Primary outcomes included alcohol intake and changes in body mass post-HFD exposure. Post hoc, we conducted neuroimmune marker analysis of the Central Amygdala (CeA), a key brain region in binge intake behaviors. Results: In male mice, brown chow diet increased HFD intake. Chow diet type did not impact HFD intake in females, although long-term alcohol intake increased HFD intake in females. In all groups, alcohol intake increased across the paradigm, but chow diet type only impacted alcohol intake in male mice. Analysis of the CeA revealed significant differences in the levels of the neuroimmune marker IL-10 among the groups, notably, increased IL-10 levels in white chow males and decreased levels in control females. Conclusion: Control diets influence binge drinking and binge eating in a sex-specific manner. The interaction of sex

and control diet appears to affect IL-10 levels in the CeA. Further validation with additional samples is needed to confirm these findings across all measured components. These findings indicate potential sex-specific neuroimmune responses to diet and alcohol intake. Funding: NIH R01AA026865.

Disclosures: Z.E. McCullers: None. **B.N. Keller:** None. **C.R. Coker:** None. **Y. Silberman:** None.

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LBA007: Theme G Late-Breaking Posters

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant: P20GM103475

Title: Diet modifications and microbiome disruption alters acute and chronic alcohol tolerance development in Drosophila

Authors: *E. RODRIGUEZ BORRERO[1], P. GUTIÉRREZ ORTIZ[2], L. MARRERO[3], A. HERNANDEZ PADILLA[3], O. ROSARIO[3];
[1]Biol., Univ. of Puerto Rico at Cayey, Cayey, PR; [2]Biol., UPR Cayey, Cayey, PR; [3]Biol., UPR-Cayey, Cayey, PR

Abstract: Alcohol Use Disorder (AUD) is an extended global health challenge. Repeated alcohol consumption leads to the development of tolerance, expressed as a reduced response to a normally consumed dose of alcohol. Tolerance has been characterized as acute, rapid, and chronic. The lasting changes in the brain caused by alcohol abuse perpetuate AUD and make individuals vulnerable to relapse. AUD risk is also influenced by the interplay between a person's genes and environmental factors such as: drinking at early age, family history on alcohol problems, mental health condition and diet. The diet has been shown to affect many components of an individual physiology and behavior and can also modify the microbiota composition thus altering the Gut Brain Axis homeostasis. The aim of this study is to determine if diet modification could alter both acute and chronic alcohol tolerance development and if microbiome disruption can alter the tolerance development using a Drosophila model. This study is focused on the use of a Normal Diet (ND, Bloomington Formulation), High Fat Diet (HFD, 30% coconut oil) or High Protein Diet (HPD, 30% autoclaved dry yeast) supplemented with or without an antibiotics cocktail to analyze how these diet variations and microbiome disruption affect the alcohol tolerance development. To test our hypothesis, 2 to 5 days post hatch females flies were exposed to diet modification for 7 consecutive days. The alcohol tolerance development assay was performed by exposing the flies for 2 consecutive days (acute tolerance)

or 5 consecutive days (chronic tolerance) to 50% ethanol injected to a cellulose acetate plug. When 80% of the flies were sedated, the plugs were changed and the difference in sedation time was scored. Our results show that HPD and HFD can significantly increase the sedation time in acute tolerance when compared to ND. Also, we found that this increase is dependent on an intact microbiome because the acute tolerance development significantly decreases when antibiotic cocktail is added to the diet. In addition, HPD decreases the sedation time on chronic tolerance development when compared with ND exposed flies. Taken together our results suggest that diet is an important environmental factor influencing the AUD and this influence is dependent on a healthy microbiome. Understanding how the diet alters the Gut-Brain Axis and its role in AUD could lead to new discoveries in AUD development and treatment.

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Late-Breaking Poster

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Title: Trigeminal circuits dictate innate rejection thresholds for ethanol through oral chemesthesis

Authors: *S. MUKERJEE, K. SONG, D. COHEN, V. MAHAJAN, A. BHATT, A. BROWN, Z. FARAHBAKHSH, K. ERICKSON, Y. QUAN, C. SICILIANO;
Pharmacol., Vanderbilt Univ., Nashville, TN

Abstract: Ethanol is highly unusual among acutely toxic chemicals in that it is readily consumed by essentially all animal species when given access. The central pharmacological effects of ethanol mediate its powerful reinforcing properties, but the neural mechanisms that control palatability of ethanol and explain innate preferences prior to intoxication are unknown. Further,

chronic heavy ethanol drinkers often substitute noxious ethanol-containing products, suggesting that dysregulated drinking may be related to disruption of innate chemical defense systems responsible for oral rejection of toxins. Ethanol's complex flavor profile includes pronounced irritant/burning sensations, termed oral chemesthesis, which become dominant at high concentrations. Following oral stimulation with palatable (15%) versus chemesthetic (50%) concentrations of ethanol, whole-brain cfos mapping revealed chemesthetic-selective activation of multiple sub-nuclei in the spinal trigeminal nucleus. Viral tracing from the tongue combined with whole-head clearing revealed TRPV1+ orotrigeminal ganglionic fibers anatomically positioned to transmit chemical concentrations from the mouth to the brainstem. Stereotaxically-targeted pharmacogenetic lesions of TRPV1+ trigeminal nerve cells produced a robust blunting of oral reactivity to ethanol, resulting in preference for low doses and augmented rejection thresholds for high concentrations. Endoscope-enabled multiphoton through-brain imaging of single cell calcium dynamics in trigeminal ganglion during consumption of tastants and chemesthetics revealed ethanol-selective, concentration-dependent sensory coding. Together, we anatomically and functionally describe a peripheral-central circuit involved in mammalian chemosensation which controls palatability of ethanol thereby altering motivation and consumption.

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Late-Breaking Poster

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant K01AA028059

Title: Chronic ethanol exposure decreases H3K9 dimethylation in cerebellar Purkinje cells

Authors: P. A. ZAMUDIO-BULCOCK, *J. WOODWARD;
Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: The cerebellum is highly sensitive to alcohol exposure with acute cerebellar ataxia being a prominent indication of intoxication, and chronic alcohol-induced cerebellar deficits persisting even after withdrawal from alcohol exposure. Epigenetic modifications of the genome have emerged as important molecular mechanisms that contribute to the pathophysiology of alcohol use disorder (AUD) and histone modifying enzymes have been suggested to have therapeutic potential for AUD. Changes in opposing covalent modifications, namely, acetylation

and methylation in histone H3, frequently at lysine 9 (H3K9), have been implicated in AUD-related behaviors. In the prefrontal cortex of mice chronically exposed to EtOH, H3K9 methylation is decreased while acetylation is increased, an effect that is associated with ethanol-induced long-lasting memory deficits. Given the abundant expression of acetyl-and methyl-transferase enzymes in the cerebellar Purkinje cells (PCs), we hypothesized that chronic alcohol treatment induces changes in chromatin structure due to covalent modifications at H3K9 in PCs. To test this, we measured H3K9 methylation and acetylation in C57BL/6J male and female CIE exposed mice, and controls. Each CIE cycle consisted of 4 days of 16 hrs of ethanol vapor followed by 8 hrs of withdrawal. H3K9-dimethyl protein expression levels were measured in lobules V, VI and VIII at 3 days of withdrawal via immunofluorescence followed by confocal microscopy. CIE treated female mice showed reduced expression of H3K9-dimethyl inside PC somas when compared to controls in posterior lobules VI and VIII, but not in lobule V (Two-way ANOVA, lobule VI: *p=0.034, lobule VIII: **p=0.0043, n=5 mice/condition, 81-120 images, 573 PCs). Conversely, protein expression levels of H3K9-acetyl were significantly higher in female CIE exposed mice (Two-way ANOVA, lobule V: *p=0.015, lobule VI: ****p=0.0032, **p=0.0073, lobule VIII: *p<0.00001, n=5 mice/condition, 78-99 images, 510 PCs). Similarly, in males, H3K9dimethyl protein expression was significantly lower in the CIE treated group in all three lobules examined (Two-way ANOVA, lobule V, VI, VIII: ****p<0.00001, n=5 mice/condition, 101-128 images, 684 PCs). H3K9acetyl expression in males are currently being analyzed. These results indicate that in cerebellar PCs CIE treatment induces a sex-independent shift in the balance between acetylation and methylation of H3K9 that is biased toward a facilitation of downstream target genes expression. This could result in pathological upregulation of neuronal activity modulators and underlie cerebellar deficits induced by CIE.

Disclosures: P.A. Zamudio-Bulcock: None. **J. Woodward:** None.

Late-Breaking Poster

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USD Center for Brain and Behavior

Title: Calcineurin-mediated immunosuppressants in binge ethanol drinking and stress responsivity

Authors: *P. J. RONAN[1], T. P. BERESFORD[2];
[1]Psychiatry and Basic Biomed. Sci., Sioux Falls VA/USD Sch. of Med., Sioux Falls, SD;
[2]Psychiatry, RMRVAMC-SOM U Colorado, Denver, CO

Abstract: We have found that the calcineurin mediated immunosuppressants cyclosporine A (CsA) and tacrolimus inhibit binge alcohol drinking in mice. Further, we have shown that this effect is mediated directly in brain, as intracerebroventricular administration also significantly decreases drinking. As these immunosuppressants have severe systemic toxic effects along with dangerous inhibition of immune function, our goal is to determine proximal mechanisms by which these immunosuppressants are working in order to develop effective treatments for alcohol use disorder (AUD) with fewer side effects. To this end, we are employing genomic, molecular, transcriptomic, metabolomic, anatomic, and behavioral approaches to explore the relationship between binge alcohol drinking, stress, and calcineurin mediated immunosuppressants. Calcineurin is a somewhat ubiquitous phosphatase, involved in a wide range of signaling pathways - both in neurons and glia. One major question is whether immunosuppressants are acting through neuronal signaling pathways, regulating reward and stress/anxiety pathways, or in glia, mediating neuroinflammatory effects. To address this, we have developed multiple transgenic models using a floxed calcineurin line (C57BL/6-Ppp3r1tm1Stl/J) crossed with various Cre driver lines to knockout CN in various neuronal or glial populations. Results will be presented from two neuronal CN knockout lines: a "panneuronal" CN knockout line (CamKIIα-Cre) and a corticotropin releasing factor specific CN knockout line (CRH-Cre). We are also investigating the effects of CsA on candidate brain signaling pathways in models of both binge drinking and stress, as stress is a primary factor driving drinking behaviors. The CeA and PVN were microdissected from 300 μm frozen sections and qRT-PCR was performed. Overall, CsA inhibited the stress-induced expression of a wide range of neuroinflammatory markers in these regions including cytokines such as IL-2, IL-1β, IL-6, TNFα; markers of glial activation: CD45 and Iba-1; chemokine and chemoattractant molecules such as CCR2 and CCL2; as well as other inflammatory signaling molecules such as COX-2. Some of the largest effects were seen on IL-1β and IL-6 expression in both CeA and PVN. While CsA inhibited the expression of CD45 and iba1 in the CeA, in the PVN these effects were striking. Together, these data suggest that immunosuppressants could be acting, at least in part, through glial mediated neuroinflammatory mechanisms to reduce binge-like alcohol consumption in mice.

Disclosures: P.J. Ronan: None. **T.P. Beresford:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Topic: G.09. Drugs of Abuse and Addiction

Support: This work was supported by the VCOM Research Eureka Accelerator Program (REAP) Grant funded to BMC.

Title: Preliminary pharmacokinetics and in vivo studies indicate analgesic and stress mitigation effects of a novel NMDA receptor modulator

Authors: *B. COSTA;
VCOM, Virginia Tech., Blacksburg, VA

Abstract: NMDA receptor (NMDAR) channel blockers, which produce analgesic and anti-depressant effects, preferentially block the GluN2D subtype of NMDAR at lower doses. Based on the knowledge of GluN2 subunit physiology, we hypothesized that compounds that concurrently modulate GluN2A and GluN2D subtypes of NMDARs to opposite directions can be useful analgesic and stress-mitigating agents. In this translational study, we explored in vivo activities of a recently discovered glutamate concentration-dependent NMDAR modulator (CNS4). Results from the pharmacokinetic study indicate that CNS4 reaches maximum plasma and brain concentration as quickly as 0.25 hours after intraperitoneal injection, and about 6% of the plasma concentration reaches brain tissue (54.5 vs 3.3 μg/ml). In preliminary in vivo studies, CNS4, a non-opioid compound, increased mice escape latency in a hotplate assay by 2.18-fold compared to saline and 1.78-fold compared to the positive control, meloxicam. Furthermore, in a fear conditioning (FC) experiment, CNS4 improved fear memory [decrease in freezing latency (11.78 vs 4.42s, p=0.0010)] and subsequent fear extinction [increase in freezing latency (3.56 vs 15.08s, p=0.049)] in male mice. CNS4 caused no changes in locomotion in 8 out of 9 parameters studied. About fifty hours after FC training, CNS4 increased water (5-fold) and sucrose intake (4.5-fold) in male mice. These results indicate that the glutamate concentration-biased modulatory effect of CNS4 could produce analgesia and stress-mitigating effects. Further studies in this direction will help develop clinically useful drugs for pain associated with stressful conditions.

Disclosures: B. Costa: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder and CEO of Clab LLC, Clab LLC.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Program #/Poster #: LBA007.077/LBA76

Topic: G.09. Drugs of Abuse and Addiction

Support: University of Utah Incentive Seed Grant

Title: Housing at moderate altitude alters brain chemistry and elevates methamphetamine preference in female rats.

Authors: *S. KANEKAR;
Psychiatry, Univ. of Utah, Salt Lake City, UT

Abstract: Background: Demographic studies find that misuse of methamphetamine (Meth), cocaine and prescription opioids increase with altitude of residence. In rodents, short-term hypoxia (10% oxygen, 48hr) can elevate electrical brain self-stimulation (Koob & Annau, 1974). Using a sex-based animal model, we therefore evaluated chronic hypobaric hypoxia (CHH) exposure at moderate altitude as a biological risk factor for Meth misuse. **Methods**: Male and female SD rats were tested in the condition place preference (CPP) after 2wks of housing at sea level, 4,500ft or 10,000ft. In the CPP, individual chamber preference was gauged on day1, followed by 8days of conditioning, and a test CPP on day10. Rats were given Meth (0.5 or 1.5mg/kg, IP) and placed in the non-preferred chamber on odd days, or given saline and placed in the preferred chamber on even days. In control rats, saline was paired with each chamber. In the test CPP, rats were given access to all chambers to assess impact of conditioning on place preference. Reward benefits were calculated as test preference (PREF: time in Meth-paired chamber - saline-paired chamber in the test session) or test difference (DIFF: time in Meth-paired chambers in the test - that in the pretest). Another set of rats at the 3 altitudes were tested for striatal dopamine by ELISA. **Results**: In the saline-paired CPP, rats did not show place preference at any altitude. In the Meth-paired CPP, females in CHH show elevated Meth preference vs those at sea level. In females, one-way ANOVA shows a significant impact of altitude on Meth at 0.5mg/kg: PREF- $F(2, 43) = 4.2$, $p=0.02$, DIFF- $F(2, 42)=5.9$, $p=0.005$, and Meth at 1.5mg/kg: PREF- $F(2, 39)=3.3$, $p=0.04$, DIFF- $F(2, 36)=3.2$, $p=0.04$. Males did not differ in Meth preference across altitude groups, as shown by one way ANOVA with Meth at 0.5mg/kg: PREF- $F(2, 36) = 0.3$, $p=0.7$, DIFF- $F(2, 36) = 1.1$, $p=0.3$, and Meth at 1.5mg/kg: PREF- $F(2, 51)=0.7$, $p=0.4$, DIFF- $F(2, 50)=0.9$, $p=0.4$. Striatal dopamine increased in females with housing at altitude ($F(2, 25)=7.1$, $p=0.004$), but decreased in males ($F(2, 35)=7.7$, $p=0.002$). Striatal dopamine rose significantly from 1wk vs 2wks at 4,500ft in females (Student's t-test, $p<0.0001$), but did not change in males. **Conclusion**: Housing at moderate altitude can elevate Meth preference in female rats, in parallel to elevated striatal dopamine. In our model, Meth preference does not change in male rats housed at altitude. Exposure to CHH at moderate altitude may thus pose a biological risk for Meth misuse, particularly in women.

Disclosures: S. Kanekar: None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA048742
NIH Grant DA056485

Title: Mapping activation patterns of precipitated cannabinoid withdrawal in the rat brain

Authors: *A. BREWER[1], S. M. SPENCER[2];
[2]Pharmacol., [1]Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Cannabis withdrawal symptoms are experienced by approximately half of individuals with regular or dependent use of cannabinoids. Here we compared patterns of cFOS expression associated with precipitated cannabinoid withdrawal in male and female rats dependent on the synthetic cannabinoid receptor agonist WIN 55212 (WIN). Rats were given escalating doses of WIN or vehicle for four and a half days via twice-daily infusions into an indwelling catheter. On the fifth day, withdrawal was precipitated via a single i.p. injection of rimonabant (3 mg/kg for females and 10 mg/kg for males) or vehicle 4 hours after the final infusion creating three comparison groups per sex: Veh+ RIM, WIN + Veh, and WIN + RIM. Withdrawal was observed for 30 minutes post-injection and rats were sacrificed and perfused one hour after the end of withdrawal observation. One hemi-section of each brain underwent antibody labeling of cFOS and tissue clearing via polyethylene glycol-associated solvent systems (PEGASOS) passive immersion procedures. Intact hemispheres were imaged on a 3i cleared tissue light sheet microscope and expression of cFOS signal was mapped in 3D space using the Waxholm Space Atlas to Quantify cFOS active cells by region in each hemi brain. Rimonabant administration to WIN-dependent male rats increased cFOS expression in the PVT [$F(2,17)=3.878$, $p<0.05$] relative to rats that received rimonabant independent of WIN . Furthermore, male global withdrawal scores positively correlated with cFOS expression in the cingulate cortex [$r(18)=.623$, $p<0.05$] and the posterior intralaminar cortex [$r(18)=.611$, $p<0.05$]. In females, rimonabant administration to WIN-dependent rats significantly increased cFOS expression in the frontal association cortex [$F(2,14)=4.529$, $p<0.05$] compared to rimonabant controls. Female global withdrawal scores positively correlated with higher cFOS expression in presubiculum [$r(17)=.510$, $p<0.05$], ventrolateral orbital frontal cortex [$r(17)=.493$, $p<0.05$], primary somatosensory face representation area [$r(17)=.505$, $p<0.05$], bed nucleus of the stria terminalis [$r(17)=.503$, $p<0.05$], and medial habenula [$r(17)=.587$, $p<0.05$], and VTA [$r(17)=.531$, $p<0.05$]. These results demonstrate interesting sex differences in the pattern of cFOS expression following precipitated WIN withdrawal.

Disclosures: A. Brewer: None. **S.M. Spencer:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.079/LBA78

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA055169

Title: Role of medial Preoptic Area projections to infralimbic cortex in preventing reinstatement of cocaine seeking in new mother rats

Authors: *A. CONTRERAS[1], A. ANDERSON[2], K. COPELAS[2], E. LOPEZ ROBINSON[2], M. PEREIRA[2];
[2]Psychological and Brain Sci., [1]UMass Amherst, Amherst, MA

Abstract: Postpartum relapse to cocaine use by new mothers continues to be a serious health problem that often has a tragic impact on the mother's ability to care for her child, with life-long consequences for the mother, her child and society. There is a window of opportunity for treatment in the peripartum period, as new mothers are more likely to achieve abstinence or reduce drug use, many for the first time ever. Unfortunately, few women maintain abstinence and relapse between 6 to 12 months after birth. To date, little is known regarding the neurobiological mechanisms by which maternal motivation can prevent drug relapse in new mothers. Our prior work in rats demonstrates that during the unique early postpartum period, new mothers also exhibit reduced cocaine seeking, and that pharmacological inactivation of the medial preoptic area (mPOA), a critical site orchestrating maternal behavior, biases the maternal choice towards cocaine-conditioned incentives in a concurrent pup/cocaine choice conditioned place preference (CPP) task. The current study builds logically on our prior work to determine the functional necessity of mPOA neurons projecting to the infralimbic medial prefrontal cortex (mPOA-to-IL), a critical site involved in cognitive functions necessary for optimal selection of behaviors, in preventing reinstatement of cocaine seeking in new mother rats. To this aim, we used a pathway-specific chemogenetic approach to determine the role of mPOA-to-IL neurons during a novel adaptation of the extinction-reinstatement CPP animal model of drug relapse. An additional goal of this study was to evaluate the impact of chemogenetic inhibition of mPOA-to-IL pathway on maternal behavior. Experimenter blind was maintained for behavioral scoring and analysis of immunostained images. Our findings show that selective inhibition of the mPOA-to-IL pathway increased reinstatement of cocaine preference, highly contrasting the reduced cocaine preference by behavioral baseline and VEH-hM4Di control groups. In addition, CNO-hM4Di inhibition of mPOA-to-IL pathway disrupted cognitive aspects of maternal behavior, as shown by inattentive maternal behaviors and disorganized caregiving sequences fragmented by non-maternal actions. Together, this new work expands our understanding of the mechanisms by which maternal motivation can facilitate abstinence.

Disclosures: A. Contreras: None. **A. Anderson:** None. **K. Copelas:** None. **E. Lopez Robinson:** None. **M. Pereira:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.080/LBA79

Topic: G.09. Drugs of Abuse and Addiction

Support: R01DA045836
R01DA058951
F31DA059203

Title: Infralimbic cortex interneurons become hyperexcitable after heroin self-administration and protect against cued relapse during acute withdrawal

Authors: *L. RUIZ-LEYVA[1], G. GIANNOTTI[2,3], R. D. VAREED[4,3], K. GLODOSKI[3], J. PETERS[1,3];
[1]Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL; [2]Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA; [3]Anesthesiol., Univ. of Colorado, Anschutz Med. Campus, Aurora, CO; [4]Anesthesiol., Univ. of Colorado, Anschutz Med. Neurosci. Grad. Training Program, Aurora, CO

Abstract: The infralimbic prefrontal cortex (IL-PFC) is important for inhibiting drug seeking. Whereas IL-PFC neurons projecting to the nucleus accumbens have been implicated in this function, the role of local, GABAergic IL-PFC interneurons is not well understood. To assess whether heroin self-administration impacts the physiology of IL-PFC interneurons, we exposed VGAT-Venus transgenic rats to heroin self-administration and measured the intrinsic excitability of VGAT+ and VGAT- neurons in cortical slices during acute withdrawal from heroin, 24 hours after the last heroin self-administration session. In wildtype rats, we then used a chemogenetic strategy to activate or inhibit IL-PFC interneurons to determine their functional role in heroin seeking. Male and female Wistar rats self-administered heroin (or saline for control) in 13 weekday sessions. For electrophysiology experiments, slices of the IL-PFC were prepared 24 hours after the last heroin/saline session. For chemogenetic experiments, rats underwent additional behavioral training to perform within-subject tests comparing the effects of vehicle to those of the chemogenetic actuator J60 hydrochloride. Rats were first tested under cued relapse conditions where the heroin cue was available, but heroin was not. They then underwent Progressive Ratio (PR) testing -to determine effects on heroin motivation (measured as break point). A DLX-promoter-driven virus delivering either an inhibitory Gi-DREADD or excitatory Gq-DREADD allowed us to bidirectionally modulate IL-PFC interneurons on each test, separated by two days of heroin self-administration. Whilst no changes were found in VGAT- neurons, the rheobase of VGAT+ neurons from rats that self-administered heroin was significantly lower than that of VGAT+ neurons from saline controls. Chemogenetic manipulation of IL-PFC interneurons did not alter heroin motivation (i.e. break points during PR tests) under these conditions. Although activation of IL-PFC interneurons with the Gq-DREADD

did not alter cued heroin relapse, inhibition with the Gi-DREADD increased cued heroin seeking during acute withdrawal. Together, these results suggest that IL-PFC GABAergic interneurons: a) are hyperexcitable during acute withdrawal, and b) their activity is necessary to limit heroin seeking when heroin cues are present. Although it was not possible to further drive this limiter function using the Gq-DREADD, IL-PFC interneurons may present a viable new target for therapeutic interventions to mitigate relapse during early withdrawal from heroin.

Disclosures: L. Ruiz-Leyva: None. **G. Giannotti:** None. **R.D. Vareed:** None. **K. Glodoski:** None. **J. Peters:** F. Consulting Fees (e.g., advisory boards); Delix Therapeutics, Inc..

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.081/LBA80

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01DA048055
NIH Grant R01DA049139

Title: Extinction of heroin seeking does not require post-lever press activity in the infralimbic cortex or its projections to the nucleus accumbens shell or amygdala

Authors: *M. S. MCGREGOR[1], K. E. NETT[1], R. T. LALUMIERE[1,2,3];
[1]Interdisciplinary Grad. Program in Neurosci., [2]Dept. of Psychological and Brain Sci., [3]Iowa Neurosci. Inst., Univ. of Iowa, Iowa City, IA

Abstract: Evidence indicates that activity of the infralimbic cortex (IL), as well as its projections to the nucleus accumbens shell (NAshell) and amygdala, following an unreinforced lever press is critical for cocaine extinction learning and retention. It is unclear whether the same neural circuitry is involved in extinction encoding for other classes of addictive drugs, such as opioids. In this study, we used a behavior-guided optogenetic approach in female and male Sprague-Dawley rats to examine the role of the infralimbic cortex and its projections in extinction of heroin seeking. Rats received bilateral microinjections of the inhibitory opsin eNpHR3.0 or eYFP control into the IL, bilateral fiber optics targeting the IL, NAshell, or amygdala, and implantation of an intra-jugular catheter. Rats then underwent 12+ d of 6 h or 3 h heroin self-administration sessions, wherein an active lever press produced a heroin infusion and light and tone cues, followed by 12 d of extinction training. Optogenetic inhibition of the IL, IL-NAshell, or IL-amygdala pathway was given for 20 s immediately following an unreinforced lever press during the first 5 d of extinction. Unlike with cocaine extinction, these manipulations had no effect on lever pressing during extinction training, nor on retention of extinction learning, as assessed during the subsequent 7 d of extinction without optogenetic inhibition. These results

suggest that the extinction of heroin seeking does not involve the same infralimbic mechanisms that are critical for the extinction of cocaine seeking. Moreover, although we did not find any sex differences in extinction learning, ancillary analyses of self-administration data revealed that females self-administered more heroin than males in 3 h, but not 6 h, self-administration sessions, indicating time-dependent sex differences in heroin taking.

Disclosures: M.S. McGregor: None. **K.E. Nett:** None. **R.T. LaLumiere:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.082/LBA81

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA R00DA043572
NIDA 1F31DA057836-01

Title: Lateral habenula inhibition alleviates stress-induced mechanical hypersensitivity and fentanyl preference regardless of stressor type

Authors: *O. DEPASQUALE, C. O'BRIEN, B. KURANI, D. DESAI, R. VEMIREDDY, K. WILKINSON, J.-Y. HA, S. SOBTI, D. J. BARKER;
Psychology, Rutgers Univ., Piscataway, NJ

Abstract: Stress is a primary risk factor in the development of mental health and substance use disorders. Our previous research has shown that footshock stress induces states of learned helplessness and can alter reward value, affect, and mechanical hypersensitivity. Moreover, we discovered that these features are predictive of future fentanyl preference. One hub known to control pain and reward, which may be responsible for driving these behaviors, is the lateral habenula (LHb). However, it remains unknown whether modulation of LHb activity during stress can reduce susceptibility to stress-induced disorders. In this study, we first examined the long-term effects of stress on mechanical hypersensitivity, which is indicative of opioid vulnerability. We then aimed to reduce stress-induced opioid susceptibility by inhibiting the lateral habenula (LHb). Here we show that stress-induced hypersensitivity (SIH) as measured by the von Frey test of mechanosensitivity occurred regardless of stressor type -inescapable footshock, escapable footshock, and restraint stress- and did not differ based on treatment or sex. However, the recovery of mechanical sensitivity was dependent on both sex and the intensity of the stressor. We next tested if stress-induced opioid susceptibility can be attenuated by chemogenetic inhibition of VGlut2 neurons in the LHb during inescapable footshock stress. Consistent with our prior results, we observed differences in negative valence behaviors, nociception, and oral opioid self-administration following stress, and found that some of these factors could be recovered.

Our results show that inhibition of the LHb during stress can block the induction of stress-induced mechanical hypersensitivity and future fentanyl consumption and preference. Although stress can trigger individual differences influencing the risk of developing a substance use disorder, our findings demonstrate that modulating LHb activity has extensive and enduring behavioral effects on mechanical hypersensitivity and fentanyl seeking following stress.

Disclosures: O. DePasquale: None. **C. O'Brien:** None. **B. Kurani:** None. **D. Desai:** None. **R. Vemireddy:** None. **K. Wilkinson:** None. **J. Ha:** None. **S. Sobti:** None. **D.J. Barker:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.083/LBA82

Topic: G.09. Drugs of Abuse and Addiction

Title: Sex differences of oxycodone intake and deltaFosB levels in rodents

Authors: *C. ZUVIA[1], T. LUGO[2], V. CHANCHYKOV[1], G. R. POE[3];
[1]UCLA, Los Angeles, CA; [2]Psychology, Univ. of California Los Angeles, Los Angeles, CA; [3]Dept. of Integrative Biol. and Physiol., UCLA Chapter, Los Angeles, CA

Abstract: Women are more likely to be prescribed opioids due to factors like higher sensitivity to pain and higher rates of chronic pain. Prolonged use of opioids, such as oxycodone, results in long-term changes in neurological function. One of the known mechanisms supporting these long-term changes in neuroplasticity and behavioral manifestations of addiction is the overexpression of the transcription factor ΔFosB. Overexpression of ΔFosB in the nucleus accumbens (NAc), a brain region involved in reward processing, has been linked to increased compulsive drug intake and seeking. We hypothesized that females will voluntarily intake higher doses of oxycodone compared to males and as a result females will have higher levels of ΔFosB in the NAc. To test levels of ΔFosB expression in the NAc in response to chronic oral self-administration of oxycodone, Long-Evans rats were subjected to a two-bottle choice (TBC) paradigm where animals had the option to choose between two bottles: one containing only water and another containing water mixed with oxycodone (0.1 mg oxycodone/1 mL water), 24 hours per day for 14 days. A control group had access to two bottles of water for the same duration. The bottles were weighed daily within the first two hours of the light cycle to measure liquid consumption, calculated as the change in weight (g) of the bottle from the previous measurement. Brain NAc sections were taken from oxycodone-exposed rats, and ΔFosB expression was assessed via immunohistochemistry. An unpaired t-test between sexes determined that females ingested significantly higher doses of oxycodone ($p < 0.0001$) compared to males. An unpaired t-test between sexes displayed that females were trending towards significantly higher levels of ΔFosB in the NAc. A strong positive correlation ($r = 0.9827$, $p =$

0.0173) showed that higher doses of oxycodone consumption were associated with an increase in NAc ΔFosB expression. This study shows individual differences in oral drug self-administration affect ΔFosB expression in the NAc. This study also reveals sex differences in chronic oral oxycodone self-administration and suggests the importance of sex-specific addiction treatments.

Disclosures: C. Zuvia: None. **T. Lugo:** None. **V. Chanchykov:** None. **G.R. Poe:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.084/LBA83

Topic: G.09. Drugs of Abuse and Addiction

Support: Genetic, Molecular and Anatomical Characterization of VTA Cell Types Involved in Pain and Addiction 5654

Title: Investigating opioid activated neurons in the dopaminergic system

Authors: *L. B. DOSTER[1], S. L. MORISON[1], E. P. PHELAN[1], M. V. CENTENO[3], A. V. APKARIAN[2], R. AWATRAMANI[4];
[1]Neurol., [2]Neurosci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [3]Physiol., [4]Northwestern Univ., Chicago, IL

Abstract: In the past two decades, the opioid crisis in the United States has contributed to unprecedented levels of addiction and overdose. The effects of opioids on reward and addiction are largely dependent on dopamine release in the nucleus accumbens from the ventral tegmental area (VTA). However, the anatomical identity of opioid activated dopamine (DA) neurons and the interaction between DA circuitry and opioids remains unclear. Here we show that DA neurons in numerous brain regions associated with reward and addiction are opioid activated. To examine neurons activated during morphine exposure, we used early gene cFos-linked capture in a transgenic mouse model, as well as where these neurons projected to. Opioid-activated DA neurons, within regions associated with reward and addiction, were isolated and counted in a rostral-caudal spread. We found significantly more activated dopamine neurons in the morphine-treated VTA and substantia nigra pars compacta (SNc) than in their respective vehicle counterparts. This difference remained true across the rostro-caudal axis, including the caudal linear nucleus of the raphe and retrorubral regions, with the highest number of morphine-activated dopamine cells exhibiting a ventro-medial bias in the central VTA. The periaqueductal gray and dorsal raphe, regions that are also implicated in addiction, were found to have more activated dopamine neurons than their vehicle counterparts in morphine-treated mice. Projections of the captured activated DA neurons were observed in the olfactory tubercle, dorsal striatum, nucleus accumbens, bed nucleus of the stria terminalis, and the basolateral and central amygdala.

These data suggest that the opioid reward-addiction paradigm may be recruiting multiple subgroups within the DA system. Additionally, although this study is focused on dopamine or tyrosine hydroxylase expressing neurons, we captured active cells across many additional regions implicated in addiction generally. The advantage of this study is that our techniques allow us to examine the projections of these neurons, as well as specify differences and similarities among the opioid paradigms. In broadening our understanding of distinct addiction circuitry, targeted therapies for both opioid replacement and opioid addiction may be developed.

Disclosures: L.B. Doster: None. **S.L. Morison:** None. **E.P. Phelan:** None. **M.V. Centeno:** None. **A.V. Apkarian:** None. **R. Awatramani:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.085/LBA84

Topic: G.09. Drugs of Abuse and Addiction

Support: TRDRP T32DT5202 to MB
TRDRP T32IR4866 to CDF
UC LEADS

Title: Characterizing the Role of Lynx2 Following Chronic Mild Stress

Authors: *J. J. ARELLANO[1], M. R. BAUTISTA[2], J. FOWLER[3], C. D. FOWLER[2]; [1]Neurobio. and Behavior, Univ. of California Irvine (UCI), Irvine, CA; [2]Neurobio. and Behavior, Univ. of California, Irvine, Irvine, CA; [3]Univ. of California Irvine, Irvine, CA

Abstract: Cigarette smoking is the leading cause of preventable death in the United States. Nicotine, the psychoactive constituent from tobacco, is responsible for the reinforcing properties of smoking. Adult smokers who attempt to quit, may relapse within the first few weeks as result of discomfort from stress. Lynx2, a negative allosteric modulator of nicotinic acetylcholine receptors (nAChRs), is enriched in brain regions associated with stress regulation and nicotine reinforcement. Our studies aim to characterize the mechanism by which lynx2 may impact stress related behaviors. To address this, we implemented a chronic mild stress (CMS) protocol including several different conditions (nesting removal, water deprivation, damp bedding, cage tilt, continuous light, and white noise with predator odor) with both wild-type (WT) and transgenic lynx2-knockout (KO) mice. Following CMS, both control and CMS mice underwent a social interaction test and a nicotine conditioned place preference (CPP) paradigm. We hypothesized that in the social interaction test, CMS mice would spend less time in a chamber containing a novel mouse in comparison to the control group, with WT mice exhibiting greater time spent in the chamber compared to TG mice. In addition, we hypothesized that CMS

conditioning would exacerbate the preference for the nicotine-paired chamber in both WT and TG mice compared to the control group as assessed in nicotine CPP. Overall, our studies suggest a potential interaction where lynx2 significantly interacts with stress exposure to alter social behavior in mice. In conclusion, our studies illustrate a role for lynx2 in nicotine cessation and stress exposure.

Disclosures: J.J. Arellano: None. **M.R. Bautista:** None. **J. Fowler:** None. **C.D. Fowler:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.086/LBA85

Topic: G.09. Drugs of Abuse and Addiction

Title: The Effects of Chronic Nicotine Exposure on Dopamine-Mediated Reinforcement Learning using Optical Intracranial Self-Stimulation

Authors: *S. BOSE[1,2,4], F. G. GNAZZO[4], A. K. PABLA[4], J. A. BEELER[4,3,2];
[1]Psychology, [2]CUNY Neurosci. Collaborative, [3]Biol., The Grad. Center, City Univ. of New York, New York, NY; [4]Psychology, Queens College, City Univ. of New York, Flushing, NY

Abstract: Despite the rates of smoking decreasing each year, nicotine use is still prevalent in the United States, affecting approximately 22% of the population. Nicotine has been known to affect cognition, motivation, and reinforcement; research suggests that nicotine induces neurological adaptations in the mesolimbic dopamine (DA) pathway, which alter the effects of reward stimuli and drive learning. However, the current literature addressing nicotine's effects on reward behavior is mainly centered around acute administration, which does not reflect the constant, low-level of nicotine found in the blood serum of smokers. Using concurrent fiber-photometry (FP) recording in the striatum and optical intracranial self-stimulation (oICSS) in the ventral tegmental area, we investigated chronic nicotine (cNIC) exposure on behavior and neurotransmission during dopamine-mediated reinforcement. *ChR2-YFP x DAT-IRES-Cre$_{(het/het)}$* mice were given either cNIC or drinking water before being trained to press a set of levers self-stimulate. After acquiring oICSS behavior, the lever contingencies were changed: one lever was reinforced on a Fixed Ratio (FR) 4 schedule, and the other lever was on FR 10. After a contingent lever press, a cue light was presented followed by optogenetic stimulation. cNIC mice exhibited increased self-stimulation behavior on the FR 4 lever when compared to controls, however this increase was not observed on the higher-cost lever. Furthermore, the dopamine transients during self-stimulation events were blunted on the FR 4 lever in comparison to the FR 10, but only in the cNIC mice. These results suggest that long-term nicotine exposure affects the reward response to different reinforcers by altering DA transmission in the striatum; decreases in DA are associated with increases in motivation, thus driving self-stimulation behavior. This bias

in reward response may explain the difficulties in quitting nicotine, and why nicotine users are more likely to abuse other drugs. Understanding the relationship between cNIC and reward is critical in elucidating the mechanisms behind addiction, abstinence, and relapse for nicotine and concurrent use of other substances.

Disclosures: S. Bose: None. **F.G. Gnazzo:** None. **A.K. Pabla:** None. **J.A. Beeler:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.087/LBA86

Topic: G.09. Drugs of Abuse and Addiction

Title: Neural Correlates of Vaping Cravings and the Impact of Cognitive Strategies on Young Adults

Authors: *Y. BAGHERZADEH BIOKI[1], J. D. GABRIELI[2];
[1]McGovern Inst. For Brain Res. at MIT, Cambridge, MA; [2]Dept Brain/Cognit Sci., MIT, Cambridge, MA

Abstract: The rapid rise of vaping among young adults is a significant public health concern. Despite safety claims, e-cigarette use is linked to addiction, lung injuries, and fatalities. In 2021, 11.0% of adults aged 18-24 were e-cigarette users, with over 2.5 million youth reporting use in 2022.This study investigated neural correlates of vaping cravings in 20 young adult e-cigarette users using fMRI. Participants viewed 75 videos across three conditions: vaping scenarios, neutral scenarios, and instruction to consider immediate or harmful consequences. Craving ratings were collected after each trial.Results showed increased activation in the occipital cortex and basal ganglia reward regions during vaping-related videos. The medial prefrontal cortex showed greater activation in the 'Watch' condition compared to the 'Suppress' condition, suggesting successful modulation of craving responses through cognitive strategies.Multivoxel Pattern Analysis using a linear Support Vector Machine identified distinct neural activation patterns for each condition, achieving 71.85% accuracy on the testing set and 71.73% ± 0.01% accuracy during cross-validation. Activation patterns in the paracingulate gyrus and frontal opercular cortex emerged as key predictors of condition/video type.This study provides insights into neural mechanisms underlying vaping cravings and demonstrates the potential for cognitive strategies to modulate these responses. The findings suggest that vaping-related videos engage attention and craving-related circuits, craving suppression involves cognitive control and inhibitory processes, and neutral watching serves as a baseline.The observed craving modulation through self-regulation strategies suggests potential pathways for targeted interventions in vaping addiction. These findings may inform the development of more effective prevention and

treatment strategies for vaping addiction in young adults, potentially leveraging cognitive techniques to enhance craving control.

Disclosures: Y. Bagherzadeh Bioki: None. **J.D. Gabrieli:** None.

Late-Breaking Poster

LBA007: Theme G Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA007.088/LBA87

Topic: G.09. Drugs of Abuse and Addiction

Support: Anonymous Donor

Title: Analyzing variance in a multi-institutional investigation of psilocybin's effects on mouse behavior.

Authors: *K. WHITE[1], O. D. LU[1], A. S. KLEIN[3], K. RAYMOND[6], S. VAILLANCOURT[6], C. LIU[4], N. GREEN[4], A. GALLAGHER[4], A. LI[4], L. SHINDY[4], R. LI[1], M. ZOU[1], V. FAYNER[1], D. MIKULEK[1], A. B. CASEY[7], L. CAMERON[6], M. B. POMRENZE[8], J. DE JONG[1], H. ADESNIK[1], V. S. SOHAL[5], M. KHEIRBEK[5], S. LAMMEL[2], B. D. HEIFETS[6], R. C. MALENKA[8], A. M. GOMEZ[2];
[2]Mol. and Cell Biol., [1]UC Berkeley, Berkeley, CA; [3]Psychiatry and Behavior, [5]Psychiatry, [4]Univ. of California, San Francisco, San Francisco, CA; [7]Anesthesiology, Pain, and Perioperative medicine, [8]Psychiatry and Behavioral Sci., [6]Stanford Univ., Palo Alto, CA

Abstract: Variation in laboratory-specific contexts, such as differing acclimation procedures, animal care facilities, and sex of the experimenter, contributes to reproducibility issues in behavioral neuroscience. These factors interact with the natural variability in mouse behavior and can obscure experimental effects. Quantifying the effect size of laboratory-specific contexts is ideal but requires extensive sampling, which may be impractical for a single lab. To address this issue in the rapidly growing field of psychedelic science, we formed Psy-BAANC, the Psychedelic Bay Area Animal Neuroscience Consortium. Psy-BAANC is a consortium of laboratories conducting mouse behavior research through a collaborative, multi-institutional approach. Here, five Psy-BAANC labs perform the same experiments to test the acute and persistent effects of a single 2 mg/kg dose of psilocybin. We use linear mixed-effects modeling to estimate the effect of psilocybin and analyze the variance of several mouse behaviors across standard laboratory tests. Our findings indicate that a single dose of psilocybin leads to several robust and reproducible acute effects on mouse behavior, including increased anxiety-like behaviors and decreased exploration of a novel object. However, we also observe a robust lab-dependency in some commonly used behavioral paradigms that test long-term psychedelic effects. The tail suspension test (TST) and the forced swim test (FST) demonstrated significant

lab-dependency, with 50% of the variance in mouse behavior in TST and FST is explained by the individual labs. Moreover, five labs could not reproduce long-term psilocybin effects in the TST and FST paradigms. Our results highlight the effect of psilocybin in commonly used mouse behavioral paradigms and confirm the value of collaborative efforts in the rapidly growing psychedelic field.

Disclosures: K. White: None. **O.D. Lu:** None. **A.S. Klein:** None. **K. Raymond:** None. **S. Vaillancourt:** None. **C. Liu:** None. **N. Green:** None. **A. Gallagher:** None. **A. Li:** None. **L. Shindy:** None. **R. Li:** None. **M. Zou:** None. **V. Fayner:** None. **D. Mikulek:** None. **A.B. Casey:** None. **L. Cameron:** None. **M.B. Pomrenze:** None. **J. De Jong:** None. **H. Adesnik:** None. **V.S. Sohal:** None. **M. Kheirbek:** None. **S. Lammel:** None. **B.D. Heifets:** None. **R.C. Malenka:** F. Consulting Fees (e.g., advisory boards); RM is on the SAB of MapLight Therapeutics, MindMed, and Bright Minds Biosciences. **A.M. Gomez:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.001/Web Only

Topic: H.01. Attention

Support: Scientific and Technological Research Council of Turkey (TÜBİTAK) grant no: 121K902

Title: Blind's visual, not deaf's auditory, cortices become domain general cognitive control regions

Authors: *H. DUYMUS[1,2], A. VAROL[2], S. KURT[2], T. GEZICI[2], A. A. FAROOQUI[2]; [1]Ankara Yildirim Beyazit Univ., Ankara, Turkey; [2]Bilkent Univ., Ankara, Turkey

Abstract: When sensory brain regions are deprived of their typical inputs, they activate differently compared to non-deprived sensory regions. In blind individuals, visual regions activate during a wide range of auditory, tactile, olfactory, and language tasks, whereas in deaf individuals, auditory regions activate during visual and tactile tasks. The exact functions that deprived sensory regions might have taken, however, remain unclear. This issue is of immense interest because of its implications for understanding the brain’s areal specialization and the extent to which the brain can change with experience. Prior reports have indicated that deprived sensory cortices, especially visual cortices in congenitally blind individuals, show activation during tasks requiring higher-cognitive functions such as working memory, response inhibition, episodic memory recall, and mathematical operations. This suggests that these deprived sensory regions might have integrated into the multiple-demand (MD) network. MD regions, a group of fronto-parietal areas, respond to any cognitive control demands across different sensory

modalities. Our study examined whether deprived sensory cortices show the key characteristics of MD regions, that is, activation of the same foci in response to diverse control demands. We had 22 congenitally and early blind, 20 sighted control participants, and 10 early deaf participants performed up to four diverse fMRI tasks involving different modalities. Each of the four tasks contained an alternating sequence of easy and hard blocks. In the hard blocks of these four tasks, participants (1) made more difficult tactile size-judgments, (2) maintained and updated more working memory items, (3) made more demanding time-duration judgments, and (4) executed speeded motor responses. We also performed task-based functional connectivity on the collected data. Our findings showed that, in addition to fronto-parietal MD regions, almost the entire occipital cortex in the blind group activated in response to the diverse control demands and was functionally connected with MD regions. The occipital cortex in the sighted group did not show such activation. Crucially, we found that the same set of individual occipital voxels, delineated on each blind subject's unnormalized and unsmoothed images, that are most sensitive to one type of control demand (e.g., tactile decision-making task) also responded robustly to the remaining three types of control demands (e.g., working memory updating, sensory-motor speed, and time-duration judgment tasks) (BF > 28). Auditory regions in the deaf group, however, did not show such control-related activation.

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Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.002/LBA88

Topic: H.01. Attention

Support: 5R01MH119091-05
1F99NS125832-01A1
K00MH138293

Title: Differences in dynamic functional connectivity in youth with ADHD on and off stimulant medication

Authors: *H. PETERSON-SOCKWELL[1], M. G. LYONS[2], H. SHAPPELL[3], J. R. COHEN[2]; [1]Psychology & Neurosci., [2]Dept. of Psychology and Neurosci., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Biostatistics and Data Sci., Wake Forest Sch. of Med., Winston-Salem, NC

Abstract: Existing studies suggest that stimulant medications effectively improve symptoms of ADHD in children, but with significant heterogeneity. This study aims to better understand the

neural mechanisms underlying ADHD and this variability in treatment success. Many studies report differences in brain networks between typically developing (TD) youth and youth with ADHD in both task-related processing networks, such as the frontoparietal network (FPN), and internally-oriented processing networks, most notably the default mode network (DMN). This analysis uses dynamic functional connectivity (dFC) to assess how dynamic interactions within and between the DMN and FPN may vary between TD youth and youth with ADHD. How the relationship between these networks is altered by the administration of a stimulant medication was also modeled. Medication naïve youth with ADHD aged 8-12 years were recruited for this study, along with matched TD youth. All participants underwent two MRI scanning sessions during which a standard go/no-go (GNG) task was conducted. Prior to one scanning session, participants in the ADHD group received a standard oral dose of methylphenidate (MPH, 0.3 mg/kg) prior to data recording. A placebo was administered prior to the alternate session. Standard image processing steps were implemented, and BOLD time series were extracted from the DMN and FPN. A hidden semi-Markov model (HSMM) was used to constructs brain connectivity states common to all participants and then map how individuals traverse those states across time. Dwell time (total time spent in a given brain state) and sojourn distributions (consecutive time points in a given brain state) were calculated for each network state for each group. Low motion MRI data was collected from 23 TD youth (11 females) and 26 youth with ADHD (12 females). When comparing youth with ADHD off medication to TD youth, the HSMM successfully identified 4 network states. Participants with ADHD spent significantly less time than TD participants in a state hallmarked by strong within network connectivity of the DMN and FPN and relatively weak between network connections ($p < 0.01$). Participants with ADHD also exhibited longer sojourn times in this state ($p < 0.01$). When comparing participants with ADHD on and off MPH, no significant differences were observed in dwell times or sojourn distributions. These results demonstrate significant disruption of DMN and FPN connectivity during an attention task in youth with ADHD, and this analysis demonstrates the novel use of dFC to examine the neurological underpinnings of ADHD. These findings highlight the need for further research exploring the effects of stimulant medications.

Disclosures: H. Peterson-Sockwell: None. **M.G. Lyons:** None. **H. Shappell:** None. **J.R. Cohen:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Topic: H.01. Attention

Support: NSF CAREER #2141860
NIH grant R01EY033628

Title: Deep learning and eye tracking: Analyzing visual search data with convolutional neural networks

Authors: *N. CROTTY[1], N. MASSA[2], N. C. BENSON[3], M. A. GRUBB[1];
[1]Trinity Col., Hartford, CT; [2]Mass Gen. Brigham, Boston, MA; [3]eScience Inst., Univ. of Washington, Seattle, WA

Abstract: Eye tracking during visual search generates spatiotemporally rich but complex data. Traditional analyses simplify data into metrics such as saccade landings and dwell time, which exclude a substantial fraction of the variance in the raw eye data. Here, we asked if deep learning might aid scientists in incorporating this discarded portion of the data into analyses. Convolutional neural networks (CNNs) are supervised machine learning tools that excel at classifying biological data. We built a series of CNNs that classify eye position data based on the most likely location of a visual search target. Each CNN produces a set of likelihoods, one for each potential target location, with the largest likelihood reflecting the CNN's prediction of the true location. We train each CNN on 2/3 of the data and cross-validate on the rest, comparing its classification accuracy (CA) to chance via frequentist and Bayesian techniques. We established the validity of this approach through four research questions. *1) Can a CNN detect overt attention towards search targets?* We trained a CNN using a dataset from Massa et al. (2024; DOI:10.3758/s13414-024-02878-7) in which participants located a color-defined target among five distractors, and found that the CNN had a CA significantly higher than chance. *2) Can a CNN detect the use of feature-based attention (FBA) during visual search?* Massa et al. (2024) found that participants' abilities to use FBA could be manipulated via a precue that provided upcoming target color with certainty (reliable condition) or uncertainty (unreliable condition). If participants use FBA to guide search, then reliably-precued eye movements should prove more informative for a CNN. We found that a CNN trained using reliable trials had a significantly higher CA than an identical CNN trained using unreliable trials. *3) Can our results from Question 1 be replicated in an independent dataset?* We trained a new CNN using a dataset by Grubb & Li (2018; DOI:10.3758/s13414-018-1494-y), in which participants located a shape-defined target among five distractors. This CNN also had a CA significantly higher than chance, replicating Question 1's findings. *4) Can a CNN detect overt attention towards task-irrelevant objects?* In Grubb & Li (2018), one of the five distractors was an "experience-driven" distractor with a history as a sought target. We trained a CNN that predicted distractor location from this dataset, and again found a significantly above-chance CA. We thus confirm the validity of our CNN-based approach as a method of oculomotor analysis, illustrating its generalizability between samples and versatility in modeling multiple forms of overt attention.

Disclosures: N. Crotty: None. **N. Massa:** None. **N.C. Benson:** None. **M.A. Grubb:** None.

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Program #/Poster #: LBA008.004/LBA90

Topic: H.01. Attention

Support: Tarble Summer Research Fellowship

Title: Developmental Differences in EEG Frequency Patterns During Object Recognition: A Machine Learning Approach Comparing Infants and Adults

Authors: *H. WANG;
Engin. Dept., Swarthmore Col., Swarthmore, PA

Abstract: This study investigates developmental differences in EEG patterns between infants and adults during object recognition tasks, focusing on frequency domain analysis. Utilizing EEG data from Ashton et al.'s 2022 study, we achieved a highest classification accuracy of 96.60% by applying the Fast Fourier Transform to convert time-domain data to frequency-domain and using Support Vector Machines (SVM). We analyzed EEG data from infants and adults during object-viewing tasks, examining 18 features, including individual band powers, power ratios, and spectral slopes across 18 electrodes located in the frontal, occipital, posterior, and parietal regions. We normalized band powers and utilized periodogram analysis to verify the comparability of infant and adult data before running the SVM models. Combining all frequency bands yielded an accuracy of 93.55%, with the theta/(alpha+beta) ratio showing the highest individual accuracy of 94.38%. Posterior regions, particularly occipital and parietal areas, provided the most informative data. Frequency band permutation analysis revealed optimal ranges for differentiation: theta [4-9 Hz], alpha [9-12 Hz], and beta [12-30 Hz], achieving the highest accuracy of 96.60%. Our findings indicate significant developmental differences in EEG frequency patterns during object recognition, with the prominence of theta/alpha and theta/(alpha+beta) ratios and the importance of posterior regions suggesting ongoing maturation of visual processing networks from infancy to adulthood(Ashton 2022).

Disclosures: H. Wang: None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.005/LBA91

Topic: H.01. Attention

Support: P50MH132642

Title: Rhythmic endogenous attention sampling under spatial uncertainty

Authors: *Y. SHI[1,3], X. LIU[1], S. KASTNER[2];
[2]Princeton Neurosci. Inst., [1]Princeton Univ., Princeton, NJ; [3]Emory Univ., Atlanta, GA

Abstract: The rhythmic theory of attention proposes that attention operates in rhythmic cycles at the theta band (4-8 Hz), reflecting alternating states of external sampling and internal processing. While previous studies tested the theory using bottom-up attention cues, this project investigates whether the same applies to endogenous, voluntary attention, and how spatial uncertainty affects the rhythmic process.Participants performed a spatial attention task where they fixated in the center while monitoring two peripheral gratings. A brief dot cloud of blue and red dots served as an endogenous spatial cue. The color dominance indicates where a target would appear with 80% validity, while spatial uncertainty was introduced by varying the blue-to-red ratio. The target would appear after the cue, with a cue-target interval (CTI) randomly selected from 300 to 1100 ms, representing a near-threshold orientation change on either of the gratings. Participants were required to indicate the target location and then rate their confidence about the cue's content.We found an endogenous attention effect; compared to the uncued condition, people displayed better detection performance for targets at the cued condition, while this effect attenuated with increasing spatial uncertainty. Importantly, preliminary results showed that detection accuracy fluctuated as a function of the CTI at the theta band. We further predict that when the spatial uncertainty increases, the rhythmic attentional sampling will accelerate to alternate between locations in a rapid manner.The study advances our understanding of how the brain allocates attention under uncertainty, with implications for underlying neural mechanisms.

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National Natural Science Foundation of China 82272116

Title: Conscious state transitions shape neural dynamic in human subcortical-cortical circuit

Authors: *M. LI;
Shanghai Inst. of Microsystem and Information Technology, Chinese Acad. of Sci., Shanghai, China

Abstract: Consciousness refers to the state of being mindful and perceptive of both internal and external realities. Despite collaborative efforts, there remains ongoing debate concerning the nature, mechanisms, and location of consciousness, particularly the neurodynamic shifts deep in the brain as consciousness transitions. By continuously monitoring neural activity throughout the human brain, covering both the superficial cortex and deep subcortical regions, we observe a robust phase-amplitude coupling between low- and high-frequency brain waves in multiple human brain sites during unconsciousness by propofol anesthesia. Furthermore, during the transitions into and out of unconsciousness, there are observable asymmetrical dynamics in the phase-amplitude couplings within the subcortical-cortical circuit. Specifically, during the gradual induction of unconsciousness, phase-amplitude coupling is propagated from subcortical areas to the cortex. However, upon emergence from unconsciousness, brief phase-amplitude coupling is predominantly observed within subcortical areas. Strikingly, our results show that the variations in the background neural activity of the subcortical-cortical circuit are linked to shifts in consciousness states. The results indicate that transient brain wave phase-amplitude coupling and its background levels in subcortical-cortical circuits provide a mechanism for forming and maintaining consciousness in humans.

Disclosures: M. Li: None.

Late-Breaking Poster

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Topic: H.01. Attention

Support: NSF Grant BCS-2122866

Title: Successful deployment of object-based attention may require memory recruitment when targets are perceptually ambiguous

Authors: *M. MASLOWSKI, D. H. HUGHES, A. S. GREENBERG;
Biomed. Engin., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Object-based attention (OBA) facilitates processing of an attended object among spatially overlapping, unattended objects (Duncan, 1984). Additionally, exposure duration modulates the object representation strength and can influence the strategy used to process attended objects (Shomstein & Behrmann 2008). We hypothesized that a compensatory cognitive mechanism (other than OBA) may be used to assist with evidence accumulation when exposure duration and object representation strength cause perceptual ambiguity, making it difficult to identify targets based on feedforward information alone. To test this, a rapid serial visual presentation (RSVP) of partially-cohered overlapping faces and houses was used to engage

OBA. The frame/exposure duration was manipulated (500 ms, 600 ms, 750 ms, 900 ms, 1000 ms, 1200 ms), which modulated the available time to accumulate evidence about object identity in order to detect a target (specific face or house). Reaction times (RTs) for correct responses (μ; = 1.6s) were significantly slower than false alarms (μ; = 1.18s) at each frame duration (p's < 0.01) except 1200 ms (p = 0.19). This RT difference suggests engagement of an additional cognitive operation (e.g., memory) that affords greater evidence accumulation and enables accurate target discrimination. To determine whether memory processes were engaged, RT data were used to indicate how many subsequent RSVP frames were presented between target and response. A correct response for shorter frame durations (500, 600, 750 ms) occurs on average 1.8 frames after target presentation and 1.03 frames at longer frame durations (900, 1000, 1200ms). Conversely, false alarms occurred 0.6 frames after the false target with a variance of 0.039 frames, showing strong consistency across all frame durations. Paired t-tests showed significant differences between the proportion of correct responses and false alarms at all frame durations (p's < 0.01). Additionally, there was a significant difference (p < 0.01) between the average number of frames following correct responses on short versus long frame durations. Thus, the amount of visual evidence accumulated on short (vs. long) frame duration trials suggest different strategies are engaged. When frame duration is shorter and subjects respond correctly, approximately two additional RSVP frames are processed prior to response. We believe that subjects may be comparing the target frame to subsequent frames, providing evidence that memory might be leveraged at shorter frame durations to compensate for limited evidence accumulation during target presentation.

Disclosures: M. Maslowski: None. **D.H. Hughes:** None. **A.S. Greenberg:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Program #/Poster #: LBA008.008/LBA94

Topic: H.02. Perception and Imagery

Support: NSF Grant BCS-2043740

Title: The neural signatures of ongoing thoughts at rest

Authors: *J. KE[1,2,4], T. CHAMBERLAIN[5], A. CORRIVEAU[1,2], H. SONG[1,2], Z. ZHANG[1,2], T. MARTINEZ[1], L. SAMS[1], Y. LEONG[1,2,3], M. D. ROSENBERG[1,2,3];
[1]Dept. of Psychology, [2]Inst. for Mind and Biol., [3]Neurosci. Inst., Univ. of Chicago, Chicago, IL; [4]Dept. of Psychology, Yale Univ., New haven, CT; [5]Dept. of Psychology, Columbia Univ., New York, NY

Abstract: Resting-state functional connectivity (rsFC) predicts traits and behaviors. However, the human mind rarely rests. Does rsFC reflect ongoing thoughts? If so, could the reason why rsFC predict behavior be that people with similar traits and behaviors have more similar thought patterns? In a 2-session fMRI study (n=60) collecting movie-watching, rest, and attention task data, we used a novel annotated rest task to probe ongoing thoughts during rest. Individuals completed up to 4 10-mins runs of the task, where they rested for 30s, verbally reported their thoughts in the previous rest period for 10s, and rated the thoughts on 9 dimensions (e.g., my thoughts were in the form of images). Ratings were widely distributed, suggesting that participants have variable thoughts at rest. We first tested whether rsFC reflects content (512-element text embeddings of verbal reports) and dimensions (9 self-report ratings) of ongoing thoughts. Individuals with more similar thought content ($r = .168$, $p < .001$) but not dimensions ($r = -.049$, $p = .968$) had more similar FC patterns. FC dynamics also tracked within-individual fluctuations in thought content ($r = .063$, $p < .001$) and dimensions ($r = .078$, $p < .001$). Next, we built connectome-based predictive models with leave-one-subject-out cross-validation, where nonlinear support vector regression and classification models were trained to predict thought dimensions and classify thought topics (9 annotator-rated speech categories). We observed significant predictions of 5 of 9 dimensions (corrected-$p < .01$; awake, external, future, valence, and in the form of images) and above-chance accuracy in classifying the topics (mean accuracy = 28.5%, $p < .01$). Applying these models to resting-state data from the Human Connectome Project (HCP), we conducted a canonical correlation analysis to examine the relationship between predicted resting-state thoughts and out-of-scanner traits and behaviors. We identified a significant positive-negative mode of population covariation linking ongoing thoughts with 158 HCP individual-difference measures, including psychometric measures, lifestyles and demographics ($r = .443$, corrected-$p = .027$). Finally, to explore the role of resting-state thoughts in everyday cognition, we related thought similarity to neural synchrony during movie-watching. Across four movie fMRI runs, people with more similar thought content showed higher intersubject correlation in multiple brain regions (corrected $p < .001$), suggesting that like-minded individuals may process the world similarly. Together, our work suggests that ongoing thoughts are reflected in rsFC and predict everyday cognition and behavior.

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Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.009/LBA95

Topic: H.02. Perception and Imagery

Support: National Institute of Mental Health Intramural Research Program (ZIAMH002783)

Title: A novel reality monitoring paradigm: Distinguishing image and afterimage conscious perception

Authors: C. M. LEVESQUE[1], N. DIJKSTRA[4], P. BANDETTINI[2,3], *S. KRONEMER[2]; [1]Section on Cognitive Neuropsychology, [3]Section on Functional Imaging Methods, [2]NIMH, Bethesda, MD; [4]Univ. Col. London, London, United Kingdom

Abstract: Reality monitoring is the ability to distinguish between sensory-dependent (e.g., viewing an image or hearing a sound) and sensory-independent conscious perception (e.g., imagining an image or dreaming a sound). When reality monitoring fails, the source of the conscious experience is confused. For example, hallucinations occur when a sensory-independent perception is misattributed to a physical source. The precise neural mechanisms of reality monitoring in healthy brains are poorly understood. Additionally, it is unknown why this system becomes dysfunctional in certain patient groups (e.g., schizophrenia) and in altered states of consciousness (e.g., psychedelic state). Challenges arise to resolve these queries due to the difficulty of developing a paradigm that generates reality monitoring failures in a controlled experimental setting with healthy participants. To address this, we developed a novel reality monitoring paradigm involving image and afterimage conscious perception. Afterimages are illusory, visual conscious perceptions that often occur following adaptation to light stimulation. In recent behavioral and fMRI studies, we found evidence that negative afterimages share perceptual characteristics and brain network responses with sensory-independent conscious perception (e.g., imagery). In the current study, participants perceived either a Gabor patch negative afterimage triggered by a preceding inducer stimulus or an on-screen Gabor patch image. The appearance (contrast, sharpness, and duration) of the on-screen Gabor patch image was manipulated to match each participant's internally generated afterimage in a separate calibration session. On a trial-by-trial basis, participants were asked to report whether they perceived an afterimage or image. To ensure that participants were not aware of the trial condition, continuous flash suppression (CFS) was used to render the inducer invisible while still allowing for conscious perception of an afterimage. We hypothesize that afterimage and image conscious perception will be regularly misattributed by healthy participants (i.e., a failure of reality monitoring), and task performance (e.g., the frequency of source errors) may predict susceptibility to hallucinations in daily life. In future investigations, this paradigm can be combined with neuroimaging to study the brain mechanisms of successful and erroneous reality monitoring.

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Late-Breaking Poster

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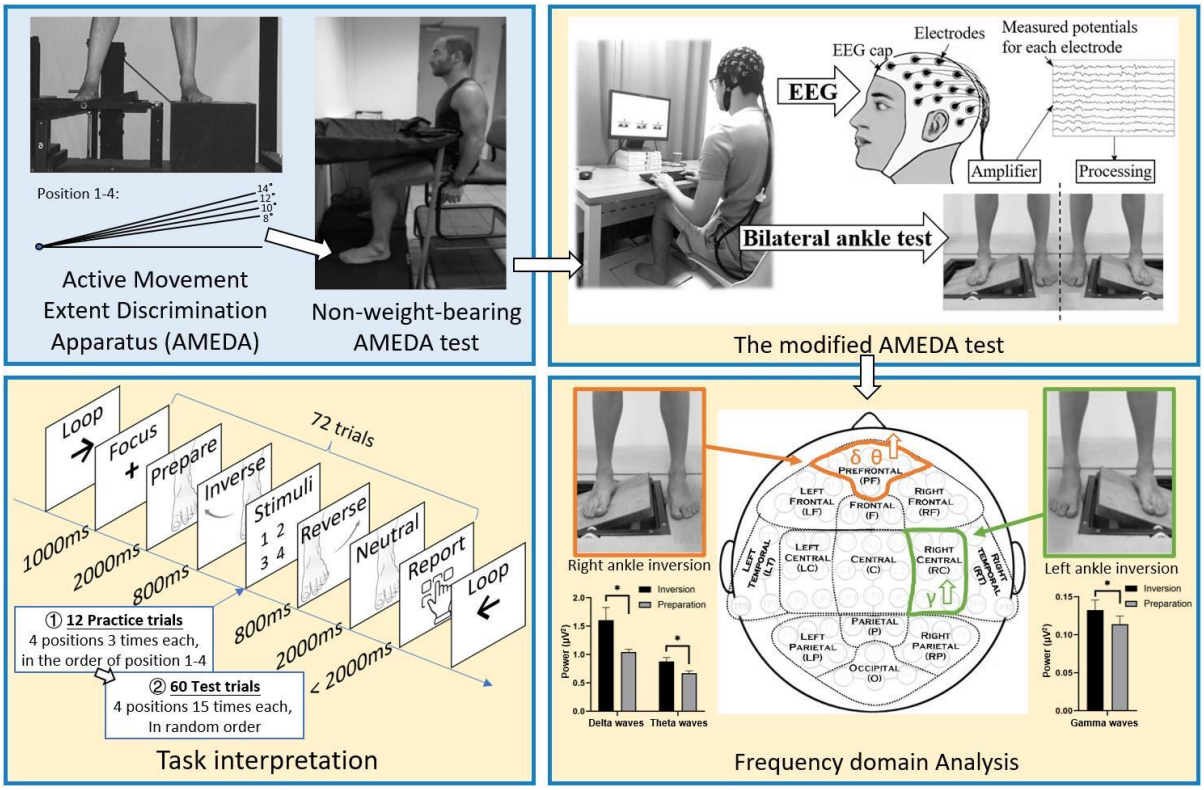
Program #/Poster #: LBA008.010/LBA96

Topic: H.02. Perception and Imagery

Title: Neural mechanism underlying hemispheric specialization in ankle proprioception control - an EEG study

Authors: *B. LIU[1], J. HAN[2];
[1]The Univerisity of Tokyo, Tokyo, Japan; [2]Shanghai Univ. of Med. & Hlth. Sci., Shanghai, China

Abstract: Background: Behavioral studies found that the right hemisphere/left ankle specializes in position-related proprioceptive control, while the left hemisphere/right ankle specializes in movement-related proprioceptive control. However, the neural mechanisms underlying this hemispheric specialization in ankle proprioceptive control remain unclear.
Purpose: This Electroencephalogram (EEG) study aimed to explore brain activation during an active ankle inversion proprioceptive test to understand the neural mechanism underlying ankle proprioceptive control.
Methods: Twelve right-footed healthy adults (7M, 5F, 26.2±2.3 yrs.) completed the ankle movement extent discrimination assessment (AMEDA) for both ankles. Participants familiarized themselves with 4 ankle inversion positions (8°, 10°, 12°, 14°), and then differentiated these positions in a randomized 60-trial test. Proprioceptive discrimination sensitivity scores were derived from the mean area under the receiver operating characteristic curve. EEG signals were recorded at 1000 Hz using 64 electrodes. A t-test examined the mean power spectral density differences across brain regions during ankle inversion and neutral position. Signal preprocessing and frequency analysis were performed using MATLAB.
Results: During left ankle inversion, mean gamma power in the right central region increased significantly ($t=2.56$, $p=0.02$). During right ankle inversion, mean delta and theta power in the prefrontal region increased significantly ($t=6.68$, $p<0.01$; $t=5.14$, $p<0.01$). No significant differences were found in ankle proprioceptive discrimination sensitivity ($p>0.05$).
Conclusion: Increased gamma power in the right central region may reflect spatial localization during left ankle inversion, while increased prefrontal delta and theta power may indicate cognitive and attentional demands during right ankle inversion. These findings suggest bilateral ankle proprioception tests involve different cognitive and motor control processes, resulting in distinct hemispheric electrical activity.



Disclosures: B. Liu: None. **J. Han:** None.
Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Program #/Poster #: LBA008.100/LBA185

Topic: H.11. Language

Support: 2017 – 2018 UTD Dean of Graduate Studies Dissertation Research Awards; Schneider, J.M. (PI)
2017 – 2017 UTD PhD Research Small Grants Program; Schneider, J.M. (PI)

Title: Pilot study on network connectivity development during semantic and syntactic error processing: Analyzing EEG signals using phase-lag index and graph theory

Authors: *M. BEHBOUDI[1], J. SCHNEIDER[2], M. MAGUIRE[1];
[1]The Univ. of Texas at Dallas, Dallas, TX; [2]UCLA, Los Angeles, CA

Abstract: Understanding how the brain processes semantic and syntactic errors is crucial for elucidating language comprehension mechanisms. Methods like EEG time-frequency and ERP analysis provide insights into the timing and spectral characteristics of brain activation during

language processing, but do not explain the mechanisms of communication within neural networks (Schneider et al. 2019; Behboudi et al. 2023). This study investigates neural network connectivity dynamics in children and adults during auditory sentence processing using EEG signals analyzed through the Phase-Lag Index (PLI) and graph theory. PLI measures phase synchrony between two signals while minimizing volume conduction effects (Stam et al 2007; Gaudet et al. 2020). Participants included 8 children (ages 8-9; F: 5) and 8 adults (F: 5). Sentences were categorized as correct, semantic violations, and syntactic violations. EEG data were recorded, epoched starting at the sentences' main verb (when both semantic and syntactic errors occurred). PLI was computed for the theta frequency (4-8 Hz) to measure phase synchronization between all electrode pairs. Average PLI values between each electrode and all other electrodes were calculated to indicate its hubness, the centrality within the information network. In the theta band, correct sentences showed no significant connectivity change compared to baseline in children or adults. Semantic and syntactic errors elicited increased synchronization in both groups. Adults exhibited significantly more synchronization over anterior frontal, left temporal, and left parietal electrodes compared to children for semantic errors ($t(12.36) = 2.76$, $p = 0.017$). For syntactic errors, no significant age group differences were observed, but adults showed more synchronization over frontal and left temporal regions ($t(11.68) = 1.56$, $p = 0.14$). Within-group comparisons revealed that adults had greater synchronization during semantic than syntactic errors ($t(7) = -1.35$, $p = 0.218$), whereas children showed minimal differences between semantic and syntactic conditions ($t(7) = 0.64$, $p = 0.543$). These results suggest that during semantic errors, the anterior frontal, left temporal, and left parietal theta networks in adults act as hubs for processing incongruent linguistic input, likely due to theta's role in lexical retrieval (Maguire et al 2022). In contrast, syntactic errors involve fewer synchronized theta networks. For children, semantic and syntactic processing differences are less pronounced, supporting previous research that children rely more on semantics than syntax in sentence processing (Skeidi et al 2014).

Disclosures: M. Behboudi: None. **J. Schneider:** None. **M. Maguire:** None.

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Title: Neural dynamics of singing versus speaking

Authors: *A. PRACAR[1], M. PAGNOTTA[4], D. R. QUIROGA-MARTINEZ[5], T. HE[8], N. BIONDO[6,9], M. IVANOVA[2], M. DASTJERDI[10], J. LIN[11], J. T. WILLIE[13], P. BRUNNER[14], N. F. DRONKERS[3,12], R. T. KNIGHT[7,15];
[1]Univ. of California, Berkeley, UC Berkeley, CA; [2]Psychology, [3]Univ. of California, Berkeley, Berkeley, CA; [4]Helen Wills Neurosci. Inst., [5]Psychology, [7]Psychology and Neurosci., [6]UC Berkeley, Berkeley, CA; [8]The Chinese Univ. of Hong Kong, Shenzhen, Hong Kong; [9]Basque Ctr. on Cognition Brain and Language, San Sebastián, Spain; [10]Neurol., Loma Linda Univ., Redland, CA; [11]Dept. of Neurol., [12]Neurol., Univ. of California, Davis, Davis, CA; [13]Neurolog. Surgery, Washington Univ. Sch. of Med., Saint Louis, MO; [14]Dept. of Neurosurg., Washington Univ., St. Louis, MO; [15]Helen Wills Neurosci. Inst., Berkeley, CA

Abstract: Introduction: For over 100 years, it has been observed that some post-stroke individuals with aphasia can sing more fluently than they can speak. Despite extensive exploration into the neurobiology of language, the neural mechanisms differentiating speech and song production remain unknown. Here, we leveraged the high spatial (mm) and temporal (ms) resolution of intracranial electroencephalography (iEEG) to define the hemispheric contributions and network dynamics of singing and speaking.**Methods:** iEEG data was collected from 15 participants with surgically-implanted electrodes for pre-surgical evaluation of pharmacologically-refractory epilepsy while repeating sentences in either a singing or speaking condition. We performed power estimation using the Irregular Resampling Auto-Spectral Analysis (IRASA) (Wen & Liu, 2016), which allowed us to distinguish rhythmic activity from fractal 1/f components. We then compared rhythmic power-spectrum components between the singing and speaking conditions. **Results & Summary:** Hemispheric asymmetries were observed across multiple frequency bands. Alpha power (~8-12 Hz) in motor and temporal regions was lower for singing in the right hemisphere and for speaking in the left hemisphere, with effect sizes ranging up to Cohen's d of 0.53 (medium). Motor regions showed increased power in the beta band (~12-20 Hz; Cohen's d of 0-0.64) in speaking compared to singing, particularly in the left hemisphere. Cluster-based permutations revealed a significant difference between singing and speaking in these regions, driven by activity in the alpha band ($p_{perm} < .002$). Taken together the observed asymmetries provide evidence for hemispheric lateralization of singing versus speaking.

Disclosures: A. Pracar: None. **M. Pagnotta:** None. **D.R. Quiroga-Martinez:** None. **T. He:** None. **N. Biondo:** None. **M. Ivanova:** None. **M. Dastjerdi:** None. **J. Lin:** None. **J.T. Willie:** None. **P. Brunner:** None. **N.F. Dronkers:** None. **R.T. Knight:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.102/LBA187

Topic: H.12. Aging and Development

Support: McKnight Brain Research Foundation

Title: Dynamics of Default Mode Network Activity Linked to Processing Speed in Cognitively Healthy Oldest-Old

Authors: *H. COWART[1], G. LING[2], S. NOLIN[3], P. STEWART[4], L. L. FLEMING[5], M. FAULKNER[2], S. MERRITT[6], R. REZAEI[9], P. K. BHARADWAJ[11], M. FRANCHETTI[12], D. A. RAICHLEN[11], C. JESSUP[11], G. A. HISHAW[11], E. J. VAN ETTEN[12], T. TROUARD[12], D. GELDMACHER[2], V. WADLEY[2], N. ALPERIN[13], C. B. WRIGHT[7], E. C. PORGES[10], A. J. WOODS[10], R. N. COHEN[14], B. E. LEVIN[7], T. RUNDEK[8], G. ALEXANDER[12], K. M. VISSCHER[15];
[1]Univ. of Alabama at Birmingham, Vestavia, AL; [2]Univ. of Alabama Birmingham, Birmingham, AL; [3]Med. Univ. of South Carolina, Charleston, SC; [4]Univ. of Alabama, Birmingham, Birmingham, AL; [5]Psychiatry, Mclean Hosp./Harvard Med. Sch., Atlanta, GA; [7]Neurol., [6]Univ. of Miami, Miami, FL; [8]Univ. of Miami, Miami Beach, FL; [10]Clin. and Hlth. Psychology, [9]Univ. of Florida, Gainesville, FL; [11]Univ. of Arizona, Tuscon, AZ; [12]Univ. of Arizona, Tucson, AZ; [13]Univ. of Miami, Miami, FL; [14]#12E, New York, NY; [15]Neurobio., Univ. of Alabama, Birmigham, Birmingham, AL

Abstract: Background: Cognition in cognitively intact “oldest-old” individuals can differ significantly, including in executive functions, memory, and processing speed. Dynamic brain activity can be clustered on the individual time-point level to produce group-averaged “brain states,” termed “co-activation patterns” (CAPs). These can offer high resolution temporal information regarding brain activity. This study marks the first attempt to explore the correlation between brain dynamics and cognition within the oldest-old demographic.Methods: In a study conducted across four sites—University of Alabama at Birmingham, University of Florida, University of Miami, and University of Arizona—146 cognitively healthy participants aged 85-99, without cognitive impairment, underwent an 8-minute, 2.4-second TR, 3T resting-state functional magnetic resonance imaging session (rs-fMRI). Additionally, the participants completed neurocognitive assessments as part of the McKnight Brain Aging Registry collaboration. Co-activation patterns (CAPs) were calculated using a k-means clustering algorithm. Dynamics were defined based on Fraction of occurrence (percentage of time spent in a specific state), persistence (consecutive time spent in a specific state), and transitions (movements from one state to another state).Results: The CAP displaying the highest stability across models (mean r = 0.92) has highly active default mode network (DMN) (z = 2.2), relatively high activation of the ventral attention network (VAN, z = 1.0) and low activation of every other network (z < -0.6). We examined the dynamics of the predominant CAP to five aggregated cognitive performance measures. These dynamics were strongly correlated only with

processing speed, where better processing speed was associated with greater transition entropy, longer persistence, and greater fraction of occurrence.Conclusions: The default mode network was identified as a stable, common group-wide measure in the oldest-old cohort, regardless of model. Better processing speed was correlated to dominant and persistent default mode network activity. CAPs add a nuanced, dynamic dimension to fMRI and hold promise as a potential biomarker for cognitive intervention in future studies.

Disclosures: H. Cowart: None. **G. Ling:** None. **S. Nolin:** None. **P. Stewart:** None. **L.L. Fleming:** None. **M. Faulkner:** None. **S. Merritt:** None. **R. Rezaei:** None. **P.K. Bharadwaj:** None. **M. Franchetti:** None. **D.A. Raichlen:** None. **C. Jessup:** None. **G.A. Hishaw:** None. **E.J. Van Etten:** None. **T. Trouard:** None. **D. Geldmacher:** None. **V. Wadley:** None. **N. Alperin:** None. **C.B. Wright:** None. **E.C. Porges:** None. **A.J. Woods:** None. **R.N. Cohen:** None. **B.E. Levin:** None. **T. Rundek:** None. **G. Alexander:** None. **K.M. Visscher:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.103/LBA188

Topic: H.12. Aging and Development

Support: Jump ARCHES

Title: Exploring recurrent neural network dynamics in Tai Chi practitioners

Authors: *J. CERNA[1], P. GUPTA[2], M. HE[3], L. ZIEGELMAN[4], Y. HU[5], M. E. HERNANDEZ[6];
[1]Neurosci., [2]Electrical and Computer Engin., Univ. of Illinois Urbana-Champaign, Urbana, IL; [3]Neurosci. Program, [4]Neurosci., Univ. of Illinois At Urbana-Champaign, Urbana, IL; [5]Kinesiology, San Jose State Univ., San Jose, CA; [6]Biomed. and Translational Sci., UIUC, Urbana, IL

Abstract: Background: Tai Chi (TC) practice has shown promise in improving cognitive function and functional connectivity (FC) in older adults, potentially mitigating age-related decline. However, the neural mechanisms underlying these benefits remain unclear, with prior research often unable to disentangle the effects of aging from those specifically attributable to TC practice. This study aims to differentiate the distinct contributions of age and TC practice on recurrent neural network dynamics (RNNDs) using source-localized electroencephalography (EEG). We hypothesize that aging will be associated with decreased FC, while TC practice will partially mitigate these age-related changes. **Methodology:** Resting-state EEG data were collected from three groups: healthy younger adult controls (YACs, n=15), healthy older adult controls (OACs, n=15), and older adult TC practitioners (TCOAs, n=15). EEG data were source-

localized and fitted to a Hidden Markov Model (HMM) to derive spatiotemporal features of RNNDs. Non-parametric Mann-Whitney U tests assessed between-group differences in temporal and spatial features by age (OACs vs. YACs) and TC practice (OACs vs. TCOAs), controlling for multiple comparisons using false discovery rate (FDR) correction. **Results:** Aging was associated with significantly decreased within-network and between-network FC across most brain networks (all FDR-adjusted p-values < 0.05 for all within/between network measures, except DAN and LIN), particularly in the default mode network (DMN), ventral attention network (VAN), and visual network (VIN). Conversely, TC practice was associated with significantly increased within-network and between-network FC across all networks (all FDR-adjusted p-values < 0.05 for all within/between network measures), suggesting a network-wide mitigating effect on age-related decline. Notably, the effect size difference between age-related and practice-related effects favorably showed that TC practice may provide strong intra- and inter-network compensatory effects (median rank biserial r-diff = 0.25). **Conclusion:** Our findings reveal distinct effects of age and TC practice on RNNDs, with TC practice potentially counteracting age-related declines in FC. The overlap in networks affected by age and modulated by TC practice supports the hypothesis that TC practice may confer neuroprotective benefits by enhancing functional integration and communication within and between brain networks. These results underscore the potential of TC as a non-pharmacological intervention for promoting healthy brain aging.

Disclosures: J. Cerna: None. **P. Gupta:** None. **M. He:** None. **L. Ziegelman:** None. **Y. Hu:** None. **M.E. Hernandez:** None.

Late-Breaking Poster

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Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.104/LBA189

Topic: H.12. Aging and Development

Support: NIH/NIA R24 AG065172
James S. McDonnell Foundation

Title: Cross-species comparison of large-scale functional brain network alterations in aging humans, marmosets, and mice

Authors: *E. WINTER-NELSON[1], E. BERGMANN[2,3], M. Y. CHAN[4], L. HAN[4], Z. ZHANG[4], I. KAHN[3,2], G. S. WIG[4,5];
[1]Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX; [2]Technion – Israel Inst. of Technol., Haifa, Israel; [3]Zuckerman Inst., Columbia Univ., New York, NY; [4]Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX; [5]Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Human aging is accompanied by alterations in the organization of resting state functional correlation (RSFC) brain systems. Increasing age is accompanied by a decline in brain system segregation, which reflects the extent to which systems are functionally differentiated (Wig, 2017). Lower system segregation is associated with worse cognitive ability in both cognitively healthy adults (Chan et al., 2014) and Alzheimer's Disease patients (Ewers et al., 2021; Zhang et al., 2023). Further, longitudinal decline of system segregation is prognostic of dementia severity during older age (Chan et al., 2021). Despite its consequentiality towards cognitive function in healthy and pathological aging, the mechanisms underlying age-related system segregation changes are unclear. Animal models offer a means of gaining direct insight towards age-related brain network decline, but it remains uncertain whether comparable age-related RSFC brain changes exist in other species, and how these changes compare to those observed in humans. Here, we establish a multi-species model of large-scale functional brain network aging, thus bridging research silos across species and catalyzing a program of interactionist aging neuroscience. Our previous work showed age-related decline in RSFC brain system segregation among mice (3-12 months; Winter-Nelson et al., in prep.). Here, we examine age-related brain network alterations in the marmoset. We analyzed data from an open-access awake resting-state fMRI marmoset dataset spanning 2-9y (MBMv4; n=39; Tian et al, 2022). Brain networks were built by first parcellating the brain into functional areas (nodes) by examining transitions of RSFC patterns and then detecting functional communities amongst the nodes. Network analyses were performed on individuals' RSFC networks. Age-associated alterations of system segregation in marmosets were compared to those observed in mice and humans (the latter calculated from data obtained from the Human Connectome Project; 20-90y). Brain system segregation differs across species, irrespective of age (main effect of species: $F(2,997)=31.37$, $p<.001$). However, age-associated declines of brain system segregation were evident in each species (main effect of age: $F(1,997)=68.62$, $p<.001$). Notably, the rate of decline varied across species (age*species interaction: $F(2,997)=20.15$, $p<.001$), with mice showing the steepest slopes, humans the shallowest, and marmosets exhibiting an intermediate rate of decline. These patterns support the viability of cross-species models of brain network aging and highlight differential constraints on network organization and decline across species.

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Late-Breaking Poster

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Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.105/LBA190

Topic: H.12. Aging and Development

Support: NIH grant RF1AG054106

Title: Aging blunts REM sleep delta waves explaining memory impairment

Authors: *T. DESEL[1], M. P. WALKER[2], C. CHEN[1], O. SHARON[3];
[1]Univ. of California, Berkeley, Berkeley, CA; [2]Dept Psychology, California Clin. Trials, Berkeley, CA; [3]Psychology, Univ. of California Berkeley, Berkeley, CA

Abstract: Motivation: REM sleep is not classically associated with slow delta waves (1-4Hz). However, recently, a study in young adults identified clusters of delta waves: frontocentral fast sawtooth delta waves and medial-occipital slow NREM-like delta waves. Two questions arise : Are REM slow waves functional and how are they affected by aging?
Methods: Overnight polysomnographic sleep EEG recordings were conducted in 61 young adults (mean age=20.24±1.91) and 72 older adults (mean age=74.79±5.73). Participants completed a paired association learning task and were tested in the morning. REM sleep delta waves and eye movements were detected using established algorithms.
Results: In young adults, topographic analysis confirmed two delta wave clusters: frontocentral fast sawtooth waves and occipital slower waves. Compared to young adults (YA) (mean=70.11±9.61w/min), older adults (OA) had significantly reduced frontocentral fast sawtooth wave density (mean = 63.71±6.92w/min, t=-4.39, $p<0.001$) and amplitude (YA=9.34±1.62μV, OA=7.14±1.77μV, t=-7.31, $p<0.001$) as well as occipital slow wave density (YA mean = 26.07 ± 2.99 w/min, OA=22.56± 2.65w/min, t=-7.06, $p<0.001$). Weaker overnight memory consolidation was observed in individuals with higher slow wave density in REM sleep (r=-0.35, $p_{cluster}<0.01$), but not in NREM sleep (r=-0.23, $p>0.05$) or for fast sawtooth wave density (r =0.10, $p>0.05$). Consistent with previous reports, young adults had a widespread increase in fast sawtooth waves during phasic REM sleep period (permutation cluster test, $p<0.01$) and an increase in slow waves during tonic REM sleep period (permutation cluster test, $p<0.01$). In older adults, the increased density of fast waves during phasic periods was limited to the frontocentral regions, with no reduction in slow waves during the phasic period. Specifically, compared to young adults, older adults show less difference in slow wave density between phasic and tonic period in central and occipital regions (permutation cluster test, p=0.01).
Conclusion: Aging significantly disrupts REM delta waves, impairing frontocentral fast sawtooth waves and occipital slow waves. Slow 'NREM-like' waves during REM sleep, but not fast sawtooth waves, are associated with aging-related overnight forgetting. Our findings provide a new explanatory framework that may contribute to age-related forgetting during REM sleep.Funding: NIH grant RF1AG054106.

Disclosures: T. Desel: None. **M.P. Walker:** None. **C. Chen:** None. **O. Sharon:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.106/LBA191

Topic: H.12. Aging and Development

Title: Impacts of healthy aging on the similarity of signals along the hippocampal long axis

Authors: *S. M. BIRR[1], C. CHARLES[1], C. R. BOWMAN[2];
[1]Psychology, [2]Dept. of Psychology, UW-Milwaukee, Milwaukee, WI

Abstract: The hippocampus is crucial for forming and retrieving episodic memories. Past work in healthy young individuals suggests a functional specialization along the hippocampal longitudinal axis in which more posterior regions support memory for fine-grained details, and representations become increasingly coarse in more anterior portions. Supporting this theory, prior work has shown higher correlation of hippocampal signals within the anterior versus within the posterior hippocampus, suggesting that anterior hippocampal signals integrate across wider spatial and temporal windows. Although it is well known that memory declines even in healthy aging, it is not known whether breakdowns in the functional signals of the posterior versus anterior hippocampus contribute to this decline. To address this gap, we used resting state data from 329 male and female participants aged 18-88 from the Cambridge Center for Aging and Neuroscience. We assessed inter-voxel similarity (IVS) as a measure of signal similarity across three hippocampal regions that spanned the long axis: the tail (most posterior), body, and head (most anterior). We found that age-related differences in IVS were largest in the most posterior hippocampal region (tail), within signals becoming increasingly similar to one another in older age. Age effects in the more anterior regions trended negatively but did not approach significance. These findings are in line with the hypothesis that the specificity of episodic memory declines in older age in part because the posterior hippocampus is less able to represent idiosyncratic details of individual events. However, we also related IVS values from each hippocampal subregion to individual differences in visual short-term memory, object recognition, and memory for the emotional context an object was presented in. While the relationship between IVS and memory performance was persistently negative for the right hippocampal tail (more similar signals associated with poorer memory), this relationship was strongest for short term memory and did not pass a correction for multiple comparisons. Thus, while we found substantial changes to signals within the posterior hippocampus with advanced age, their relationship to memory performance was relatively weak, suggesting that older adults may employ other neural systems to compensate for differences in hippocampal processing.

Disclosures: S.M. Birr: None. **C. Charles:** None. **C.R. Bowman:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Program #/Poster #: LBA008.107/LBA192

Topic: H.12. Aging and Development

Title: The effect of age on pigeon (columba livia) decision-making in a variable reward, spatial memory task

Authors: *T. M. BURNS[1], V. P. BINGMAN[2];
[2]Psychology, [1]Bowling Green State Univ., Bowling Green, OH

Abstract: The process of aging leaves a notable impact on the nervous system. The nature of this impact and its consequences are well-known in humans and other mammals, but there remains a dearth of research focused on aging processes of most other taxa, including birds. However, recent studies on the avian hippocampus, a key brain area for spatial memory, suggest that older pigeons do experience changes in hippocampal function and cognitive decline. Given that homing pigeons are one of nature's foremost navigators, the present research compared the behavior of young and old homing pigeons in a spatial memory task. Twelve (12) unsexed homing pigeons (*Columbia livia*) were divided into two experimental groups consisting of a younger group aged less than 7 years and an older group aged greater than eleven years. Subjects were trained to locate baited food bowls in an open floor arena with scattered landmark cues. Two food locations were never baited with food, while two others were baited with either a small, constant reward (2 food pellets per trial) or a large, variable reward (5 food pellets intermittently available). The intermittent schedule of the large, variable reward changed pseudorandomly between an even number of low variable (25%) and high-variable (75%) trials. The constantly and intermittently baited bowls oscillated between another pair of locations depending on which intermittent schedule was active on each trial, such that their placement served as a cue to the availability (high or low) of the large, variable reward. After being shaped to task, subjects completed 160 trials over the course of 23 days. First order results suggest that the older pigeons do not suffer from spatial memory decline: there was no significant difference between the two experimental groups with respect to error rates (choosing an empty food bowl location). Further analysis revealed that older pigeons preferred the small, constant reward location in both the low and high variable conditions, whereas young pigeons only preferred the small, constant reward location in the low variable condition. In the high variable condition, younger, but not older, pigeons preferred the large, variable reward location. We propose that the avian hippocampus undergoes functional changes because of aging. Older pigeons may not struggle to remember food locations, but their choice preferences indicate a deviation from rational decision-making (over time, the high variable bowl would have yielded more food). Further research will be necessary to probe how the avian hippocampus and related structures evaluate risk and reward, and how that evaluation may change as a function of age.

Disclosures: T.M. Burns: None. **V.P. Bingman:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.108/LBA193

Topic: H.12. Aging and Development

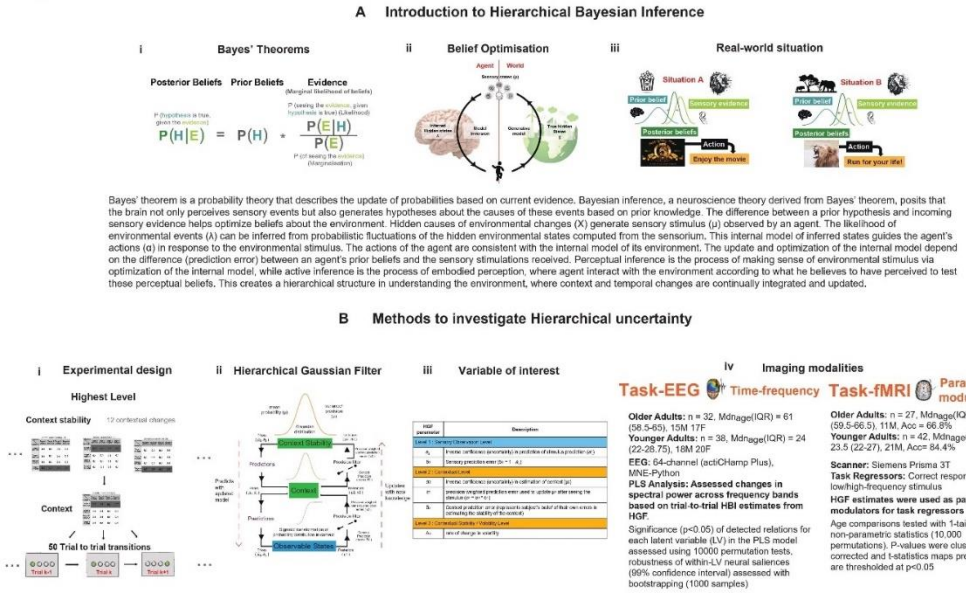
Support: MOE AcRF Tier2 grant MOE2019-T2-1-019

Title: Differential neural activity across Hierarchical Bayesian inference under uncertainty in Older and Younger adults

Authors: J. ZHANG, W. P. H. LIM, *S. CHEN;
Nanyang Technological Univ., Singapore, Singapore

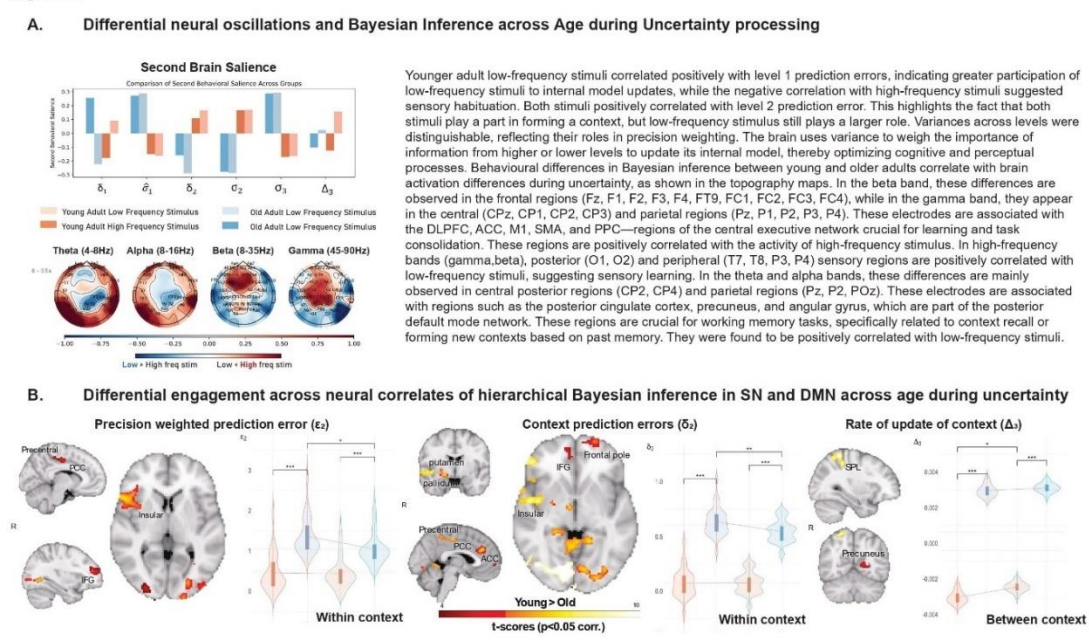
Abstract: Hierarchical relations drive state changes in environments. The brain may encode these through Bayesian inference. Neural correlates of Hierarchical Bayesian Inference (HBI) are not well studied. We studied HBI across ages in a probabilistic task using EEG and fMRI. Partial Least Squares analysis on EEG data revealed inverse correlation between age groups in HBI parameters and uncertainty. Younger adults exhibited expected correlations, with age differences in CEN regions correlated with high-frequency stimuli, suggesting context consolidation, and sensory regions correlated with low-frequency stimuli, indicating sensory learning in gamma-beta bands. DMN regions correlated with low-frequency stimuli in theta-alpha bands, suggesting context processing. FMRI data shows that younger adults had higher activity in the salience network (SN) during estimation of context update and its errors. They had higher activity in parts of DMN and subcortical regions during context update errors, and in precuneus during volatility updates. Overall, older adults exhibited lower brain response but higher behavioral estimates for HBI compared to younger adults. Differing patterns of HBI observed across behavior, neural oscillations, and network activity, suggest that as we age, reliance on familiarity increases, and skills required for uncertainty estimation decline, reflected as changes in neural dynamics, where overall functional network connectivity becomes less efficient and granular.

Figure 1.



To capture subjects' Hierarchical Bayesian Inference behaviours under uncertainty, we designed a probabilistic serial reaction time task with three levels of uncertainty. In this experiment, subjects observed four circles, with one highlighted in green. They were required to predict and react to the green circle as quickly as possible. Unbeknownst to the subjects, for every 50 trials (one block of context), one position was most likely (70% chance) to be green, representing a high-frequency stimulus. This probabilistic context changed 12 times throughout the experiment. Subjects could only observe the state-to-state changes to approximate the probabilistic context at the next level. When subjects encountered a significant prediction error that did not align with their internal model, they had to address the discrepancy by recurrently updating and estimating the parameters in neighbouring levels to adjust their internal models accordingly. The Hierarchical Gaussian Filter (HGF; Mathys et al., 2011; 2014) was chosen as the analysis model as it tracks subject-wise Bayesian inference behavior for each trial. It breaks down HBI into 3 levels (Level 1 Observable level, Level 2 Contextual level, and Level 3 Stability level). HGF models subjects' estimates at each level by representing the mean (subject's current estimate) and variance (confidence of that estimate) of both the prior (μhat, σhat) and posterior (μ, σ) distributions using a Gaussian distribution. The inverse of the variance is the precision of that estimate. When the subject observes a stimulus, a prediction error (δ) is generated between the prior and posterior values. This prediction error is multiplied by precision weights, resulting in a precision-weighted prediction error (ε). The precision-weighted prediction error (ε) updates the prior values (μhat, σhat) at higher levels for the next prediction. This iterative process allows for continuous refinement of the internal model based on incoming sensory information.

Figure 2.



Younger adult low-frequency stimuli correlated positively with level 1 prediction errors, indicating greater participation of low-frequency stimuli to internal model updates, while the negative correlation with high-frequency stimuli suggested sensory habituation. Both stimuli positively correlated with level 2 prediction error. This highlights the fact that both stimuli play a part in forming a context, but low-frequency stimulus still plays a larger role. Variances across levels were distinguishable, reflecting their roles in precision weighting. The brain uses variance to weigh the importance of information from higher or lower levels to update its internal model, thereby optimizing cognitive and perceptual processes. Behavioural differences in Bayesian inference between young and older adults correlate with brain activation differences during uncertainty, as shown in the topography maps. In the beta band, these differences are observed in the frontal regions (Fz, F1, F2, F3, F4, FT9, FC1, FC2, FC3, FC4), while in the gamma band, they appear in the central (CPz, CP1, CP2, CP3) and parietal regions (Pz, P1, P2, P3, P4). These electrodes are associated with the DLPFC, ACC, M1, SMA, and PPC—regions of the central executive network crucial for learning and task consolidation. These regions are positively correlated with the activity of high-frequency stimulus. In high-frequency bands (gamma,beta), posterior (O1, O2) and peripheral (T7, T8, P3, P4) sensory regions are positively correlated with low-frequency stimuli, suggesting sensory learning. In the theta and alpha bands, these differences are mainly observed in central posterior regions (CP2, CP4) and parietal regions (Pz, P2, POz). These electrodes are associated with regions such as the posterior cingulate cortex, precuneus, and angular gyrus, which are part of the posterior default mode network. These regions are crucial for working memory tasks, specifically related to context recall or forming new contexts based on past memory. They were found to be positively correlated with low-frequency stimuli.

Subjects' mean Hierarchical Gaussian Filter (HGF) parameters for correct trials were modeled for age group, trial frequency, and their interaction effects while controlling for covariates of order, block number, and inter-subject variability. Post-hoc analysis with FDR correction revealed that, despite having higher precision-weighted prediction error for low-frequency trials, older adults showed lower activation in brain regions associated with the Salience Network (SN), including the insular cortex, posterior cingulate cortex (PCC), and inferior frontal gyrus (IFG), compared to younger adults. The SN, which is crucial for adaptive control and responding to high uncertainty, is expected to direct neural resources to pertinent environmental stimuli that resolve uncertainties. Older adults' higher precision-weighted prediction error in low-frequency trials suggests frequent context switching, indicating a lack of understanding of level 2 context. Behaviorally, older adults exhibited higher context estimation errors, particularly in low-frequency trials, yet showed lower brain responses in SN regions, decision-making frontal areas, and subcortical regions like the striatum, known for encoding prediction errors. Additionally, older adults perceived a higher rate of context change, especially in high-frequency trials, the key context-defining stimulus. Despite higher behavioral indices, brain responses in regions like the precuneus and superior parietal lobe were lower in older adults. These results suggest that older adults compensate behaviorally for reduced neural activation in response to Bayesian inference parameters.

Disclosures: J. Zhang: None. **W.P.H. Lim:** None. **S. Chen:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Topic: H.12. Aging and Development

Support: NIH Grant F32AG071263
NIH Grant R21AG073973

Title: Age-related and disease-related differences in navigational spatial working memory using immersive virtual reality

Authors: *K. K. NGUYEN[1,4], T. T. TRAN[2], E. JOHNSON[4,5], D. F. TADEO[4], O. CHATZIFOTI[6,7], L. DACORRO[4], J. BAILENSON[3], A. D. WAGNER[2], H. HOSSEINI[4]; [2]Psychology, [3]Communication, [1]Stanford Univ., Stanford, CA; [4]Psychiatry and Behavioral Sci., Stanford Med., Stanford, CA; [5]Psychology, Palo Alto Univ., Palo Alto, CA; [6]Natl. and Kapodistrian Univ. of Athens, Athens, Greece; [7]Studio Bahia, San Antonio, TX

Abstract: Visuospatial processing and navigational deficits are frequently observed during the preclinical stages of Alzheimer's disease (AD). Declines in navigational ability may also be predictive of the development of AD, as the earliest regions affected by the disease overlap with navigational neural networks. Neuropsychological tests like the Corsi Block Test (CBT) have been utilized to assess visuospatial working memory deficits during the preclinical stage of AD and in patients with amnestic mild cognitive impairment (MCI), a transitional stage between healthy aging and Alzheimer's disease dementia. The CBT involves tapping out spatial sequences of increasing length on a board containing an arrangement of nine blocks, and performance is thought to predominately depend on visuospatial working memory.

In the current study, we adapted the CBT to a real-life scale using immersive virtual reality (VR) to assess both visuospatial working memory and navigation in young adults (N=21, 11 females, age range: 18-24 years old), older adults (n=21, 11 females, 65-85 years old) and patients with MCI (N=10, 5 females, age range: 65-85 years old). Our implementation of the Virtual Reality Corsi Block Test (VR-CBT) uses the same standard layout of squares scaled-up on the floor. Participants observe a virtual avatar walking a path connecting a span of squares of increasing length (starting at 2 locations and increasing up to 8 locations), and are then asked to recreate the same path. Using eye-tracking during the VR-CBT, we can explore whether these deficits in visuospatial performance arise from a failure to encode and/or poor retrieval. Participants' movements are tracked by external cameras as they wear a head-mounted display, allowing for independent ambulation as they navigate the open space and cameras within the headset track the participants' eye movements.

Preliminary data reveal clear age-related differences in performance, specifically in terms of the longest path successfully completed, such that young adults performed significantly better than

older adults and older adults with mild cognitive impairment performed significantly worse than cognitively normal older adults. Furthermore, eye-tracking measurements during encoding significantly predicted performance, such that a greater number of fixations during encoding was associated with decreased accuracy during retrieval in both young and older adults. These findings suggest that immersive VR has high potential for measuring both visuospatial working memory and spatial navigation ability performance in patient populations, healthy older adults, and young adults.

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Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.011/LBA97

Topic: H.02. Perception and Imagery

Support: JSPS KAKENHI Grant Number 20H03794
JMU Graduate Student Start-Up Award

Title: The Involvement of the Subthalamic Nucleus in Bistable Perception

Authors: *A. LKHAGVASUREN, Y. ONUKI, T. NAKAJIMA, K. KAWAI;
Dept. of Neurosurg., Jichi Med. Univ., Shimotsuke City/ Tochigi Prefecture, Japan

Abstract: The role of the basal ganglia network in visual bistable perception, where perception spontaneously switches due to ambiguous stimuli, remains poorly understood. The subthalamic nucleus (STN) has emerged as a potential key player due to its direct interactions with multiple cortical areas, including the prefrontal cortex, via the hyper-direct pathway. Bistable perception is often explained as a top-down process, and the STN is involved in this top-down mechanism through its role in cognitive control and decision-making. To investigate this, we conducted a study recording local field potentials (LFPs) from the STN through depth electrodes implanted for deep brain stimulation in Parkinson's patients during both ambiguous and unambiguous visual tasks. Our study involved nine patients (three males and six females, mean age = 62.8 ± 5.1 years). We adopted the spinning dancer illusion, to create an ambiguous stimulus that induced visual perceptual switching and a control task with explicit depth cues to provide an unambiguous visual experience. During these tasks, patients were instructed to report any changes in perceived rotation direction by pressing a button. We identified electrodes connected to the STN and divided them into dorsal and ventral sections using patient brain imaging data (preoperative MRI and postoperative CT) to account for the functional diversities within the

STN. Our findings revealed a significant increase ($p < 0.05$, cluster-based permutation test) in the alpha-beta (10-30 Hz) power from 500 to 1250 milliseconds after the motor response following the detection of perceptual changes in the spinning dancer illusion, compared to the control task. Notably, this increase was observed only in the dorsal STN, whereas the ventral STN did not demonstrate any such variation. Our findings suggest that higher alpha-beta power in the dorsal STN after perceptual changes in the ambiguous task reflects higher effort for top-down processes. This is because the ambiguous task requires internal perceptual decision-making, while the unambiguous task does not.

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LBA008: Theme H Late-Breaking Posters

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Program #/Poster #: LBA008.110/LBA195

Topic: H.13. Schizophrenia

Support: NIH Grant K01MH133970 (RHP)
Emory SURE Program

Title: Transferrin receptor as a mediator of gene-environment interactions in the schizophrenia-associated 3q29 deletion

Authors: *Y. DU[1], A. LANE[2], B. R. ROBERTS[3], V. FAUNDEZ[4], G. J. BASSELL[5], R. H. PURCELL[4];
[2]Physiol., [3]Biochem., [4]Cell Biol., [1]Emory Univ., Atlanta, GA; [5]Emory Univ. Sch. of Med., Atlanta, GA

Abstract: The 3q29 deletion (3q29Del) is a 1.6Mb copy number variant that is the strongest known genetic risk factor for schizophrenia. 3q29Del results in hemizygosity of 22 protein-coding genes, including *TFRC*, which encodes transferrin receptor protein 1 (TFRC). The transferrin receptor is ubiquitously expressed and binds to iron-bound transferrin at the cell surface, thus constituting the major pathway for cellular iron uptake that is essential for mitochondrial function. Iron deficiency during development is an environmental risk factor for schizophrenia, and mitochondrial dysregulation was recently identified as a functional consequence of 3q29Del. However, it is unclear how environmental factors affect 3q29Del phenotypes. We conducted a dose-response curve to the iron chelator deferoxamine (DFX) and determined the half maximal inhibitory concentration (IC50). We also determined mitochondrial respiration using the Seahorse mitochondrial stress assay. We found that 3q29Del-engineered HEK (*3q29*) cells were more susceptible to iron deficiency in vitro. *3q29* cells displayed reduced viability and impaired mitochondrial function in the presence of DFX and, unlike intact control

(*CTRL*) cells, failed to increase *TFRC* mRNA or protein levels under iron-deficient conditions. Moreover, we used inductively coupled plasma-mass spectrometry (ICP-MS) to measure iron content. *3q29* cells contained less iron at baseline and failed to import additional iron when challenged to increase aerobic respiration. Functional deletion of one allele of *TFRC* in HEK cells ($TFRC^{+/-}$), using the CRISPR/Cas9 system, recapitulated key respiratory phenotypes of *3q29* cells. In contrast to *CTRL* cells, $TFRC^{+/-}$ cells did not increase basal oxygen consumption rate (OCR) when challenged to use mitochondria for respiration. Together, our data indicate *TFRC* may be a mediator of gene-environment interactions in the schizophrenia-associated 3q29Del. Our ongoing experiments are aimed at testing the haploinsufficiency of *TFRC* in human induced pluripotent stem cell-derived neural models.

Disclosures: Y. Du: None. **A. Lane:** None. **B.R. Roberts:** None. **V. Faundez:** None. **G.J. Bassell:** None. **R.H. Purcell:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.111/LBA196

Topic: H.13. Schizophrenia

Support: NIMH Grant 5R01MH125528-04

Title: Investigating schizophrenia-associated SETD1A mutations in isogenic human neural model

Authors: *T. LE[1], X. SU[2], H. ZHANG[3], L. CHERUVU[4], K. MENDEZ-MALDONADO[5], L. WANG[1], S. ZHANG[6], Q. YANG[7], H. SONG[8], J. DUAN[10], G.-L. MING[9], Z.-P. PANG[11]; [1]Child Hlth. Inst. of New Jersey, New Brunswick, NJ; [2]Child Hlth. Inst. of New Jersey, Rutgers Univ. Grad. Program In Cell Develop. and Biol., New Brunswick, NJ; [3]Ctr. for Psychiatric Genet., Evanston, IL; [4]Child Hlth. Inst. of NJ, New Brunswick, NJ; [5]Cell and Mol. Physiol., Loyola Univ. Chicago Stritch Sch. of Med., Chicago, IL; [6]Dept. of Psychiatry, NorthShore Univ. HealthSystem, Evanston, IL; [8]Neurosci., [7]Univ. of Pennsylvania, Philadelphia, PA; [9]Dept Neurosci, Univ. of Pennsylvania, gladwyne, PA; [10]NorthShore Univ. HealthSystem/University of C, Evanston, IL; [11]Child Hlth. Inst. of New Jersey, Rutgers Univ., New Brunswick, NJ

Abstract: Rare mutations in *SETD1A (SET domain-containing protein 1A)* are strongly associated with schizophrenia (SCZ), a debilitating mental disorder affecting 1% of the population. *SETD1A* encodes a component of the histone methyltransferase complex producing mono-, di, and trimethylated histone H3 at Lysine 4 (H3K4). H3K4 trimethylation (H3K4me3) and H3K4me1 are epigenomic marks of active gene transcriptional promoters and enhancers, respectively. Interestingly, histone methylation has also been suggested as one of the top

enriched pathways in SCZ genome-wide association studies (GWAS). However, the detailed molecular mechanism by which it causes neuronal dysfunction and contributes to SCZ pathophysiology remains unclear. Recent advances in stem cell biology have allowed the efficient conversion of human stem cells into defined neuronal cell types to address this question. Using CRISPR/Cas9 gene editing, we have generated isogenic pairs of human induced pluripotent stem cell (iPSC) lines carrying SCZ-associated *SETD1A* heterozygous mutations including two human engineered mutations exon16 p. L 1533fs, exon4 16bp deletion and two patient-specific knock-in mutations c. 4582-2delAG> and p. Y42fs. Using qPCR and western blotting, we confirmed that two mutations, exon16 p. L 1533fs and c. 4582-2delAG>, resulted in reduced SETD1A expression at both the mRNA and protein levels in iPSCs and human Ngn2-induced neurons (iNs), while the other two early exon mutations, exon4 16bp deletion and p. Y42fs, displayed a mild reduction in mRNA levels in iPSCs and protein levels in Ngn2 iNs. Nevertheless, the reduction in SET1A expression does not affect their neural induction since SETD1A mutant iPSCs can be induced into mature human excitatory neurons using ectopic expression of Ngn2 (iNs). We also observed that the expression level of SETD1A mRNA and protein is reduced in human iN cells carrying SETD1A mutations. We next investigated the role of nonsense-mediated decay in regulating the degradation of mutant *SETD1A* mRNA and found that the impact varied depending on the location of the premature stop codon caused by different SETD1A mutations. Moreover, ongoing experiments evaluate SETD1A mutations with functional, morphological, biochemical, and genomic parameters to better understand the mutation-specific impact in the human neural model. The study enables us to perform a well-controlled assessment of the impact of *SETD1A* mutations that strengthens the understanding of molecular and cellular mechanisms underlying *SETD1A* mutations associated pathogenesis of SCZ.

Disclosures: T. Le: None. **X. Su:** None. **H. Zhang:** None. **L. Cheruvu:** None. **K. Mendez-Maldonado:** None. **L. Wang:** None. **S. Zhang:** None. **Q. Yang:** None. **H. Song:** None. **J. Duan:** None. **G. Ming:** None. **Z. Pang:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Topic: H.13. Schizophrenia

Support: NIH Grant R01DA055823 (Maynard)
NIH Grant T32MH015330 (Yalcinbas)
NIMH Grant MH132019 (Carr)

Title: Cross-species characterization of dopamine receptor D5 expression in the human and rodent habenula

Authors: *A. CHANDRA[1,2], E. A. YALCINBAS[2,3], K. D. MONTGOMERY[2], M. MASI[2,4], S. V. BACH[2], R. BHARADWAJ[2], T. M. HYDE[2,5,3], G. V. CARR[2,4], K. R. MAYNARD[2,3,6]; [1]Johns Hopkins Univ. Undergraduate Neurosci. Program, Baltimore, MD; [2]Lieber Inst. for Brain Develop., Baltimore, MD; [3]Dept. of Psychiatry and Behavioral Sci., [4]Dept. of Pharmacol. and Mol. Sci., [5]Dept. of Neurol., [6]The Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: The habenula (Hb) is a small epithalamic brain region that modulates the activity of dopaminergic neurons in the midbrain. It is linked to many neuropsychiatric disorders involving dysregulation of dopamine signaling, including schizophrenia (SCZD). In a previous transcriptomics study, we performed bulk RNA-sequencing of Hb-enriched epithalamic tissue from post-mortem brains of SCZD patients and neurotypical controls, and identified 173 differentially expressed genes (FDR < 0.1), including dopamine receptor 5 (DRD5). Downregulation of DRD5 in SCZD was unique to Hb-enriched tissue compared to other brain regions, including the hippocampus, prefrontal cortex, and caudate. As DRD5 has been relatively understudied compared to other dopamine receptors, such as DRD1 and DRD2, little is known about its cell type localization. To better understand the spatial distribution and cell type-specific expression of DRD5 in the human Hb, we used multiplex RNAScope single molecule fluorescent in situ hybridization (smFISH) to investigate DRD5 expression in epithalamic tissue from 3 post-mortem human neurotypical control donors. We also performed analogous RNAscope experiments in the mouse Hb (n=3 mice). We utilized HALO software (Indica Labs) to quantify RNA puncta and colocalization of DRD5 with various Hb cell type markers, including subpopulations of medial and lateral Hb neurons. We compared results from human and mouse Hb to understand the extent to which cell type-specific expression of DRD5 is conserved across species. Here, we present a spatial molecular map of DRD5 expression in the human and rodent Hb to better understand the role of DRD5 in neuropsychiatric disorders.

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Late-Breaking Poster

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Topic: H.13. Schizophrenia

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Yale UNiversity Department of Psychiatry
Connecticut Mental Health Center (CMHC)
Connecticut State Department of mental Health and Addiction Services (DMHAS)

Title: Low frequency fluctuations in belief-updating identify psychosis risk

Authors: *P. SUTHAHARAN[1], S. M. SILVERSTEIN[3], J. M. GOLD[4], J. SCHIFFMAN[5], J. A. WALTZ[6], T. WILLIAMS[7], A. R. POWERS[1], S. W. WOODS[2], R. ZINBARG[8], V. MITTAL[8], L. ELLMAN[9], G. STRAUSS[10], E. WALKER[11], J. LEVIN[10], J. KENNEY[2], P. R. CORLETT[12]; [2]Dept. of Psychiatry, [1]Yale Univ., New Haven, CT; [3]Psychiatry, Neuroscience, Opthalmology, Univ. of Rochester Med. Ctr., Rochester, NY; [4]Psychiatry, Univ. of Maryland, Baltimore, MD; [5]Dept. of Psychological Sci., Univ. of California Irvine, Irvine, CA; [6]MPRC/Dept Psychiatry, Univ. Maryland Sch. Med., Baltimore, MD; [7]Psychological Sci., Kent State Univ., Kent, OH; [8]Dept. of Psychology, Northwestern Univ., Evanston, IL; [9]Psychology and Neurosci., Temple Univ., Philadelphia, PA; [10]Psychology, Univ. of Georgia, Athens, GA; [11]Psychology, Emory Univ., Atlanta, GA; [12]Psychiatry, Yale, New Haven, CT

Abstract: Psychosis affects how people perceive reality, often leading to severe consequences. Identifying those at risk early can help reduce its impact. However, precise markers for early detection remain unknown. Here we use Fast Fourier Transform (FFT) and Autocorrelation Factor (ACF) to reveal trial-by-trial patterns in win-switching and belief-updating as human participants performed a three-choice probabilistic reversal learning (PRL) task. We show those at risk for psychosis (CHR; n=201) have unique patterns of cognitive instability ($F_{2,57}$= 5.46, p = 0.028) and rigidity ($F_{2,57}$= 2.54, p= 0.07), characterized by low frequency fluctuations in switching behavior and beliefs about volatility. Specifically, CHR individuals exhibit less consistent and more erratic decision-making over time compared to those seeking help for other mental health symptoms (HSC; n =163) and healthy comparisons (HC; n=129). These trial-resolution behavioral metrics may serve as markers of an at-risk mental state, and proffer the exciting possibility that computational psychiatry may furnish cheap, scalable, and efficient tools for the clinic.

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Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.114/LBA199

Topic: H.13. Schizophrenia

Title: Quantifying the relationship between Oculomics & Schizophrenia - A meta-analysis.

Authors: *N. D. LALTA[1], B. KREKELBERG[2];
[1]Ctr. for Mol. & Behavioral Neurosci., [2]Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ., Newark, NJ

Abstract: Numerous studies have reported that oculometric parameters such as pupillary responses, fixation, saccades, and smooth pursuit are affected by schizophrenia. Given the relative ease of collecting these oculometric parameters, they are appealing as potential biomarkers of the disease. We performed a meta-analysis of the oculomics literature in schizophrenia to investigate replicability and robustness, and to identify oculometric subcategories with most utility as a diagnostic tool. We used PubMed, Web of Science, and Scopus to identify papers for inclusion based on (1) a keyword search of title and abstract, (2) quality of the eye tracking methods, and (3) quantification of the results that allowed us to extract measures of homogeneity, summary effects, and effect sizes. We included papers only if they reported oculometric parameters for both adult schizophrenic patients and a control population. Studies were divided into seven categories: pupil, eye scanning, eye blink, fixation, smooth pursuit, anti-saccades, and saccades. Based on our preliminary analysis (96 of 2,211 studies targeted for inclusion), we report that effect sizes in most subcategories were in the small to moderate clinical significance range (effect size of 0.2 to 0.5). Across categories, the fixation and saccades category stood out both for the largest number of studies with 30 and 33 studies respectively, and for effect sizes that were in the moderate to large clinical significance range (effect size above 0.5). However, the eye scanning category had an average effect size in the large significance range (effect size above 0.8). Even though eye scanning hasn't been researched as extensively as fixation or saccades, it has the potential of being a biomarker and should be considered in future research. Our meta-analysis supports the general view that oculometric parameters are reliably altered in people living with schizophrenia. However, only some oculometric parameters have effect sizes that are sufficiently robust to serve as a diagnostic tool.

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Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Topic: H.13. Schizophrenia

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Title: Large-scale Dynamical Fingerprints of Distributed Synaptic Alterations in Early-Stage Psychosis

Authors: *A. ARAZI[1], A. TOSO[2], T. GRENT-'T-JONG[4], P. J. UHLHAAS[5,4], T. H. DONNER[3]; [2]Cognitive Neurosci., [3]Dept. of Neurophysiol. & Pathophysiology, [1]Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; [4]Dept. of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany; [5]Inst. of Neurosci. and Psychology, Univ. of Glasgow, Glasgow, United Kingdom

Abstract: Psychotic disorders, such as schizophrenia, present a major challenge for research and clinical practice. Psychiatry lacks biomarkers for early diagnosis of psychosis. Aberrations in GABAergic inhibition and glutamatergic excitation in the cortex have been implicated in psychosis. Properties of cortical circuits, such as the ratio between synaptic excitation and inhibition are critical for healthy cognition and altered in schizophrenia. Changes in such microcircuit properties alter certain parameters of spontaneous cortical population activity measurable in humans.Here, we aimed to (i) identify putative large-scale neurophysiological signatures of early-stage psychosis; (ii) unravel their underlying synaptic mechanisms; and (iii) relate them to clinical symptoms. We identified large scale patterns of changes in cortical population dynamics during MEG resting state recordings in two datasets: a clinical dataset included participants at high risk for psychosis, first episode psychosis patients, and healthy controls; a pharmacological dataset measured the effect of lorazepam (GABA-A receptor agonist) or memantine (NMDA-receptor antagonist), administered orally to healthy participants. Across 180 well-defined cortical regions, we parameterized the power spectra of cortical dynamics in terms of the exponent, knee frequency, and area under-the-curve of the aperiodic component, the power and peak frequency of peaks within the alpha range. We also mapped the Hurst exponent of long-range temporal correlations of 7-13 Hz amplitude envelope fluctuations.Changes in cortical dynamics in the clinical groups compared to healthy controls ("psychosis signatures") varied across cortical areas, with patterns that were remarkably similar between both clinical groups. These large-scale spatial patterns resembled those induced by pharmacological manipulation of GABA-A and NMDA receptors ("drug effects"). The spatial similarities between individual psychosis signatures and group-average drug effects varied between first-episode patients in a manner that related to symptoms: Individual similarity to NMDA-R blockade effects was correlated with negative symptoms. Individual similarity to GABA-A effects was related to positive symptoms (e.g. delusions).We conclude that early-stage psychosis is associated with large-scale patterns of changes in cortical dynamics which result from alterations in GABA-A or NMDA receptor functions and differentially related to symptoms severity. Our approach opens new perspectives for a neurophysiological-biomarker assay of psychotic disorders.

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Topic: H.13. Schizophrenia

Support: MH077851
MH077945
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MH103366
MH103368

Title: Partial replication of Resting state auditory-language cortex connectivity associating with hallucination severity in a biological subtype of psychotic disorders

Authors: *I. TOSCANO[1], C. A. TAMMINGA[2], E. I. IVLEVA[3], B. A. CLEMENTZ[4], J. E. MCDOWELL[5], G. PEARLSON[6], M. S. KESHAVAN[7], E. GERSHON[8], S. KEEDY[9]; [1]Univ. of chicago, chicago, CA; [2]UT Southwestern Med. Ctr., Dallas, TX; [3]Psychiatry, UT Southwestern Med. Center, Dept. of Psychiatry, Dallas, TX; [4]Departments of Psychology and Neurosci., [5]Psychology, Univ. of Georgia, Athens, GA; [6]yale, new haven, CT; [7]Harvard Univ., boston, MA; [8]university of chicago, chicago, IL; [9]Psychiatry and Behavioral Neurosci., Univ. of Chicago, Chicago, IL

Abstract: Altered properties of auditory and language brain systems may contribute to auditory hallucinations. Previously both common and psychosis subgroup-specific functional connectivity associations were found with hallucination severity in the Bipolar Schizophrenia Network on Intermediate Phenotypes-1 (B-SNIP-1) sample (Okuneye et al., 2020). Subgroups included diagnosis (schizophrenia, schizoaffective, bipolar) or the three B-SNIP Biotype groups based on neurobiological similarity. All patients showed increased connectivity within left auditory regions associated with greater hallucination severity. Interhemispheric auditory cortex connectivity was increased for bipolar subjects and decreased for Biotype 1 in association with greater hallucination severity. We sought to replicate these observations.We used data (n=377) from B-SNIP-2, a replication of B-SNIP-1. From resting state fMRI data, we extracted connectivity from the same clusters of voxels reported in Okuneye et al. to show altered connectivity in association with hallucination severity. We conducted similar linear regressions on these connectivity values with the PANSS hallucination severity assessment, using the same covariates (age, sex, recruitment site, antipsychotic medication dose, and head motion), as done previously. Neither the all-patient finding nor the bipolar-specific finding was replicated. We did

replicate greater hallucination severity in Biotype 1 (N=146) associating with reduced connectivity of right auditory association cortex to posterior portions of left auditory cortex (p=0.028). Replicating only the Biotype finding reinforces the potential of this subgrouping approach. Biotype 1 has low auditory processing signal per EEG measurements. Reduced interhemispheric connectivity of auditory cortex may be another manifestation of this group's unique neural pathology. Further work in other brain areas, such as those that regulate auditory cortex, may identify alterations leading to hallucinations in other Biotypes.

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Topic: H.13. Schizophrenia

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NIMH R01MH124047
BWF PDEP Award

Title: Disorganized Inhibitory Dynamics and Functional Connectivity in Hippocampal area CA1 of 22q11.2 Deletion Mutant Mice

Authors: *S. HERRLINGER[1], B. RAO[2], M. A. CONDE[2], A. A. TUTTMAN[3], H. ARAIN[4], E. VAROL[6], J. A. GOGOS[2], A. A. LOSONCZY[5];
[1]Zuckerman Inst., Columbia Univ., New York, NY; [2]Zuckerman Inst., [3]Columbia Univ., New York City, NY; [4]Columbia Univ., New York, NY; [5]Neurosci., Columbia Univ., New York City, NY; [6]Computer Sci. and Engin., New York Univ., Brooklyn, NY

Abstract: Individuals with the 22q11.2 deletion syndrome, one of the strongest genetic risk factors for schizophrenia, demonstrate cognitive impairments such as episodic memory dysfunction. Place cell dynamics in the hippocampus supporting episodic memory are also impaired in a mouse model for the 22q11.2 deletion (Df(16)A+/-). While hippocampal neural dynamics are under strong inhibitory control, there is no available information about functional alterations of molecularly identified inhibitory circuits in mouse models for the 22q11.2 deletion. Here, we examined interneuron subtype-specific activity dynamics in hippocampal area CA1 of Df(16)A+/-mice performing random foraging and goal-oriented reward learning tasks. We found that Df(16)A+/- inhibitory interneurons carry markedly reduced spatial information during random foraging. Mutant mice perseverate at rewarded locations during reward learning, and

multiple interneuron types exhibit aberrant responses to reward locations. We observe task-dependent changes in functional correlation structure among multiple GABAergic subtypes, suggesting a broadly disorganized microcircuit functional connectivity in mutant mice. Overall, we identify widespread and heterogeneous subtype-specific alterations in interneuron dynamics during learning, depicting inhibitory microcircuits with impaired flexibility. Our study provides novel biological insights into how schizophrenia-risk mutations affect local-circuit interactions among diverse cell types in the mouse hippocampus during learning.

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Program #/Poster #: LBA008.118/LBA203

Topic: H.13. Schizophrenia

Title: Animal modeling for schizophrenia: Stereotyped-rotations induced by ketamine in adult male rats are significantly increased after postnatal inactivation of the prefrontal cortex but not of the ventral subiculum.

Authors: S. HEINTZ, ***A. LOUILOT**;
INSERM U1329- CRBS- U.d.S., Strasbourg, France

Abstract: Schizophrenia is a complex and disabling neuropsychiatric disorder thought to result from a defective connectivity between several integrative regions stemming from neurodevelopmental failures, affecting mainly young men. Various anomalies reminiscent of early brain development disturbances have been observed in the left prefrontal cortex (PFC) and left ventral subiculum (SUB) of patients with schizophrenia. Non-competitive NMDA/glutamate receptors antagonists such as ketamine, can induce psychotic symptoms in healthy humans and exacerbate these symptoms in patients with schizophrenia. Moreover, it has been emphasized that patients frequently present perseverative or stereotyped behaviors (Geyer and Moghaddam, 2002). From an experimental point of view, in animals, stereotyped rotations (circlings) is the most commonly observed behavior with psychotropic substances. The aim of the present study, taking into account all the above points, was to compare the effects of ketamine in adult male rats on circlings (rotations of 360° in the same direction), following a postnatal inactivation of the left PFC (infralimbic/prelimbic region) or the left SUB. During the neurodevelopmental period, impulse electrical activity appears to be crucial for shaping connections once developing axons reach the target structure. Therefore, functional inactivation of the left PFC or the left SUB was carried out by local Tetrodotoxin (TTX) microinjections in 8-day-old (PND8) rats. Controls received the solvent (PBS). Then in adult rats (11weeks), circlings towards the left or the right

were investigated after ketamine was administred sc with different doses (NaCl; 5mg/kg; 10mg/kg; 20mg/kg). Main significant results were the followings: 1) A clear dose effect for the total left +right circlings, was observed during the 90mins following ketamine administration, for the microinjected animals with PBS or TTX at PND8 in the PFC or SUB; 2) Total left+right circlings were significantly increased in TTX vs PBS animals only after neonatal left PFC blockade, but not left SUB blockade; 3) Moreover after TTX blockade of the left PFC, only left circlings were significantly increased, but not right circlings. Inasmuch PFC and SUB neonatal inactivations have been both reported to induce disruption in latent inhibition responses and increased locomotor responses to different psychostimulants, the results obtained in the present study with the stereotyped rotations suggest that neonatal functional disturbance of the PFC is more relevant than that of SUB in the context of the animal modeling of schizophrenia and merits further consideration for the understanding of schizophrenia.

Disclosures: S. Heintz: None. **A. Louilot:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.119/LBA204

Topic: H.13. Schizophrenia

Title: The auditory steady-state response as a translatable EEG biomarker is sensitive to the state of arousal in a rodent model

Authors: *N. SCHUELERT[1], E. M. TUNBRIDGE[2], R. H. WILLIAMS[3];
[1]Boehringer Ingelheim Pharma GmbH & Co.KG, 88400, Germany; [2]Oxford Univ., Biberach, Germany; [3]CNS, Helmholtz Zentrum Muenchen, Biberach, Germany

Abstract: Arousal plays an important role in a variety of psychiatric diseases. Patients frequently deviate from healthy subjects, being either hyper- or hypo-aroused. EEG biomarkers, such as the auditory steady state response (ASSR), are used as diagnostic marker for Schizophrenia. These translatable assays are also used preclinically to investigate Schizophrenia-like pathologies in rodents, ASSR is considered mainly unaffected by attention, yet there are new clinical studies showing that the state of arousal can have a substantial impact on early sensory processing. Detailed information regarding the state of arousal in preclinical research is often not considered. Therefore, we evaluated how vigilance state impacts the magnitude of ASSR readouts, and if readouts can be pharmacologically modulated. We have previously shown that a mGluR2/3 agonist can reverse ASSR deficits in a pharmacological challenge model. ASSR amplitude and inter-trail coherence (ITC) was measured using a wireless recording technique [2]. Epidural electrodes were implanted above the primary auditory cortex and medial prefrontal cortex. Animals were placed in a sound attenuated cubicle for recordings. All readouts were acquired

with a 40Hz auditory steady-state response (ASSR) paradigm during the active an inactive cycle. Recordings were stratified into active and non-active periods during each recording sessions based on the activity index derived from the head-mounted accelerometer. In addition, a mGluR2/3 agonist (LY-379268) was administered prior to initiation of ASSR recordings.The amplitude and phase precision (ITC) of the ASSR were increased during low arousal state (ínactive cycle) compared to the high arousal condition (active cycle). In addition, separating active and quite phases during the recordings also revealed that ASSR ITC was negatively correlated to the motoric activity. Basal gamma oscillation in contrast was increased during the high arousal phase. The mGluR2/3 agonist reduced motoric activity and increased ASSR ITC under high arousal state. Our results show that evoked gamma entrainment elicited under passive conditions in mice is sensitive to the level of arousal.These results recapitulate clinical findings showing a significant impact of arousal on ASSR measurements and emphasize the importance of monitoring vigilance state in preclinical EEG studies. The modulation of ASSR amplitude and ITC by arousal states warrants caution when investigating oscillatory brain activity and interpreting treatment effects in animal models. It also emphasizes the necessity of standardized EEG recording procedures in preclinical research.

Disclosures: N. Schuelert: None. **E.M. Tunbridge:** None. **R.H. Williams:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.012/LBA98

Topic: H.02. Perception and Imagery

Support: CEPID NeuroMat - FAPESP 2013/07699-0
SPEC - FAPESP 2018/18900-1
FAPESP Grant 2023/17520-9
CAPES Finance Code 001

Title: Erp analysis of motor imagery in the dominant and non-dominant hands during serial reaction time task

Authors: *P. CAMARGO[1], A. L. AREVALO[3], G. LEPSKI[4,5], A. F. HELENE[2];
[2]Dept. of Physiol., [1]Univ. of São Paulo, São Paulo, Brazil; [3]Dept. of Exptl. Surgery, Univ. of São Paulo Med. Sch., Sao Paulo, Brazil; [4]Univ. of São Paulo Med. Sch., São Paulo, Brazil; [5]Dept. of Neurosurg., Eberhard Karls Univ., Tübingen, Germany

Abstract: Motor imagery is a mental representation of movements without the action per se. Handedness can impact how individuals imagine and plan these movements,particularly in tasks requiring serial reaction time. Such tasks may involve varying strategies for motor imagery

during both preparation and execution. Notably, left-handers may adopt distinct strategies and present an increased recruitment of the kinaesthetic modality when imagining movements of the non-dominant hand. Electroencephalographic analysis to obtain event-related potentials (ERPs), such as P300, is a valuable tool for examining motor imagery and the expectation of event occurrence. This study investigated the P300 component in the dominant versus non-dominant hand during motor imagery in a serial reaction time task with a probabilistic structure. The experiment (CAAE 15274718.8.0000.5464) included healthy volunteers: a right-handed (RH) group (n=9; 25.334.97 y.o), and two left-handed (LH) individuals (LH1 - 25 y.o.; LH2 - 28 y.o.). Edinburgh Handedness Inventory (EHI) and Kinesthetic/Visual Motor Imagery Questionnaire (KVIQP-10, Brazilian version) were applied. The serial reaction time task consisted of 750 auditory stimuli, with each stimulus followed by an imagined action of pressing the correct button. All participants imagined themselves performing the task with their right hand. The probability of each of the three possible auditory stimuli followed a context tree: 24% (rare event), 76%, or 100%. Groups showed consistent scores on EHI (RH: 83.3322.91 | LH1:-100; LH2: -20), KVIQP-10V (RH: 27.569.93 | LH1: 31; LH2: 41), and KVIQP-10K (RH: 26.676.76 | LH1:15; LH2: 26). ERP analyses revealed regions of significance in the Fz channel: LH1 showed differences at 90-120ms (N100), 150-200ms, 220-280ms (P200), and 340-500ms (P300); LH2 had variations at 100-160ms (N100), 170-400ms (P200, P300, N300), and 420-500ms (N400). The RH group exhibited P200 effects around 200-220ms and a typical P300 effect for rare events at 320-380ms post-stimulus. Additionally, the P300 component in response to rare events aligns with stimulus probability. These results indicate similarities in motor imagery for the dominant-hand in the RH group and the non-dominant hand in LH individuals within Fz, suggesting potential adaptive cognitive processing in left-handers.

Disclosures: P. Camargo: None. **A.L. Arevalo:** None. **G. Lepski:** None. **A.F. Helene:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.120/LBA205

Topic: H.13. Schizophrenia

Title: Evaluation of the effects of clozapine on behavioral and electroencephalography-recorded mismatch negativity and spontaneous oscillations in an acute schizophrenia rat model

Authors: *C. DRIEU LA ROCHELLE[1], **F. ADRAOUI**[2];
[1]Biotrial Pharmacol., Rennes, France; [2]BIOTRIAL PHARMACOLOGY, RENNES, France

Abstract: Schizophrenia (SZ) is one of the most severe psychiatric disorders and affects nearly 1% of the world's population. Yet, there has been no major improvement in the therapeutic management of this disorder since the commercialization of atypical antipsychotics. This is

mainly due to the complexity of SZ pathophysiology, the limited understanding of the available antipsychotics and the poor translation of output parameters from preclinical to clinical investigations. Recently, the use of behavioral measures combined with electroencephalography (EEG) has been highlighted as a better approach in SZ drug development. Hence, we report here the different effects of the antipsychotic clozapine on behavioral and EEG features of an acute model of SZ induced by the NMDA receptor antagonist MK-801. Separate cohorts of Sprague Dawley rats were evaluated in the Y-maze as well as for EEG biomarkers, such as mismatch negativity (MMN) and spontaneous oscillations, following acute MK-801 dosing (0.1-0.2 mg/kg, subcutaneously). The effects of the atypical antipsychotic clozapine (1-10 mg/kg, intraperitoneally) were then evaluated on behavioral and electrophysiological changes induced by MK-801. MK-801 significantly and dose-dependently reduced cognitive performance, MMN, while it also increased spontaneous gamma oscillations. Clozapine differentially reversed these behavioral and EEG changes provoked by MK-801. These results further our understanding on Clozapine and show that the acute NMDA-receptor-antagonism model could be a reliable and translational pre-clinical tool for drug developers working in the field of SZ.

Disclosures: C. Drieu La Rochelle: None. **F. Adraoui:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.013/LBA99

Topic: H.03. Decision Making

Title: Neural Correlates of Metacognitive Processes in the medial prefrontal cortex

Authors: *Y. NANJO;
Ctr. for Brain Sci., RIKEN, Nerima-ku/Tokyo, Japan

Abstract: Metacognition is theorized to encompass two key functions: generating confidence in behavioral states (metacognitive monitoring) and regulating these states based on confidence (metacognitive control). Previous research has primarily focused on confidence in single-decision tasks, associating the role of metacognitive monitoring with the prefrontal cortex (PFC). However, the functioning of metacognition in sequential decision-making and the corresponding neural mechanisms remain largely unexplored. We posited that (1) confidence at a given decision point would modulate the likelihood of continuing the same decision in subsequent choices, and (2) distinct neural substrates within the PFC would underlie metacognitive monitoring and control during sequential decision-making. To test these hypotheses, we conducted an experiment using functional magnetic resonance imaging (fMRI) with 34 healthy volunteers engaged in a sequential perceptual decision-making task accompanied by confidence ratings. Subjects viewed two circular stimuli, determined which was larger, and rated their

confidence in this decision. They then viewed the same stimuli again, made another size comparison, and rated their confidence a second time. Decisions could either be consistent or differ from the initial choice. Across trials, stimuli varied in size difference, and for each subject, trials were categorized into high or low confidence based on the median initial confidence. Results indicated a higher frequency of changed decisions in low-confidence trials, suggesting a significant role of metacognitive monitoring in subsequent decision-making. fMRI analyses revealed increased activity in the anterior medial PFC during high-confidence trials at the initial decision phase, while the dorsal anterior cingulate cortex (ACC) showed greater activity during subsequent decisions involving a change of mind. Additionally, overlapping activity patterns were observed in the perigenual ACC. These findings indicate that metacognitive processes are interrelated and suggest that metacognition plays an integral role in sequential decision-making.

Disclosures: Y. Nanjo: None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.014/LBA100

Topic: H.03. Decision Making

Title: Functional microstructure of value tuning in primate orbitofrontal cortex

Authors: *R. READ[1], J. D. WALLIS[2], T. W. ELSTON[3,4];
[1]Dept. of Neurosci., Univ. of California at Berkeley, Berkeley, CA; [3]Neurosci., [2]U.C. Berkeley, Berkeley, CA; [4]Neurosci., Univ. of Texas at Austin, Austin, TX

Abstract: The orbitofrontal cortex (OFC) is crucial for encoding value information about stimuli to guide decision-making. Despite this, its functional microstructure remains poorly understood compared to well-characterized sensory regions like the visual cortex. For example, value encoding OFC neurons can be tuned positively (firing rate increases with value) or negatively (firing rate decreases with value). Here we investigated whether neurons exhibiting these different value-tuning properties exist in anatomically distinct patches of OFC. To address this issue, we performed high-density neuropixel recordings to monitor the activities of hundreds of simultaneously recorded OFC neurons in monkeys performing a value-based choice task. We report evidence of functionally distinct parcellations of positive and negative value-encoding neurons within the OFC. Specifically, we found that ensembles of positively and negatively tuned value neurons occupy non-overlapping patches within the OFC. This result challenges prior reports of salt and pepper value tuning within the OFC and suggests a deeper functional microarchitecture than previously appreciated.

Disclosures: R. Read: None. **J.D. Wallis:** None. **T.W. Elston:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.015/LBA101

Topic: H.03. Decision Making

Support: BIOSURF Award

Title: A network-based theory of optimal coding for economic decisions

Authors: *T. G. CRIMMINS, Y. KANAZAWA, C. PADOA-SCHIOPPA, G. TAVONI; Neurosci., Washington Univ. in St. Louis, St. Louis, MO

Abstract: Neurons in the orbitofrontal cortex (OFC) are causally involved in the computation and comparison of subjective values underlying economic choices [Ballesta et al 2020; 2022]. Different groups of neurons in OFC represent the input (offer values) and the output (chosen good, chosen value) of the choice process, suggesting that these cell groups constitute the building blocks of a decision circuit. Two fundamental and closely related questions concern the organization and the optimality of this neural circuit. A previous study proposed that the encoding of offer values is optimal if it ensures maximal expected payoff [Rustichini et al 2017]. This normative principle could correctly predict some tuning properties of offer value cells in a simple decision model, where choices were determined by comparing the firing rates of these neurons (i.e., ignoring the rest of the network). However, this simple decision model made clear predictions on the strength of synaptic connections between offer value cells and other groups of neurons, which we found to be inconsistent with connectivity estimates inferred from neural data. Here, we propose a new and expanded network model that - under the same normative principle (maximum payoff) - predicts the complete structure of the decision network in OFC. In our model, choices are determined by the firing output (rather than the input) of the network, which reflects the linear integration of activity across different cell groups and the overall circuit processing of subjective values. In the fully-connected network, we find that roughly 50% of synaptic weights strongly influence the expected payoff. The model makes quantitative predictions about the strength and relative significance of different sets of connection weights. To test these predictions, we recorded from large populations of neurons in OFC, and we used network inference analysis to estimate the connectivity between different cell groups [Schneidman et al 2006; Cocco et al 2017]. We found a striking match between the theoretical predictions and the estimates of connectivity derived from neuronal data. These results indicate that neural mechanisms in OFC are set to maximize the expected payoff of choices, and that the complete neural circuit in OFC is required to perform this computation.

Disclosures: T.G. Crimmins: None. **Y. Kanazawa:** None. **C. Padoa-Schioppa:** None. **G. Tavoni:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.016/LBA102

Topic: H.03. Decision Making

Support: NIMH ZIA MH002951
NIMH MH002952

Title: Noradrenergic modulation of stress induced catecholamine release Opposing influence of FG7142 and yohimbine

Authors: *V. VISOCKIS[1], C. TURNER[2], M. LOWRIE[3], K. MESSANVI[3], Y. CHUDASAMA[3];
[1]NIH, Rockville, MD; [2]Georgetown Univ., Washington, WA; [3]NIMH, Bethesda, MD

Abstract: In humans, loss aversion is sensitive to stress, and patients with neurological or psychiatric illnesses are particularly vulnerable to the detrimental effects of stress that lead to suboptimal life altering choices. The basolateral amygdala (BLA) and nucleus accumbens (NAc) are stress sensitive brain areas that alter extracellular levels of norepinephrine (NE) and dopamine (DA), respectively. However, the dynamics of neurotransmitter release in these brain regions during stress has not been systematically explored. We used pharmacology and fiber photometric analysis to elucidate the impact of stress, DA and NE on brain activity during decision making behavior. Long-Evans rats were trained on an operant touchscreen decision-making task in which they chose between a safe stimulus that delivered a certain 50µl sucrose, or a risky stimulus that delivered either a 'loss' (10µl sucrose 75% of the time) or 'win' (170µl sucrose 25% of the time). Stress, induced by an inverse GABAA agonist, FG7142, biased rats' decisions towards safety due to increased loss sensitivity. The aversion to loss was blocked with co-treatment of the a2A receptor antagonist, yohimbine. We also captured the rapid dynamic properties of stress induced changes in NE and DA release in the BLA and NAc, respectively. We discovered that these dynamics could be modulated with systemic injections of yohimbine by altering stress induced catecholamine release to optimize decision strategy and motivational state

Disclosures: V. Visockis: None. **C. Turner:** None. **M. Lowrie:** None. **K. Messanvi:** None. **Y. Chudasama:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.017/LBA103

Topic: H.03. Decision Making

Support: Whitehall foundation research grant #2021-12-045

Title: Work Hard, Play Hard: Comparing Food and Non-food Reward on a Foraging Task for Rats

Authors: *R. S. LOGUE[1], R. K. KENDALL[2], A. K. GARCIA[3], B. A. BEJARANO[4], A. M. WIKENHEISER[5];
[1]Delaware State Univ., Dover, DE; [2]Psychology, UCLA, Santa Monica, CA; [3]Psychology, UCLA, North Hollywood, CA; [5]Psychology, [4]Univ. of California Los Angeles, Los Angeles, CA

Abstract: Laboratory tests of decision making in rats are typically motivated by food or water deprivation, and experimenters implicitly assume that rats seek to rationally maximize their earnings of these reinforcers. However, a rat's home cage environment is also lacking in opportunities to interact with novel objects, explore new spaces, and engage in other forms of play. Performing a decision making task thus affords opportunities to engage in behaviors that are not normally available. Apparent departures from rational decision making might, therefore, reflect subjects balancing pursuit of standard reinforcers alongside less well-defined behavioral objectives. Here, we systematically investigated how rats allocated their time between food and non-food reinforcement in the context of a patch foraging task. Food-restricted Long-Evans rats (n = 10; 5 female) distributed their time between two open-field foraging patches. While rats occupied a food-reward patch, sucrose pellets were scattered into the enclosure following a schedule in which reward rate decreased over time, encouraging rats to transition between patches to optimize their overall reward gain. In non-food patches, sucrose pellets were never delivered but rats had access to a play structure that included chew toys, climbing structures, and tunnels. To switch patches, the rats entered a travel corridor, which imposed a wait time of 10 seconds or 60 seconds to imitate travel time in natural foraging conditions. The reward rate was reset to its maximum value every time the rat switched between patches. Each 30-minute session involved one of eight randomized combinations of patch type and travel time. There was no significant difference in the amount of time rats spent in food and non-food patches, and rats visited both patch types with equal frequency. Rats were therefore willing to incur a considerable cost in terms of food earnings by engaging with toys, earning around half as much food as they could have by only visiting food patches. Rats were sensitive to travel time when foraging for both food and non-food reward, spending significantly longer on each patch visit in sessions where the travel time was long and switching between patches was costly. These data provide evidence that rats rationally pursue exploratory activities even when food is available, indicating a complex decision-making process influenced by environmental enrichment and travel time. This behavioral task suggests a novel means of inferring rats' utility functions for arbitrary reinforcers, enabling a comparison of the neural mechanisms that support decisions motivated by a wide range of possible outcomes.

Disclosures: R.S. Logue: None. **R.K. Kendall:** None. **A.K. Garcia:** None. **B.A. Bejarano:** None. **A.M. Wikenheiser:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.018/LBA104

Topic: H.03. Decision Making

Support: United Arab Emirates University UAEU31R002-6306-CPPL
Northern Kentucky University NKU4001465

Title: Brain activation associated with making decision to apply earnings management techniques in business managers

Authors: A. ABDEL-MAKSOUD[1], H. HASSABELNABY[2], A. SAID[2], A. COTTON[3], **A. WANG**[4,5], *X. WANG[4], H. ELSAMALOTY[4];
[1]Zayed Univ., Abu Dhabi, United Arab Emirates; [2]Northern Kentucky Univ., Highland Heights, KY; [3]Johns Hopkins Univ., Baltimore, MD; [4]Univ. of Toledo, Toledo, OH; [5]Ottawa Hills High Sch., Toledo, OH

Abstract: Business managers employ various earnings management techniques (EMTs) to prevent debt covenant breaches. Understanding the underlying decision-making processes related to such techniques may help a manager choose the optimal approach to avoid a violation, but these cognitive processes remain poorly understood. The current functional magnetic resonance imaging (fMRI) study aims to explore the brain activation associated with making the decision to apply 3 commonly employed EMTs: accounting earnings management (AEM) involves increasing reported earnings by manipulating the recognition of revenue or expenses, classification shifting (CS) involves reclassifying core expenses to increase reported earnings, and total real earnings management (REM) involves making operational changes to increase earnings in the short-term but deviate from the ideal long-term strategy. During the fMRI scans, local business managers (n = 50) read the text presentations of multiple scenarios where companies were at different proximities to debt covenant violations. Then the managers decided whether to apply one of the three EMTs or not. The activation was significant after multiple comparison correction using FSL Gaussian Random Field theory-based cluster thresholding at a voxel-wise z threshold > 3.1 (i.e., p< 0.001, one-tailed) and a cluster-wise p threshold of 0.05. The results revealed
deciding whether or not to apply any EMTs commonly activated the primary occipital cortex, lateral occipital gyrus, occipital fusiform gyrus, and posterior middle temporal gyrus in the ventral stream of visual processing. All 3 techniques also activated the regions in the inferior, middle, and superior frontal gyri that underlie language processing, working memory, and

cognitive inhibition control. On the other hand, making decisions to apply individual EMTs involved unique brain activation including the temporal pole in AEM scenarios; left thalamus and hippocampus in REM scenarios; and temporal pole, brainstem, thalamus, and basal ganglion in CS scenarios. These brain activation patterns suggest making decision to apply EMTs may involve common visual processing and frontal cognitive functions, but deciding to apply individual EMTs requires additional cognitive processes such as delay reward processing in the temporal pole for AEM; inhibitory control for errors in the left thalamus and visual memory in the left hippocampus for REM; and processing of explorative choice in the brainstem, thalamus, and basal ganglion for CS. These unique cognitive processes may underlie different earnings management behaviour.

Disclosures: A. Abdel-Maksoud: None. **H. HassabElnaby:** None. **A. Said:** None. **A. Cotton:** None. **A. Wang:** None. **X. Wang:** None. **H. Elsamaloty:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.019/LBA105

Topic: H.03. Decision Making

Support: NSF Grant 2050833

Title: A neural signature of evidence accumulation during memory-guided perceptual decision making

Authors: *A. THOKSAKIS[1], E. F. ESTER[2];
[1]Univ. of Nevada, Reno Integrative Neurosci. Grad. Program, Reno, NV; [2]Psychology, Univ. of Nevada, Reno, Reno, NV

Abstract: Decision making is the process of committing to a choice or course of action based on relevant evidence and is traditionally studied using tasks that require agents to sample information from a single external (sensory) or internal (mnemonic) source. However, many decisions, such as determining whether you've identified a friend in a crowded poster hall, require agents to sample and compare information across external and internal sources. To study this process, we developed an experimental task that required human observers (N = 38, both sexes) to calculate decision-relevant evidence by comparing the features of an external stimulus with a memorized template. We show that this task elicits a scalp EEG signal associated with perceptual decision making - the centro-parietal positivity (CPP). CPP amplitudes increased over time and reached a maximum immediately prior to participants' responses, consistent with the operation of an evidence accumulation process. However, unlike prior work, CPP amplitudes scaled with the total amount of decision-relevant information available to participants. These

findings extend electrophysiological studies of perceptual decision making into the realm of multi-source decision making and establish the CPP as a robust marker of accumulated and total evidence during this process.

Disclosures: A. Thoksakis: None. **E.F. Ester:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.020/LBA106

Topic: H.03. Decision Making

Support: Max Planck Society 549771

Title: Meg captures human neural dynamics during value learning and computation

Authors: *L. SEAK[1], Y. LIU[2], Z. KURTH-NELSON[3], R. J. DOLAN[1];
[1]Max Planck UCL Ctr. for Computat. Psychiatry and Ageing Res., London, United Kingdom;
[2]State Key Lab. of Cognitive Neurosci. and Learning, Beijing Normal Univ., Beijing, China;
[3]Google DeepMind, Univ. Col. London, London, United Kingdom

Abstract: Value-based cognition is fundamental to everyday decision making and is proposed to be compromised in a range of psychiatric disorders. Animal data highlight the contribution of hippocampal and dopamine function to value-based decisions. In humans, recent studies have focused on the neural dynamics of value computation within a trial (P. Pinheiro-Chagas et al., 2024). The question of how underlying neural dynamics evolve with value-based learning has not been well investigated. Therefore, we here focus on studying how humans learn values during a task and how our brain activities reflect this process. We report Magnetoencephalography (MEG) data, from 44 subjects, where we examine neural dynamics related to how humans plan value-based decisions, and learn choice-based values across trials. During the planning phase of each trial, subjects were tasked to determine an optimal route (within a 4-step decision tree) to maximize accumulated value, where the value of each state drifted over time. We analyzed the MEG data using the dynamic time warping method and generalized linear regressions (GLMs), which normalised diverse planning times and allowed for diverse final trial values (monetary reward the subject received in a trial), respectively. We found significantly stronger and earlier value coding signals (GLM betas reflecting the final values), at the later trials of the experiment (i.e. after value learning). There was also a temporal evolution in brain topography mediating value estimation, where an early phase dominance of temporal regions shifted to prefrontal regions over the course of the task, evident in sensor-based GLM betas. Importantly, how well individual subjects learnt throughout the task was significantly correlated with the value-coding activity (GLM betas), and this was even within the earliest

experimental trials. These findings provide a new perspective on value-based neural dynamics and how they change with learning, providing insight into value-based decisions and learning.

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Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.021/LBA107

Topic: H.03. Decision Making

Title: Many roads to managing risky business: Asymmetric access to social vs. economic resources during childhood differentially calibrates psychological and neural underpinnings of risk-taking behaviors in young adults

Authors: *M. LEE, M. Z. GONZALEZ;
Dept. of Psychology, Cornell Univ., Ithaca, NY

Abstract: Ecological and evolutionary developmental theories suggest that the developmental context calibrates psychological and neural factors towards capitalizing on available resources to solve the problems of living. However, most studies look at social and economic resources as one and do not consider their differential impacts on adult psychophysiology. Addressing this gap, we conducted a functional magnetic resonance imaging (fMRI) study with 45 healthy adults (mean age: 20.1±3, male N = 26) who completed surveys on their developmental and current economic and social context. They also completed a modified version of the Balloon Analog Risk Task which allowed us to model decision-making in the context of monetary gain under risk (risky reward, RR) or with no risk (safe reward, SR). We first used a clustering algorithm to split participants based on their developmental experience; a High-Social/Low-Economic Resource Group (HS/LE, N = 23) and a Low-Social/High-Economic Resource Group (LS/HE, N = 22) emerged. We then computed loss aversion for the task using an Exponential-Weighted Mean-Variance Model and analyzed neural activations and task-based functional connectivity associated with RR and SR in relation to their developmental group (HS/LE vs. LS/HE) and their current psychosocial context. Groups were comparable in demographics, survey responses, loss aversion, and total gains obtained. Current social context was associated with loss aversion for HS/LE but not the LS/HE group (social avoidance, SIAS, r = .52, p = .01; social support K-SF-42; r= -.43, p = .02). Interactions between loss aversion and developmental group revealed greater activations in the precuneus, middle temporal gyrus (MTG), lingual gyrus, and other regions implicated in loss anticipation for the HS/LE group. Further, higher current social support coincided with reduced risk-related activation in these regions and functional connectivity between the supramarginal gyrus and MTG for the HS/LE group. Taken together, our data suggest that those afforded relatively more social than economic resources in

development show 1) greater association between psychosocial context and loss aversion 2) greater recruitment of loss-associated and motor-behavior associated neural regions with greater loss aversion, and 3) decreased connectivity between these neural regions with greater current social support. These suggest that psychological and neural factors calibrate and become sensitive to social resources when it was the predominant resource in the developmental context and this impacts mechanisms of non-social decision making.

Disclosures: M. Lee: None. **M.Z. Gonzalez:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.022/LBA108

Topic: H.04. Executive Functions

Title: Associations between brain structure and cognitive performance in children and adolescents

Authors: *S. TOTXO[1], Z. GRACIA-TABUENCA[2], F. DE LA PENA[3], S. ALCAUTER[4]; [1]Inst. Nacional de Psiquiatría "Ramón de la Fuente Muñiz", Mexico City, Mexico; [2]Dept. of Statistical Methods, Unviersity of Zaragoza, Zaragoza, Spain; [3]Adolescence Clin., Inst. Nacional de Psiquiatría «Ramón de la Fuente Muñiz», Mexico, Mexico; [4]Neurobiología Conductual y Cognitiva, Inst. De Neurobiologia. Univ. Nacional A, Queretaro, Mexico

Abstract: Introduction: Adolescence is a period during which important processes occur in brain maturation, along with the acquisition of skills that allow the regulation of behavior, such as executive functioning. In this scenario, the characterization of brain structural features as cortical thickness throughout this stage could be useful in identifying the neurobiological substrates underlying the development of such cognitive abilities. Furthermore, brain morphometric features can then be explored in search of associations with variables such as performance on cognitive tests. The aim of this study was to identify associations between brain structure and cognitive performance in a sample of children and adolescents with a typical development. Methods:We conducted an analysis of a dataset containing neuroimaging and executive functioning tests information from a sample of children and adolescents with typical development. For the assessment of cognitive performance, we used the Neuropsychological Battery of Executive Functions and Frontal Lobes (BANFE), which has been validated on Mexican population. For the analysis of brain structure, high-resolution anatomical images (1x1x1 mm^3 voxels) were obtained on a 3T General Electric scanner. Image processing and statistical analysis were performed on FreeSurfer version 7.1.1. General linear models including age and sex as covariates were implemented in search for associations between cortical thickness and the total BANFE scores. To correct for multiple comparisons, Monte Carlo simulations were

performed at 10,000 iterations with an adjusted significance value set at $p<0.05$. Results:The sample included 61 subjects (38 female) with a mean age of 13.9±2.5 years. We identified a cluster in the anterior cingulate cortex (ACC) of the left hemisphere (MNI x=5.4, y=37.8, z=7.8), spanning an area of 1201mm² where cortical thickness was found to have a statistically significant positive association with the total BANFE score when controlling the effects of age and sex (FWE-corrected p=0.035). Conclusions: This study found an association between cortical thickness in the ACC with the total score of a test of executive functioning in a sample of typically developing children and adolescents. Such results are in line with previous findings leading to consider this brain region as an information integration center involved in different cognitive functions related to the ability to select goal-directed behavioral responses. Future studies on the longitudinal trajectories of the structure of the ACC could provide relevant information on the neurobiological substrates of the development of executive functions.

Disclosures: S. Totxo: None. **Z. Gracia-Tabuenca:** None. **F. de la Pena:** None. **S. Alcauter:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.023/LBA109

Topic: H.04. Executive Functions

Support: National Institute on Drug Abuse Grant R0107418
JPB Foundation
National Science Foundation GRFP Grant DGE 2036197

Title: Spns dynamics in reward-based learning: unraveling striatal pathways and behavioral adaptations in mice

Authors: *S. CATALDI[1], C. LACEFIELD[2], N. SHASHAANK[1], D. L. SULZER[3];
[1]Columbia Univ., New York, NY; [2]New York State Psychiatric Inst., New York, NY; [3]Columbia university, New York, NY

Abstract: Learning is classically modeled to begin with an acquisition period, followed by a mastery period when the skill no longer requires conscious control, and actions become automatic. Brain activity eventually shifts from responding to the rewarding or aversive event to the presence of the associated cue or the action necessary to accomplish the task. To investigate these processes, we've developed an operant conditioning paradigm using open-source microcontrollers. This paradigm involves training mice through three stages, each emphasizing different aspects of the learning process. The first phase associates a sound cue with the delivery of a sucrose-water reward. The second phase introduces a lever press as a requirement for reward

delivery. The final phase integrates the cue to signal when the mouse can press the lever to receive the reward. During these training stages, we record GCaMP6f fluorescence from D1-expressing spiny projection neurons (D1-SPNs) in the ventral striatum (VS). Our preliminary data indicate that there is a specific activation pattern as the cue or the lever press predicts the acquisition of the reward, suggesting a refinement of D1-SPNs for a specific learned task. Interestingly, SPNs activity over training is increased around the lever presses but not during the association of a sound with the reward. D1-SPNs appear to show depression in activity as the mouse is actively acquiring the reward, independent of whether the reward is provided. In summary, our research employs a sophisticated operant conditioning paradigm and neuroimaging techniques to unravel the complex neural dynamics involved in reward-based learning. The insights gained from our work may contribute to a better understanding of the neural mechanisms underlying maladaptive behaviors and could potentially inform strategies for addressing conditions such as addiction and mental illness.

Disclosures: S. Cataldi: None. **C. Lacefield:** None. **N. Shashaank:** None. **D.L. Sulzer:** None.

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LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.024/LBA110

Topic: H.04. Executive Functions

Support: ONR N00014-16-1-2829

Title: Ripple synchronization facilitates cortical integration during an auditory task

Authors: *S. WILSON[1], I. VERZHBINSKY[2], J. C. GARRETT[3], W. K. DOYLE[4], O. DEVINSKY[4], S. S. CASH[5], T. THESEN[6], E. HALGREN[7];
[1]UCSD Dept. of Neurosciences, La Jolla, CA; [2]Univ. Of California San Diego Neurosciences Grad. Program, San Diego, CA; [3]Radiology, Univ. Of California San Diego Neurosciences Grad. Program, La Jolla, CA; [4]NYU, New York, NY; [5]Harvard, Cambridge, MA; [6]New York Univ., New York, NY; [7]Multimodal Imaging Lab. (MC0841), Univ. of California at San Diego, San Diego, CA

Abstract: Ripples are emerging as a promising substrate for information binding in the human cortex. Recent work has demonstrated that these brief (~100ms), high frequency (~90 Hz) oscillations co-occur and phase-lock at zero lag in the human brain prior to correct semantic judgments. Published work on cortical co-rippling has investigated only the visual word modality, where widespread co-rippling was initiated by the left fusiform gyrus area that encodes visual stimuli as word forms. It remains to be seen if widespread ripple synchronization extends to other modalities. Building on this work, our study investigates whether similar patterns of

widespread ripple synchronization occur in the human cortex during similar tasks in the auditory word modality. Using data from patients implanted with electrocorticography grids (ECoG), arrays that cover large portions of the cortex and record local field potentials (LFPs), we measured ripples during two auditory word semantic judgment tasks. During the tasks, we measured co-rippling (ripples with >25ms overlap), phase-locking (ripples with consistent phase lag), and coordination of single units in one patient who was also implanted with a Utah Array. Our analysis demonstrated that auditory semantic judgment tasks elicit similar widespread ripple synchronization in the human cortex, mirroring the patterns reported in the visual word task. However, in these auditory tasks, the widespread co-rippling is initiated by the posterior superior temporal gyrus (pSTG), a region associated with auditory word form encoding. Furthermore, co-ripples were shown to phase-lock at long distances in target conditions during the auditory word task, as was seen in the visual word task. These findings indicate that ripple synchronization may be a general mechanism for cortical integration that extends across multiple modalities. These results have broad implications for understanding the neural mechanisms of cortical integration during cognitive tasks and support the long-debated idea that synchronized high-frequency oscillations may facilitate information integration in the brain.

Disclosures: S. Wilson: None. **I. Verzhbinsky:** None. **J.C. Garrett:** None. **W.K. Doyle:** None. **O. Devinsky:** None. **S.S. Cash:** None. **T. Thesen:** None. **E. Halgren:** None.

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LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.025/LBA111

Topic: H.04. Executive Functions

Support: NSERC Discovery Grant

Title: A decrease in cerebral blood flow does not impact executive function: Evidence from a three-hour head-down tilt protocol

Authors: *C. EDGAR, J. VAN RIESEN, A. RAHIMIDARABAD, E. SENNE, M. D. HEATH; Western Univ., London, ON, Canada

Abstract: Background: A chronic reduction in cerebral blood flow (CBF) as a result of disease state is associated with impaired executive function (EF), whereas increased CBF arising from high-level physical fitness is associated with improved EF. Moreover, some work has shown that a transient increase in CBF (via exercise) benefits EF; however, it is unclear whether a transient decrease in CBF impairs EF. To that end, the present work employed a 3-h head-down tilt (HDT) protocol involving intermittent assessments of CBF and EF. The HDT protocol was employed because it has been shown to reliably and safely decrease CBF. **Methods:** A sex-balanced

sample (n = 24) of healthy participants completed two 3-h sessions of -12° HDT and a no-tilt control while EF (Stroop task) and physiological assessments (i.e., heart rate (HR), blood pressure (BP) and middle cerebral artery velocity (MCAv)) were completed at 30-min timepoints throughout the protocol. **Results:** The HDT condition demonstrated a linear decrease in MCAv as a function of time ($p>0.001$), however, the control condition did not show a reliable time-based decrease ($p>0.05$). Notably, in spite of the time-based decrease in MCAv during the HDT condition, neither congruent nor incongruent trial Stroop reaction times (RT) or response errors differed from baseline (all ps >.25), and MCAv and RT values were not reliably related ($r<0.04$, $p>0.87$). **Conclusion:** Acute HDT provides a transient and linear time-based reduction in CBF, and this physiological change is independent of a change in high-level EF. These findings may in part reflect an adaptive mechanism that enhances the brain's efficiency in oxygen extraction during transient periods of reduced CBF.

Disclosures: C. Edgar: None. **J. Van Riesen:** None. **A. Rahimidarabad:** None. **E. Senne:** None. **M.D. Heath:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.026/LBA112

Topic: H.04. Executive Functions

Support: NSERC Discovery Grant

Title: The Impact of Music Listening and Aerobic Exercise on Cerebral Blood Flow and Executive Function: Insights from a Synergistic Protocol

Authors: *A. AYAZ[1], A. RAHIMIDARABAD[1], L. BUWADI[1], G. JEYARAJAN[2], M. D. HEATH[2];
[1]Neurosci., [2]Kinesiology, Western Univ., London, ON, Canada

Abstract: Background: A single bout of aerobic exercise (AE) across a continuum of metabolically sustainable intensities provides a postexercise executive function (EF) benefit that has been linked to an exercise-based increase in cerebral blood flow (CBF). Notably, music listening (ML) increases CBF in EF networks via an arousal-based increase in heart rate and the magnitude of this increase is comparable with "light" intensity AE. The present study sought to determine whether comparable changes in CBF induced by AE and ML benefit EF and whether combined AE and ML elicit an additive EF benefit. **Methods:** Healthy young participants (N=22: 14 female) completed four 10-min conditions on separate days consisting of: (1) non-exercise, non-music control, (2) ML entailing a 5-song playlist of rock music in a randomized order, (3) "light" intensity AE (via cycle ergometer) at an intensity of 20-39% of predicted heart

rate reserve and (4) combined ML and AE (i.e., ML+AE). Pre- and post-intervention EF was evaluated via the antisaccade task (i.e., saccade mirror symmetrical to target location) because it provides a reliable basis to identify subtle changes in EF. Transcranial Doppler ultrasound (TCD) measured middle cerebral artery velocity (MCAv) throughout each condition to estimate changes in CBF and heart rate and blood pressure were continuously recorded. **Results:** ML, AE and ML+AE produced a baseline to steady-state increase in MCAv (ps<.05); however, only the AE and ML+AE conditions produced a reliable post-intervention decrease in antisaccade reaction times (RT) (p<.001). Moreover, the magnitude of the MCAv change in all conditions did not reliably relate to the magnitude of pre- to post-intervention changes in antisaccade RTs (ps >.35). **Conclusion:** A single bout of ML increases CBF but does not elicit an EF benefit in line with a single bout of AE. Moreover, the introduction of a combined ML+AE protocol neither elicits an additive increase in CBF nor produces an increased magnitude EF benefit.

Disclosures: A. Ayaz: None. **A. Rahimidarabad:** None. **L. Buwadi:** None. **G. Jeyarajan:** None. **M.D. Heath:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.027/LBA113

Topic: H.04. Executive Functions

Support: Innovations in Medical Research Award, Stephens Family Clinical Research Institute at Carle Health

Title: Alterations of Cortical Thickness Associated with Colorectal Cancer Related Cognitive Impairment

Authors: J. NGUYEN[1], N. NGUYEN[6], S. CHAO[6], T. RIDDLE[2], D. DUTTA[3], R. YU[4], K. ROWLAND[3], *Z. SHI[5];
[1]Clin. Imaging Res., [2]Neurosciences, [3]Carle Cancer Inst., [4]Digestive Hlth. Inst., [5]Carle Fndn. Hosp., Urbana, IL; [6]Carle Illinois Col. of Med., Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: About 45% of early-stage colorectal cancer survivors exhibit significant cancer-related cognitive impairments (CRCI) in objective attention/working memory, verbal learning, and information processing speed after surgery with no added effects from adjuvant therapy. Little is currently known regarding its neural mechanisms, which greatly impedes the development of effective therapies. Towards addressing this issue, our study aims to utilize 7T MRI to investigate the relationship between colorectal CRCI and gray matter (GM) morphometry as regional variations in cortical thickness, area, and volume may be associated

with differences in cognitive abilities. Twenty-six subjects were recruited including 13 colorectal cancer survivors (stage I or II, aged 58.92 ± 8.43 yrs) who have had surgery without adjuvant therapy within six months and 13 age/sex/education matched healthy controls (HC). All subjects had no prior malignancy or history of neurological disorders. Each subject underwent neuropsychological testing (Hopkins Verbal Learning Test-Revised, Trail Making Test, and Controlled Oral Word Association Test), Beck Depression Inventory, State-Trait Anxiety Inventory, and MRI in a Siemen's MAGNETOM Terra 7T scanner within the same day. Cortical surface reconstruction was accomplished using FreeSurfer's automated cortical measurement technique. Analysis of covariance was utilized to determine the specific neuropsychological tests and GM measurements that significantly differentiate between HC and survivors while controlling for the effects of age, education, depression, and anxiety. These were then fit to generalized linear models (GLM) to determine the GM measurements with significant relationships to the neuropsychological test results. We found that the Recognition Discrimination Index (RDI) (p=0.014) and Trail Making Test A (TMT-A) (p=0.037) results were significantly different between HC and survivors. GLM analysis of survivors indicated that the thickness of the left orbital gyrus was significantly correlated with RDI results (p=0.038) while the thickness of the left inferior temporal gyrus was significantly correlated with TMT-A results (p=0.037). These regions are known to be involved in executive functions and language/memory processing. Our preliminary results present evidence of alterations and associations between cortical thickness and cognitive functioning in colorectal cancer survivors. Further data collection is underway that will help elucidate the neural mechanisms and biological targets needed for treating colorectal CRCI.

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Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.028/LBA114

Topic: H.04. Executive Functions

Support: NIH/NIGMS 5P20GM103475-18
NIH/NIEHS 1R15ES035973

Title: Interleukins involvement in diesel exhaust particles induced cognitive deficits in juvenile mice

Authors: *L. B. MENDEZ, K. CASILLAS, H. J. ROSA LOPEZ;
Sci. & Technol., Univ. Ana G. Mendez, Carolina, PR

Abstract: Epidemiological studies have found associations between exposure to particle pollution and neurocognitive outcomes. The life stages of childhood and adolescence are particularly vulnerable to the effects of particle pollution, since their CNS is still in development, especially in regions related to executive functions. The goal of this study was to assess if exposure to diesel exhaust particles (DEP) impairs the postnatal development of executive functions. We hypothesized that DEP exposure will impair executive function in juvenile mice by inducing neuroinflammatory responses. To test the hypothesis, female and male C57BL6/J mice were exposed intranasally to either saline or increasing doses of DEP during postnatal days (PND) 25 to 33. Behavioral and cognitive outcomes were assessed on PND 36 to 38. Mice locomotor and exploratory behaviors were evaluated with the Open Field Test; and problem-solving skills, short- and long-term memory with the Puzzle Box paradigm. Mice were euthanized on PND 39 and brain tissue was collected to measure the concentration of cytokines and chemokine. Mice exposed to DEP exhibited a hyperactive phenotype with concurrent deficits in problems-solving skills (mid dose) and short- and long-term memory at the highest dose. Dose-dependent increases were observed for IL-1, IL-6, IL-12, IL-17; while dose-dependent decreases were observed for IL-9, IL-13 and TNF alpha. Overall, results show that CNS immune responses were skewed towards a pro-inflammatory state. In addition, a principal component analysis discriminated the immune responses into IL-9 vs. IL-17 driven, suggesting the involvement of adaptive immune response in DEP induced neurotoxicity.

Disclosures: L.B. Mendez: None. **K. Casillas:** None. **H.J. Rosa Lopez:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.029/LBA115

Topic: H.05. Working Memory

Title: Orthogonal-rotational dynamics supports continuous memory encoding and updating in artifical neural network and human brain

Authors: *B. YANG, S. YU;
Inst. of Automation CAS, Beijing, China

Abstract: To deal with the perpetual stream of information coming from the environment in daily life, we rely on the working memory (WM) to store information temporarily. This requires 1) efficient encoding framework to separate stimuli coming at adjacent times, and 2) flexible updating mechanisms to discard the information no longer needed and to accommodate newly arrived one. To investigate the computational mechanism underneath such functional implementation of the WM, we analyzed the information representation of both a recurrent neural network (RNN) model and human subjects (n=28) in the same N-back task (N=2 or 3).

The *N*-back task requires subjects to encode and update memory items continuously. Specifically, we examined the neural representations of memory items and dynamics during memory updating in the low-dimensional representational space, through implementing principle components analysis (PCA) on the hidden state of RNN model or the phase locking value (PLV) matrix extracted from the EEG signals recorded from the prefrontal cortex during the task. We found that an orthogonal-rotational dynamics supports the memory encoding and updating, allowing the information in the memory to be stored and proceed in a “first in, first out” manner. In the RNN model, we found orthogonal representations of memory items , each of which occupied a fixed subspace according to their relative ordinal rank. A rotational operation transferred information across different subspaces in a certain direction for updating memory items dynamically while maintaining their order. Meanwhile, the representations of memory information extracted from EEG signals in humans showed similar representations, i.e., the orthogonal-rotational dynamics, as found in the RNN model. Our findings reveal a potentially common framework of orthogonal-rotational dynamics that is implemented in both artificial and biological neural network, which supports efficient encoding and dynamical updating of memory during the processing of information steam.

Disclosures: B. Yang: None. **S. Yu:** None.

Late-Breaking Poster

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.030/LBA116

Topic: H.05. Working Memory

Title: Revisiting alpha-theta frequency shifts during working memory: a mechanism for brain communication?

Authors: *J. RODRIGUEZ-LARIOS;
Brunel Univ. London, London, United Kingdom

Abstract: Working memory, defined as the ability to maintain and manipulate information, requires the interplay of different brain areas. A prominent theory proposes that connectivity between brain areas is implemented by the synchronization of neural oscillations. It has been recently proposed that frequency shifts could play a key role in the synchronization of neural oscillations and therefore, inter-areal communication. Specifically, it has been suggested that harmonic relationships between brain rhythms would facilitate brain communication via cross-frequency phase synchrony. In this study, we assess whether changes in the frequency of posterior alpha (8-14 Hz) and frontal theta (4-8 Hz) neural oscillations during a working memory task are accompanied by changes in inter-areal communication as quantified through information theory metrics. For this purpose, we recorded High Density Electroencephalography (HEEG) in

23 subjects (13 male) while they performed a spatial working memory task. In line with previous studies, working memory retention was associated to a posterior alpha frequency increase and a frontal theta frequency decrease. These frequency shifts during memory retention led to an increased occurrence of a 2:1 harmonic frequency arrangement (alpha ~ 11 Hz; theta ~ 5.5 Hz) and therefore, greater 2:1 phase synchronization. However, information theory metrics did not identify a significant change in information transmission (as assessed through Transfer Entropy) during working memory delay. Instead, a significant decrease in Mutual Information during the working memory delay was found. Together, our results show that harmonic frequency arrangements (and therefore cross-frequency phase synchrony) do not necessarily lead to greater inter-areal communication in the brain.

Disclosures: J. Rodriguez-Larios: None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Program #/Poster #: LBA008.031/LBA117

Topic: H.05. Working Memory

Support: NSF Grant NJ1YPQXQG7U5

Title: Human-like Capacity Constraints in Vision Language Models

Authors: *L. REMON[1], D. I. CAMPBELL[2], J. D. COHEN[2];
[1]Neurosci., [2]Princeton Univ., Princeton, NJ

Abstract: Recent work has documented striking heterogeneity in the performance of state 2 of-the-art vision language models such as GPT-4v and the DALL-E text-to-image models. These models are able to describe and generate an incredibly diverse array of complex, naturalistic images, yet they exhibit surprising failures on basic multi-object reasoning tasks - such as counting, localization, and simple forms of visual analogy - that humans perform with near perfect accuracy. To better understand this puzzling pattern of successes and failures, we draw on theoretical accounts from cognitive science that postulate a fundamental trade-off between representational flexibility (i.e., the use of compositional representations to promote generalization) and channel capacity (i.e., the number of entities that can be represented at any one time). This trade-off gives rise to the classic binding problem, leading to severe constraints on the ability to rapidly process multi-object scenes, and necessitating the use of serial processing to prevent interference. Drawing on this perspective, we hypothesize that VLMs, under pressure for generalization, also learn structured representations, but lack the serial processing mechanisms to effectively use these to process and generate multi-object scenes, resulting in severe capacity constraints similar to those observed when humans are forced to rely

on rapid, parallel visual processing. We test this hypothesis through a combination of classic cognitive tasks and novel benchmarks. Our results provide a unique perspective on VLMs, informed by work in cognitive science, suggesting that their capacity for generalization paradoxically gives rise to many of their most notable limitations, possibly for the same reasons humans exhibit a similar profile of competencies and limitations.

Disclosures: L. Remon: None. **D.I. Campbell:** None. **J.D. Cohen:** None.

Late-Breaking Poster

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Topic: H.05. Working Memory

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Title: Temporal regularities tune the prioritisation of sensory and motor working-memory contents

Authors: *I. ECHEVERRIA-ALTUNA[1], S. BOETTCHER[1], F. VAN EDE[2], A. NOBRE[3,1]; [1]Univ. of Oxford, Oxford, United Kingdom; [2]Vrije Univ. Amsterdam, Amsterdam, Netherlands; [3]Dept. of Psychology, Yale Univ., New Haven, CT

Abstract: Internal selective attention prioritises working-memory contents to prepare us for prospective behaviours. The prioritisation of visual contents in working memory is flexible and temporally tuned. In addition to visual contents, action-related contents can also be prioritised in working memory, highlighting the pragmatic nature of internal attention. An open question is whether the prioritisation of action-related contents is similarly flexible and tuned to the temporal structure of the task. Additionally, it is unclear if the modulation of co-existing sensory and action-related contents in working memory is intrinsically coupled. Here, we designed a task that encourages the flexible prioritisation of two item locations and two associated prospective actions as a function of dynamically evolving temporal expectations. The design orthogonally manipulated item location (left vs right side) and prospective action (left vs right hand), enabling the independent tracking of the prioritisation of sensory contents (through alpha EEG activity modulation and gaze biases) and prospective actions (through mu-beta EEG activity changes).

Results across two sessions showed that sensory- and action-related prioritisation co-exist in working memory. Both are flexible and temporally tuned, as indexed by reaction-time benefits, modulations in alpha and mu-beta EEG activity, and shifts in gaze biases. Interestingly, modulations of visual and action signals were not continuously temporally coupled. The findings highlight a variety of modulatory processes that co-occur to prepare internal representations for adaptive behaviour.

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LBA008: Theme H Late-Breaking Posters

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Program #/Poster #: LBA008.033/LBA119

Topic: H.05. Working Memory

Support: Wellcome Trust

Title: Task Context Shapes Short-Term Memory Localisation

Authors: *J. LI[1], Z. XU[1], A. ALBESA GONZALEZ[2], C. BAO[1], L. LI[3,4], C. CLOPATH[2], J. C. ERLICH[1,3];
[1]Sainsbury Wellcome Ctr., Univ. Col. London, London, United Kingdom; [2]Imperial Col. London, London, United Kingdom; [3]New York Univ. Shanghai, Shanghai, China; [4]East China Normal Univ., Shanghai, China

Abstract: In 2-alternative forced choice (2AFC) memory-guided tasks, activity in M2 predicts upcoming choice and is causally involved in planning. However, in the real world, planning can take place in different reference frames. For example, turn left/right versus go south/north. Does the role of M2 in planning generalize across different reference frames for planning?To address this, we trained rats on one of two novel auditory memory-guided orienting tasks using an 8-port wall (7 operant ports and 1 reward port). In both tasks, the start position was cued with a light and varied from trial to trial. Rats had to fixate in the start port for 1.5 seconds. The 0.75s had a sound cue (A:35 Hz or B:68 Hz click train). The second 0.75s was a silent delay period. In the ‘allo’ task, sound A directed the rats to the bottom-left port and sound B to the bottom-right port, regardless of their starting position. In the ‘ego’ task, sound A directed the rats to move left and sound B to move right from their starting position. Behaviorally, we observed that in the "allo" task: the response time was 35 ms slower and the decodability of choice from animals’ posture was significantly weaker compared to ego.Decoding of upcoming choice from neural activity in FOF was significantly more accurate in the ego than allo task. Consistent with decoding, optogenetic silencing of the FOF during the memory period impaired performance significantly

more in the "ego" task than the "allo" task.Together, our findings suggest that in the allo task, the sensorimotor transformation is delayed until the end of the fixation period and that the FOF is not involved, demonstrating that the role of FOF in M2 is not general, but depends on the mnemonic strategy of the animal. We reasoned that one possible reason for this, is that in the allo task there are 12 different possible movement vectors (3.6 bits) vs. 2 (1 bit) in the ego task. However, both tasks could be solved by remembering 1-bit of sound information. We developed a computation model that evaluates the cost of short-term memory in real-time, allowing for rapid adaptation when transitioning from the "allo" task to the "ego" task or a simpler 2-choice task.We validated this prediction experimentally: after transferring "allo" task-trained animals to a simpler 2-choice task, silencing the FOF impaired task performance and also increased decodability during the memory period. Our results suggest a fast and flexible mechanism for recruiting different short-term memory mechanisms based on task context, determined by the memory cost associated with each mechanism.

Disclosures: J. Li: None. **Z. Xu:** None. **A. Albesa Gonzalez:** None. **C. Bao:** None. **L. Li:** None. **C. Clopath:** None. **J.C. Erlich:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.034/LBA120

Topic: H.05. Working Memory

Title: Abstract codes guide prospective working memory

Authors: *J. LEE[1], D. DE VITO[1], J. MILLER[3], D. E. NEE[2];
[2]Dept. of Psychology, [1]Florida State Univ., Tallahassee, FL; [3]Wu Tsai Inst., Yale Univ., New Haven, CT

Abstract: Working memory (WM) allows us to use past sensory information to prepare for the near future. Although substantial work has focused on the neural mechanisms involved in maintaining past sensory signals, it remains unclear how the recent past is transformed into more abstract codes that guide future cognition. To examine the prospective nature of WM, we used a novel sequence-matching task. While being scanned with functional MRI, human participants maintained a separate spatial location in each hemifield wherein locations were embedded in a star-shaped sequence. On each trial, participants made a sequence-match decision to a spatial probe and then updated their WM with the probe. The same abstract star-shaped sequence guided judgments in each hemifield allowing us to separately track concrete spatial locations (hemifield-specific) and abstract sequence positions (hemifield-general), while also tracking representations of the past (last location/position) and future (next location/position). A combination of multivariate decoding, representational similarity analysis, and multidimensional scaling

revealed that both the intraparietal sulcus (IPS) and visual cortex (VC) initially maintained concrete past locations with concrete, retrospective coding particularly prominent in VC. Over time, these representations became progressively more abstract and prospective with abstract, prospective coding particularly prominent in the IPS. Taken together, these results suggest that WM guides future cognition by reformatting sensory signals of the past into abstract codes reflecting prospective expectations.

Disclosures: J. Lee: None. **D. De Vito:** None. **J. Miller:** None. **D.E. Nee:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.035/LBA121

Topic: H.05. Working Memory

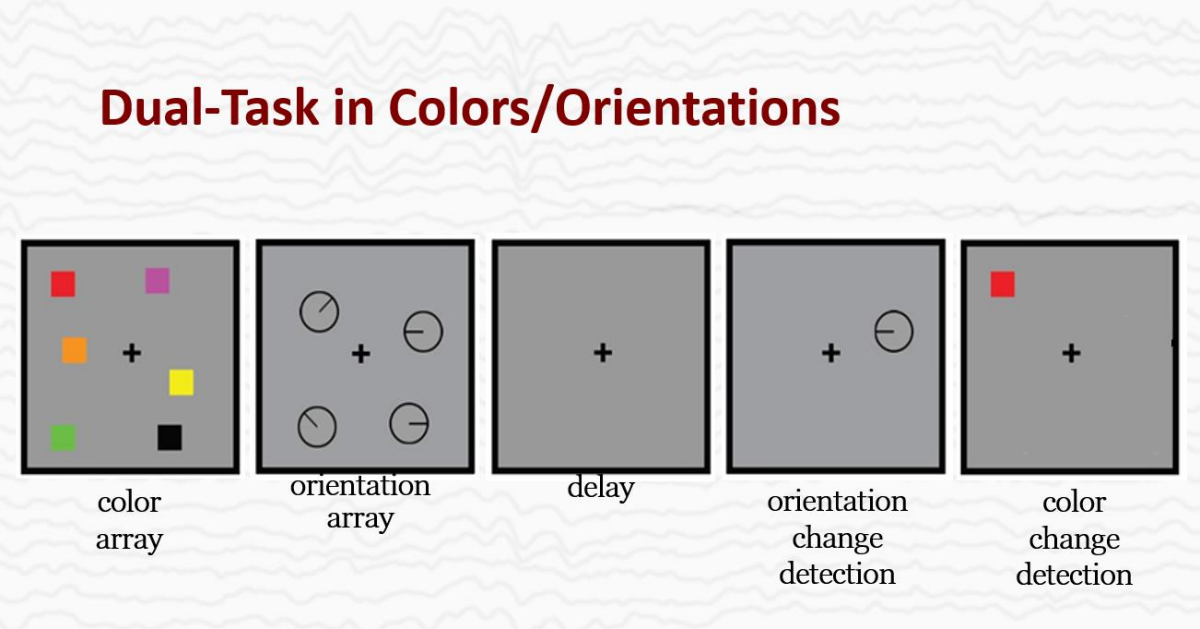
Support: NIMH Grant ROIMH087214

Title: Enhancing Working Memory Capacity Through Long-term Memory Utilization: The Role of Event Boundaries

Authors: *A. FRONTERA[1], E. AWH[2], D. SUPLICA[2], C. ZHAO[3];
[1]Dept. of Biol., Univ. of Puerto Rico Rio Piedras, San Juan, PR; [2]Psychology, [3]Dept. of Psychology, Univ. of Chicago, Chicago, IL

Abstract: Working memory (WM) allows us to temporarily store and manipulate information but has limited capacity. For example, in a color change detection task, observers see 6 colors and then indicate whether one of them has changed after a one second blank memory period. Surprisingly, this test reveals that people can only store about 2-3 simple colors at a time. However, when we ran a "dual task" version of this experiment (pictured below) that combines two of these simple tasks into one procedure, we found substantially higher performance than in the single task. In our dual task, observers saw an array of colors, followed by a test of memory for the orientations and a test of memory for the colors. On average, observers stored about 50% more information during the dual task than during the single task. Our hypothesis is that observers were able to take advantage of storage in *both* working memory and long term memory. By this account, observers encoded the colors into working memory, but then offloaded those colors into long term memory, thereby freeing up working memory for the orientation task. This collaboration between WM and LTM was encouraged by the presence of a subjective "event boundary" between the color and orientation tasks that may have motivated the offloading of the colors into LTM when the orientation task began. To test this hypothesis, we attempted to disrupt the event boundary by *randomizing* the order of testing for the color and orientation stimuli. Because testing order was unpredictable, we predicted observers would be more likely to

view the colors and orientations as part of a single event, thereby eliminating offloading into LTM. In line with these predictions, our prior work showed that randomizing testing order led to a large drop in dual task performance such that it was now substantially *worse* than in the single task condition. Thus, event boundaries may motivate the flushing of working memories for the earlier event, revealing the dynamic collaboration between capacity-limited working memory and long term memory.



Disclosures: A. Frontera: None. **E. Awh:** None. **D. Suplica:** None. **C. Zhao:** None.
Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.036/LBA122

Topic: H.05. Working Memory

Support: St Olaf CURI
St Olaf Psychology Vision Fund

Title: Sex, drugs, and working memory: The effect of sex differences and MK-801 administration on learning in the delayed alternation task in the rat

Authors: L. ECKSTROM[1], K. HOWLES[1], R. SEEBACHER[1], ***N. J. POWELL**[2];
[1]St Olaf Col., Northfield, MN; [2]St Olaf College, Northfield, MN, Minnetonka, MN

Abstract: The prefrontal cortex (PFC) is implicated in working memory (WM) processing in both humans and rats. Impaired working memory function is a common symptom in patients with Schizophrenia (Jannus et al 2023, Wozniak et al 1990). Past research suggested that the deficit in schizophrenia patients may be associated with an inability to accurately encode information to be held in working memory (Lee and Park, 2005). This raises the question of whether working memory deficits seen in patients with schizophrenia or models of the disease are an acute effect of working memory performance, or an effect of impaired learning due to the chronic nature of the disorder. In order to answer this question, we have employed the non-competitive NMDA receptor antagonist MK-801 to create a chronic learning impairment in one group of male rats (MLI) and one group of female rats (FLI) which we will compare to two control (MC and FC) groups given saline injections. We used 18 Long-Evans rats (10 F, 8 M) to compare the effects of sex on WM and drug effects, due to the historical prevalence of male rats in neuroscience research. We trained both groups of rats to perform a delayed alternation lever press task under the differential drug conditions, followed by 2 test phases. In phase 1, all animals performed the WM task with saline injections to compare the effect of LI without acute drug effects. In phase 2, all groups received MK-801 to assess the effects of LI combined with drug effects in both groups. Preliminary results indicate that MK-801 administration induced a significant performance deficit on this task (in terms of percentage of correct trials). We additionally found that female rats had a significant performance deficit relative to male rats on this task, but there was no evidence of a significant interaction effect of sex and MK-801. We conclude that MK-801 is effective at inducing a performance deficit, but this difference does not differ across sexes. Further analyses will discuss the nature of this cognitive deficit in terms of performance vs learning and its effect on WM.

Disclosures: L. Eckstrom: None. **K. Howles:** None. **R. Seebacher:** None. **N.J. Powell:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.037/LBA123

Topic: H.06. Social Cognition

Title: Investigating Associations Between Genes Linked to Social Behavior and Early Covid19 Spread Using Multivariate Linear Regression Analysis

Authors: *G. C. EICHFELD;
Neurosci., Colgate Univ., Hamilton, NY

Abstract: Variation in global Covid-19 spread is partly explained by social and behavioral factors. Many of these behaviors are linked to genetics. The short polymorphism of the 5-HTTLPR promoter region of the SLC6A4 gene is linked to collectivism, the seven repeat

polymorphism of the DRD4 gene is linked to risk taking, migration, sensation seeking, and impulsivity, and fewer CAG repeats in the androgen receptor gene is linked to impulsivity. This study investigates an association between the country-level frequency of these variants and early Covid-19 spread. Results of multivariate linear regression analysis indicate a significant association between increased country-wide prevalence of the short allele of the SLC6A4 gene and decreased Covid-19 spread, when other factors that have been linked to Covid-19 are controlled for. Additionally, results show that the short allele of the SLC6A4 gene is associated with Covid-19 spread through GDP and percent urbanization, rather than collectivism. Results showed no significant association between the frequency of the DRD4 polymorphism nor the androgen receptor polymorphism with early Covid-19 spread.

Disclosures: G.C. Eichfeld: None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.038/LBA124

Topic: H.06. Social Cognition

Support: Palm Health Fellowship

Title: In-phase and anti-phase parent-infant neural synchrony and associations with dyadic behaviors during freeplay

Authors: *L. RIERA-GOMEZ[1], J. STOTLER[1], H. Z. GVIRTS[2], T. G. WILCOX[1];
[1]Psychology, Florida Atlantic Univ., Boca Raton, FL; [2]Ariel Univ., Ariel, Israel

Abstract: Rationale: parent-infant neural synchrony (coordinated brain activity between social partners) is crucial for the formation of the social brain, and social-adaptive and self-regulatory processes. Synchrony can reveal an additional layer of dyadic neurological responses during social interaction, above study of a single brain. Researchers investigating neural synchrony often ignore directionality (whether partners are demonstrating concurrent activation in the same vs opposing directions) of concurrent activation between partners. Research question: in an exploratory study, we explored how synchrony patterns and directionality may hold implications for the parent-infant relationship by assessing their associations with important behavioral outcomes during freeplay. Twelve infants (7 - 23 months; male = 3) and their mothers participated in fNIRS hyperscanning (recording simultaneous brain activity from two social partners) during a four-minute freeplay task. Parents were asked to play with their child using toys just as they normally would. We used the LeaderFollowerByPhase Toolbox (Gvirts Provolovski et al., 2023) to interpret results from WTC analyses, and calculated percent time spent **in-phase** (concurrent activation between partners in same direction), and **anti-phase**

(concurrent activation between partners in opposing directions) neural synchrony between infants and their parents. Synchrony in the social brain areas (TPJ, STS, STG, SMG, and IFG) were assessed. Parent sensitivity, parent intrusiveness (controlling parenting), and dyadic reciprocity (turn-taking and social adaptation) were coded using the Coding Interactive Behaviors scale (CIB; Feldman, 1998). Spearman's correlations revealed **in-phase** neural synchrony in the left middle temporal area (STG; implicated in language processing and social interaction) is positively associated with parent intrusiveness and negatively associated with parent sensitivity and dyadic reciprocity; variables less optimal for the parent-infant relationship and child development. **Anti-phase** synchrony in the left middle temporal area is negatively associated with parent intrusiveness, and positively associated with parent sensitivity and dyadic synchrony; variables more optimal for child development. These findings underscore the importance of considering the directionality of neural synchrony and demonstrate the applicability of this method for studying parent-infant play. Anti-phase synchrony patterns appear to indicate a more adaptive, turn-taking dynamic during freeplay interactions between parents and infants that is more optimal for child development.

Disclosures: L. Riera-Gomez: None. **J. Stotler:** None. **H.Z. Gvirts:** None. **T.G. Wilcox:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.039/LBA125

Topic: H.06. Social Cognition

Support: NS114191

Title: Differential Perception of Affective Touch in Hairy and Glabrous Skin

Authors: *Y. LUO[1], K. H. WANG[2], M. GOMEZ-RAMIREZ[1];
[1]Brain and Cognitive Sci., [2]Dept. of Neurosci., Univ. of Rochester, Rochester, NY

Abstract: Affective touch is a fundamental aspect of mental and physical health, playing an essential role in hierarchical and causal social interactions. Most studies in humans have focused on how affective touch is perceived as the receiving agent of the tactile stimulation. However, typical interpersonal touch scenarios involve an agent who passively receives touch stimuli, usually through the hairy skin (e.g., during grooming), and an acting agent who actively delivers the affective touch usually with the glabrous part of the hand. Critically, the person delivering the touch stimuli must also have a sense of how pleasant (or unpleasant) the touch stimuli feels like in order to potentially recalibrate their applied touch. This actor/receiver pairing leads to specific hypotheses about how the different ways that touch stimuli are perceived. Here, we will

test the hypothesis that pleasantness will be maximal in the hairy skin vs. glabrous skin when touch stimuli are passively vs. actively sensed, respectively. To test this hypothesis, we performed a human experiment where participants sensed different valence stimuli (Pleasant, Neural, and Unpleasant) either passively (experimenter applying a stimulus), or actively (by making an overt movement to sense the object). Tactile stimuli were delivered in one of three speeds (slow, medium, and fast) to the glabrous skin of the hand or the hairy skin on the forearm. Participants were asked to rate the pleasantness of the stimulation. Preliminary data (N = 7) shows higher pleasantness ratings for passively vs. actively sensed stimuli applied to the hairy vs. glabrous skin, respectively. In support, we found that unpleasant stimuli are rated less unpleasant for passively vs. actively sensed stimuli applied to the hairy vs. glabrous skin, respectively. Our preliminary findings show differential perception of affective touch depending on the mode of stimulation and location on the body. Our study provides a novel understanding of how touch is affectively perceived during active and passive sensation.

Disclosures: Y. luo: None. **K.H. Wang:** None. **M. Gomez-Ramirez:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.040/LBA126

Topic: H.06. Social Cognition

Support: NSF IUCRC BRAIN University of Houston Site Award #2137255
Center for the Ballet and the Arts (New York University)
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The New York Department of Cultural Affairs
New York Council on the Arts
National Endowment for the Arts
Associate Dean of Research Office
Mechatronics Department at the School of Engineering and Sciences (Tecnológico de Monterrey)

Title: Unveiling Brain Activity during Dancing: Insights from mobile EEG Hyperscanning of Professional Butoh Dancers

Authors: *Y. E. LIMA CARMONA[1], C. THEOFANOPOULOU[2], J. L. CONTRERAS-VIDAL[1];

[1]Electrical and Computer Engin., Univ. of Houston, Houston, TX; [2]Rockefeller Univ., New York, NY

Abstract: Dissecting the neurobiology of dance would shed light on a complex, yet ubiquitous, form of human communication. In this experiment, we sought to study the brain activity of five experienced dancers while dancing Butoh, a postmodern dance that originated in Japan. Butoh is a type of dance that falls out of the narrow and Western definition of dance, mostly consisting of very slow movements, often not entrained to a specific rhythmic pattern, but to specific sound cues and features, such as sound intensity. We used a hyperscanning protocol (Theofanopoulou et al. 2023 bioRxiv), which enabled us to combine mobile electroencephalography (EEG), electrooculography (EOG), inertial measurement units (IMU), and video recording. EOG and IMU were used to record eye and head/neck movements, respectively, allowing for the offline removal of relevant motion artifacts. We focused this analysis on ultra-slow EEG rhythms in dancing segments with specific annotated body movements, building on previous literature suggesting that ultra-slow rhythms display stereotypical spatiotemporal patterns time-locked to motor actions (Hari 2006; Jensen et al. 2005). EEG data was denoised by implementing a pipeline that combined bandpass filtering, adaptive filter H-Infinity, Artifact Subspace Reconstruction, and Independent Component Analysis (ICA). To identify dipoles, we first clustered the sources obtained from the Independent Components (ICs) and for each cluster, we calculated the centroids, which represent the central point of the clustered sources. These centroids were then used to identify the corresponding Brodmann Areas (BAs) by projecting them into an MNI (Montreal Neurological Institute) template. Our analysis revealed that during slow Butoh dance movements specific brain regions were recruited: the premotor and supplementary motor areas (BA6, @ 0.03 Hz), the precuneus and superior parietal lobule (BA7, @ 0.12, 0.06 Hz), the occipital cortex (BA18, @ 0.05 Hz), the angular gyrus (BA39, @ 0.045, 0.018 Hz), and the dorsolateral prefrontal cortex (BA46, @ 0.012, 0.03 Hz). Activity in these areas has been associated with various relevant behaviors and cognitive functions, including sequence learning and planning (BA6), visuospatial processing (BA7), motion recognition (BA18), and spatial imagery (BA39). Being, to our knowledge, the first study to analyze brain activity during Butoh dancing through simultaneous mobile EEG, we expect that our findings will inform future art-science collaborations.

Disclosures: Y.E. Lima Carmona: None. **C. Theofanopoulou:** None. **J.L. Contreras-Vidal:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.041/LBA127

Topic: H.06. Social Cognition

Support: Ilene Gordon Wittels Fellowship
R01 DC007703 18

Title: Novel playpen enrichment reduces anxiety without changes in taste preferences

Authors: *G. WERNICK[1], K. MAIGLER[1], C. MAZZIO[1], D. B. KATZ[2];
[1]Neurosci., [2]Psychology, Brandeis Univ., Waltham, MA

Abstract: Environmental enrichment (EE) promotes resilience to stress, enhances cognitive abilities, and increases behavioral variability in rodents. In the taste system, EE leads to the attenuation of conditioned taste avoidance, but the effects of EE on innocuous taste experience remain unknown. Here, we investigate how a playpen-style EE impacts individual taste preferences (and variability therein). It was previously shown that rats lacking EE exposure display variability in their individual taste preferences. We hypothesize that enriched rats will consume unpalatable tastes more frequently than non-enriched controls as a function of their reduced anxiety from EE. We also expect EE to increase variability in taste. We measure licking to a panel of tastes using the Brief Access Task (BAT) for both enriched and non-enriched groups, evaluating their preferences as well as the inter- and intra-individual variability. To verify the effectiveness of our EE protocol, we will measure anxiety and exploratory behavior in both groups using open field and novel object tests in addition to staining for brain-derived neurotrophic factor (BDNF) and doublecortin (DCX). In addition to providing further insight into the impact of experience on taste, my results will determine whether EE should be made a standard animal welfare tool. Preliminary results suggest that environmental enrichment, contrary to our initial hypothesis, does not impact individual taste preferences or the variability of taste preferences for each group of animals. Furthermore, the open field test shows a significant difference between anxiogenic unenriched and anxiolytic enriched animals, in addition to clear trends in other measures of anxiety, suggesting that playpen EE successfully reduces anxiety. However, any anxiolytic effect does not interfere with taste preferences and variability.

Disclosures: G. Wernick: None. **K. Maigler:** None. **C. Mazzio:** None. **D.B. Katz:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.042/LBA128

Topic: H.06. Social Cognition

Support: R00MH124435, Simons Foundation Autism Research Initiative Winter Pilot Award, Brain & Behavior Research

Title: Exploring Cooperative and Selfish Behavior in C57BL6 and CD1 Mice

Authors: *E. ILLESCAS-HUERTA[1], A. VILLAMIZAR[2], M. CUM[2], N. PADILLA-COREANO[2];
[1]McKnight Brain Institute, Univ. of Florida, United States, FL; [2]Neurosci., Univ. of Florida, Gainesville, FL

Abstract: Social animals adjust their decision according to their social context and social interactions. While some decisions focus on self-benefit, others, such as cooperation behaviors, are intentionally made to benefit others. The neural mechanisms that underlie cooperative and selfish behavior remain poorly understood. Recently, new behavioral tasks have been developed to study prosocial behaviors using preferentially C57BL6 mice as an animal model. Although C57BL6 mice show different forms of prosocial behaviors, including cooperation, it is uncertain whether these findings can be replicated in mice with greater genetic variability, such as CD1 mice. To assess this, we designed a novel two-choice cued social decision-making task, to compare cooperation behavior in C57BL6 and CD1 mice. CD1 and C57BL6 mice were trained to choose between a choice that delivers a reward to familiar conspecifics (cooperative choice) or one that only provides a reward by themselves (selfish choice). Two distinct tones were used to signal each choice, ensuring that the mice developed a preference based on cooperative or selfish outcomes. Additionally, forced-choice trials were presented to ensure mice explored both options before showing a preference. As expected, C57BL6 mice preferred cooperation and shared the reward with their cagemates. In contrast, CD1 mice exhibited selfish behavior with their cagemate, suggesting differences in the development of prosocial behaviors between strains of mice. We next asked if brain activity differences explain prosocial behavioral differences. Using the neural activity marker c-Fos, we found that during the social decision-making task, CD1 mice showed an increase in medial prefrontal cortex (mPFC) activity compared to C57BL6 mice. No differences in c-Fos expression were observed in the mPFC when both strains of mice were trained alone, suggesting that the differences observed were due to the expression of selfish behavior more than differences in brain activity across the strains. Notably, we did not observe differences in the expression of c-Fos in subcortical areas such as the basolateral amygdala, lateral hypothalamus, or mediodorsal thalamus in both strains. Future experiments will involve multi-site electrophysiological recordings to study the dynamics of mPFC activity and their subcortical projections during cooperative or selfish behavior.

Disclosures: E. Illescas-Huerta: None. **A. Villamizar:** None. **M. Cum:** None. **N. Padilla-Coreano:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.043/LBA129

Topic: H.06. Social Cognition

Support: SFARI

Title: Characterization of a new mouse model of autism with a missense mutation in the Cacna1d L-type Ca^{2+} channel gene

Authors: *S. OTSUKA, J. XU, S. ZHAI, D. SURMEIER, A. CONTRACTOR;
Northwestern university, Chicago, IL

Abstract: Autism Spectrum Disorders (ASDs) are characterized by problems with social engagement, social communication, enhanced perseveration and restricted and repetitive behaviors that can be comorbid with other psychiatric problems. ASD has a strong inheritability and there are multiple genetic variants that have been described that cause ASD in people. Many of these variants occur in genes that encode for synaptic proteins including receptors and ion channels involved in synaptic communication mechanisms in neurons. One such *de novo* missense mutation was reported in the gene that encodes for the α subunit of L-type voltage-gated Ca^{2+} channel (Cav 1.3). This mutation causes a single amino acid substitution (G407R) that reduces inactivation and increases Ca^{2+} influx through the channel and is causal to ASD in patients who do not demonstrate cognitive delay. In order to understand the consequences of this mutation in the brain we created a mutant mouse with the equivalent mutation (*Cacna1d*^{G407R}) engineered into the genome. The homozygous mutation was lethal but mice with heterozygous mutation were viable. We performed a battery tests on the *Cacna1d*^{G407R} mice to determine how their behaviors deviated from control mice. The mice showed significant impairment in a test for social memory but had normal activity in a test for sociability. Testing mice in an instrumental learning paradigm with an automated touch screen spatial discrimination task, we found that the mice learned the task normally but demonstrated perseverative behaviors when task contingencies were reversed. *Cacna1d*^{G407R} mice did not demonstrate any impairments in tests of basal locomotor function or in tests for anxiety. Taken together these results demonstrate that *Cacna1d*^{G407R} mice demonstrate altered behaviors consistent with social discrimination dysfunction and increased perseverative behavior and could be a valuable tool for the preclinical establishment of therapies for aspects of ASD.

Disclosures: S. Otsuka: None. **J. Xu:** None. **S. Zhai:** None. **D. Surmeier:** None. **A. Contractor:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Topic: H.06. Social Cognition

Support: National Institute of Mental Health (R21 MH126072, S.W.C.C., A.S.N., M.P.J.)

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National Science Foundation Graduate Research Fellowship (DGE2139841, O.C.M.)
Wu Tsai Institute Postdoctoral Fellowship (W.S.)

Title: Investigating the Role of Vocalizations in Cooperative Behavior Between Marmoset Dyads

Authors: *G. NANDY[1], O. C. MEISNER[2], W. SHI[2], A. NAIR[3], N. FAGAN[3], M. P. JADI[4], A. S. NANDY[2], S. W. CHANG[5];
[1]Brandeis Univ., Waltham, MA; [2]Dept. of Neurosci., [3]Psychology, [4]Psychiatry, [5]Dept. of Psychology, Yale Univ., New Haven, CT

Abstract: Studies have shown that marmosets modulate their vocalizations depending on social context suggesting that these vocalizations could play a crucial role in their social behaviors and relationships. However, it is not known if these vocalizations play a significant role in cooperative behaviors. Characterizing vocalizations can present valuable insights into the complexities of cooperative learning and strategies in the context of species' natural ecology. Here, we investigated the role of vocalizations during cooperative interactions in common marmosets (*Callithrix jacchus*) and examined how social factors influence these vocalizations. Specifically, we focused on chirp (food-related call) and phee (long-distance contact call) calls during coordinated lever pulls performed by marmoset dyads using the Marmoset Apparatus for Automated Pulling (MarmoAAP), a fully automated behavioral apparatus designed for studying cooperative pulling behaviors in common marmosets. In this task, the marmosets had to coordinate their lever pulls within a certain time window to earn rewards. To facilitate learning, the initial time window for coordinated pulling was large and progressively decreased until the marmosets could coordinate their pulls within one second of each other. We compared vocalizations across three task conditions: during the marmosets' learning of the cooperative task, in sessions where they had fully learned the task, and in sessions where they were blocked from visual access to each other (No Vision). We found that while the average number of chirp calls remained steady over all session types, the average number of phee calls increased during the No Vision sessions. To investigate the role of vocalizations in facilitating cooperative pulling, we studied chirps and their relation to successful and unsuccessful pulls. We found that marmosets were more likely to chirp around successful pulls, and there were distinct patterns between the dominant and non-dominant marmosets. This reinforces the findings that chirps are food-related calls but brings forward insights into how they are used differently depending on the social status of the marmoset. Furthermore, we found that the probability a marmoset will chirp around a successful pull greatly increased across learning in comparison to the probability of chirping around an unsuccessful pull, suggesting that marmosets use and manipulate their vocalizations during the process of learning to efficiently cooperate over time. Overall, our results shed light on the complexities of cooperative social behaviors and reveal the role of vocalizing in successful social interactions.

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Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.045/LBA131

Topic: H.06. Social Cognition

Support: ANR-21-CE37-0016

Title: Comparative Analysis of Socio-Emotional Subcortical Circuitry Across Macaque Monkey Species

Authors: S. SILVERE[1], C. PO[2], J. SALLET[3], J. LAMY[2], ***S. BALLESTA**[1];
[1]Primate Ctr. - Silabe (LNCA - UMR 7364), Univ. of Strasbourg, STRASBOURG, France; [2]ICube, Univ. de Strasbourg-CNRS, Strasbourg, France; [3]INSERM / Univ. of Oxford, Oxford, France

Abstract: Understanding the neural substrates underlying primates' social behaviour is a fundamental question in neuroscience. This study leverages macaque species diversity in social behaviour to unravel the structural connectivity of subcortical socio-emotional circuits. We compared diffusion MRI scans of *postmortem* brains from 5 macaque species including intolerant rhesus macaque (*Macaca mulatta*) and the more egalitarian Tonkean macaque (*M. tonkeana*). We computed the structural connectome of 14 individuals based on a semi-automatic parcellation (SARM, 70 regions) and the total connectivity of each region (sum of weighted tracks terminating at a region) was modelled using a Bayesian linear model. We compared connectivity across the cohort for both sexes, social tolerance grades 1 and 4, and ages 1 to 30 years. We found significant differences in the connectivity of several brain regions, all critical for emotion processing and social behaviour, such as the habenula, the amygdala, and the periaqueductal gray. Socially intolerant individuals (such as rhesus monkeys) exhibit enhanced connectivity in these neural circuits. The fornix, a bundle of nerve fibers important for emotional state, learning and memory, also displayed species-specific connectivity patterns. In terms of neuromediators related area, the medial raphe and the locus coeruleus are also more connected in more intolerant species, suggesting an involvement of serotonin and noradrenaline in the species-specific behavioural modulations involved in variations in social tolerance grades. Differences in the limbic circuits may be rooted in genetic differences among species or the consequences of living in more or less despotic and violent monkey societies. Our model accounts for the effect of age on these neuronal connections, allowing us to tackle the innate versus acquired dimension of our results. In summary, our analysis is unique in its use of rarely studied macaque species to further identify neural circuitry that has evolved to adapt primates' social and emotional

behaviours. Further research will focus on cortical connectivity to investigate correlates of social tolerance grades using similar methods. Overall, our study highlights the intricate relationship between limbic circuitry connectivity and social behaviour in macaque monkeys. These findings provide valuable insights into the neural mechanisms of sociality and emphasize the importance of species-specific studies in understanding the evolution of the social brain of primates

Disclosures: S. Silvere: None. **C. Po:** None. **J. Sallet:** None. **J. Lamy:** None. **S. Ballesta:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.046/LBA132

Topic: H.06. Social Cognition

Title: Effects of group huddling on individual sleep dynamics and neural activity in mice

Authors: *J. LEE[1], B. KIM[2], I. TIKHONOV[3], H.-B. HAN[4], J. CHOI[3];
[1]Korea Inst. of Sci. and Technology, Korea Univ., Seoul, Korea, Republic of; [2]Univ. of Pennsylvania, Pennsylvania, PA; [3]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [4]MIT, Cambridge, MA

Abstract: Huddling, or sleeping together in physical contact, is a thermoregulatory behavior observed in social animals. Mice, known as social animals, also exhibit group sleeping behavior. While individual sleep patterns have traditionally been the focus, recent studies have highlighted synchronization in sleep initiation and waking times during group sleep. However, the effects of group sleep on neural activities remain less understood. This study aimed to investigate changes in sleep patterns when mice huddle in groups compared to when they sleep alone. We conducted 12-hour recordings using wireless neurophysiological devices and video monitoring. Each experimental group consisted of four male mice, with recordings of each mouse alone on one day and all four mice together on the next day. We collected electroencephalogram (EEG) from the frontal and parietal cortex, along with electromyography (EMG) signals from neck muscles using CBRAIN (Kim et al., Sci Adv, 2023). Our findings revealed that group sleep reduced the duration of both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep phases. As overall wakefulness increased, the REM to NREM ratio decreased. Despite the stable power across different frequencies in both sleep conditions in each sleep state, we noted a peak frequency shift in the theta band (5 - 10 Hz) during REM sleep for huddled mice. Furthermore, phase synchrony in the theta band during REM sleep increased among the huddling mice, indicating enhanced inter-brain synchrony. These results highlight the significant influence of huddling on neural activity during sleep in mice as showing theta coherence during REM sleep, indicating potential mutual modulation of neural activity in social sleep dynamics.

Disclosures: J. Lee: None. **B. Kim:** None. **I. Tikhonov:** None. **H. Han:** None. **J. Choi:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.047/LBA133

Topic: H.06. Social Cognition

Support: R01 MH132727

Title: Hippocampal-vmpfc interactions predict distortions in memory for social feedback

Authors: *G. SHIN[1], M. QUAMLEY[3], J. M. JARCHO[4], V. P. MURTY[2];
[2]Psychology, [1]Univ. of Oregon, Eugene, OR; [3]Neuropsychiatry, Hosp. of the Univ. of Pennsylvania, Philadelphia, PA; [4]Psychology and Neurosci., Temple Univ., Philadelphia, PA

Abstract: To adaptively navigate our social world, it is important for individuals to store memories of prior social interactions. A large amount of behavioral literature has shown that memories can be distorted by schemas, including recent work from our lab that shows a strong positivity bias for social feedback (Johnston et al., 2023). However, research has yet to characterize the neural systems underlying successful and distorted social memories, and putative circuits underlying this well-documented positivity bias. Previous research has shown that the hippocampus is involved in successful encoding of social feedback, while the ventromedial prefrontal cortex (vmPFC) is thought to hold social schemas. In this study, we examined the interactions between the anterior hippocampus (aHPC) and vmPFC during the encoding of social interactions to better understand the positive bias in social memory. Participants underwent fMRI while completing the Recall After Feedback Task, which included selecting which of two purported peers liked or disliked the participant based on their photo, encoding their subsequent feedback. A surprise cued response phase was completed after scanning. Using parametric analysis, we examined how brain activation during encoding related to subsequent recall of positive and negative social feedback. This univariate analysis revealed a positivity bias on subsequent social memory was exclusively related to aHPC engagement. To further understand how schemas may influence this process, we characterized aHPC-vmPFC connectivity and found that interactions between the aHPC and vmPFC resulted in distorted memories for positive, but not negative feedback. These results align with models suggesting that schemas distort memory for social feedback, providing a neural basis for the observed positive bias in memory recall and enhancing our understanding of the intricate relationship between brain regions involved in social cognition and memory formation.

Disclosures: G. Shin: None. **M. Quamley:** None. **J.M. Jarcho:** None. **V.P. Murty:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.048/LBA134

Topic: H.06. Social Cognition

Title: Predictive modeling of others' attention in the brain: Increased activity when expectations are violated

Authors: *S. KIMMEL[1], K. ZIMAN[2], M. S. GRAZIANO[1], I. CHRISTIAN[1];
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Psychological and Brain Sci., Princeton Univ., Princeton, NJ

Abstract: How do we conceptualize the minds of others? To understand what another person is thinking, or what they might do next, it can be useful to know what they are attending. For example, if I see John staring at a doughnut (overt attention), I might guess that he is hungry or thinking of eating the doughnut. Recent evidence suggests people do not just notice other people's attention, but rather, they build a rich predictive model of other people's attention. They predict how others' attention will move over time (e.g. noticing John is attending the doughnut and predicting he will next attend the coffee), and they know when that predictive model is violated. Here, we explore the neural basis of this process. We created videos showing where real people attended over time while naturalistically viewing images, using their eye tracking data. We then showed new subjects the videos with these natural attention sequences as well as artificially manipulated versions of the sequences. After each video, we asked the subjects to judge if the attention was from "a real person" or "a fake." In line with recent evidence, we find that people can correctly distinguish fake versus real attention sequences, comporting with a predictive modeling account. Second, we find that judging attention as "fake" versus "real" increases activity in brain regions associated with social cognition and visual attention. This suggests that subjects' discrimination of attention sequences is driven largely by increased blood flow to social and attention-related regions when attention sequences violate the expected pattern. These results shed light on the neural underpinnings of predictive attention modeling and the ways our brains conceptualize the minds of others.

Disclosures: S. Kimmel: None. **K. Ziman:** A. Employment/Salary (full or part-time):; Princeton University. **M.S. Graziano:** A. Employment/Salary (full or part-time):; Princeton University. **I. Christian:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.049/LBA135

Topic: H.07. Long-Term Memory

Support: FRQNT masters fellowship 330199

Title: Effects of blocking hippocampal amyloid-beta on long-term object memory

Authors: *C. SCIANDRA[1], X. GAO[1], A. LENG[1], D. DEVI DEWAN[1], O. M. HARDT[2,1]; [1]Psychology, McGill Univ., Montreal, QC, Canada; [2]The Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: The toxic dysregulated accumulation of the amyloid-beta (Aβ) protein in the brain is one key event in Alzheimer's disease (AD), characterized by synaptic dysfunction and memory impairments and disproportionately affecting aging women more so than aging men. (Scheyer et al., 2018) However, Aβ is also constitutively present in the healthy brain and its secretion follows synaptic activity and impacts memory processes and synaptic activity: while low concentrations of Aβ peptides promote long-term potentiation (LTP) and memory consolidation, high concentrations as well as complete or partial depletion of Aβ impair these processes and promote long-term depression (LTD) (Puzzo et al., 2013). However, these findings were obtained exclusively with male animals and using aversive conditioning tasks. Therefore, we aimed to examine the role of endogenous hippocampal Aβ in everyday (non-reinforced) memories in both sexes, using a rat model of declarative memory (one-trial novel object recognition task). Male and female Long-Evans rats (3-4 months old) were exposed to two identical objects in an open field for 5 min, followed by a test for long-term memory for these objects 24 h later. We blocked Aβ with the monoclonal antibody 4G8, specific to amino acid residues 17-24 of Aβ in aggregated and precursor forms, as well as a control antibody (MG2a-53). We infused these drugs into the dorsal hippocampi of rats before (i.e., to affect encoding) and after learning (i.e., to affect memory consolidation). Our results show that infusing the antibody before encoding strongly enhanced the acquisition of long-term object memories in female rats but had no effect on male rats. Furthermore, infusing the antibody during the consolidation phase had no effect on recognition memory in female rats compared to controls. These initial findings suggest that Aβ can promote formation of object memories in female but not in male rats, and highlight the importance of studying both sexes when investigating Aβ mechanisms in long-term memory. We are currently exploring whether sex-specific factors moderate these effects and test whether similar effects can be obtained during the forgetting of object memories, their reconsolidation, and retrieval.

Disclosures: C. Sciandra: None. **X. Gao:** None. **A. Leng:** None. **D. Devi Dewan:** None. **O.M. Hardt:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.050/LBA136

Topic: H.07. Long-Term Memory

Support: CIHR Grant PJT-153155

Title: Novel characterization of pacemaker neuron subtypes associated with differential memory consolidation following operant conditioning

Authors: *J. BANDURA[1], Z.-P. FENG[2];
[2]Dept. of Physiol., [1]Univ. of Toronto, Toronto, ON, Canada

Abstract: Associative learning is an essential physiological function. However, while the neural mechanisms underlying many forms of classical conditioning are well-defined, neural mechanisms of operant or instrumental conditioning have proven challenging to study due to the interactions of complex neural circuits in operant learning in mammals. The freshwater pond snail, mollusc *Lymnaea stagnalis*, can be used to great advantage to study LTM which forms following aversive operant conditioning of aerial respiratory behaviour (Lukowiak et al. 1996). Our lab has previously reported differences in the ability of animals to form LTM, which correlates with neuronal activity of the pacemaker neuron of the respiratory central pattern generator (Dong & Feng 2017), suggesting that within the same inbred laboratory population, endogenous differences in both basal respiratory behaviour and responses to conditioning exist. In this study, we hypothesized that endogenous population-level variability in basal respiratory behaviour is associated with behavioural and neural responses to operant conditioning. To test this hypothesis, we first conducted an in-depth, multiparametric characterization of endogenous differences in basal aerial respiration in a large population of inbred animals (n=285) to characterize three phenotypes of basal respiratory behaviour using unsupervised hierarchical clustering. We then conditioned (n=267) or yoked (n=18) animals and systematically categorized the distribution of behavioural responses to operant conditioning and identified four distinct underlying phenotypes of behavioural response. Finally, we characterized spontaneous and evoked activity in RPeD1 from trained snails exhibiting these phenotypes (n=33), and used a dimensionality reduction approach to identify four distinct electrophysiological clusters of RPeD1, of which two were associated with specific behavioural responses, including LTM formation. Using this combined behavioural, electrophysiological, and unsupervised clustering approach, we have for the first time systematically characterized phenotypes of respiratory behaviour and responses to conditioning present in a genetically similar population. Together, we report a correlation between electrophysiological identity of a pacemaker neuron and conditioning-related behaviour, suggesting that intrinsic properties of this neuron exhibit plasticity in response to learning. The neural mechanisms identified may thus constitute fundamental mechanisms of LTM formation following operant conditioning across species.

Disclosures: J. Bandura: None. **Z. Feng:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.051/LBA137

Topic: H.07. Long-Term Memory

Support: NIH Grant F31MH129073
NSF Grant 2123474

Title: Threat-related arousal bias of amygdala sub-nuclei and the medial temporal lobe during distance estimations in temporal memory of movie clips

Authors: *D. F. GREGORY[1], B. TANRIVERDI[2], E. COWAN[1], N. L. BALDERSTON[3], V. P. MURTY[4];
[2]Psychology and Neurosci., [1]Temple Univ., Philadelphia, PA; [3]Psychiatry, Univ. of Pennsylvania Deptartment of Psychiatry, Philadelphia, PA; [4]Psychology, Univ. of Oregon, Eugene, OR

Abstract: Threat-related arousal bias of amygdala subnuclei and the medial temporal lobe during distance estimations in temporal memory of movie clips
David F Gregory, Büşra Tanrıverdi, Emily T Cowan, Nicholas L Balderston, Vishnu P Murty
The capacity to form episodic memories of environmental threats is crucial to avoid future dangers. While most prior work on emotional memory has focused on how threat enhances item and spatial memory, relatively less research has focused on temporal memory. Here, we characterized the neural systems underlying the encoding of temporal distance of short movie clips that varied in arousal using fMRI. We focused our analyses on how amygdala sub-nuclei, including regions of interest (ROIs) of basolateral (BLA) and central-medial (CEM) sub-regions, interacted with the anterior hippocampus (aHIP) and perirhinal cortex (PRC). We found that functional coupling of the BLA with the aHIP predicted temporal compression of duration estimates at lower levels of arousal ($p<0.001$), but not high levels of arousal ($p=0.63$). Next, we found that functional coupling of the CEM to aHIP predicted temporal compression at high levels of arousal ($p=0.03$ but, surprisingly, temporal expansion at low arousal levels ($p=0.01$). Finally, we found that functional coupling of the CEM to PRC predicted temporal compression at high ($p=0.03$) but not low levels ($p=0.81$), however, the arousal by connectivity interaction of these ROIs was only marginally significant ($p = 0.09$). Together, these findings highlight circuits within the medial temporal lobe responsible for temporal memory, and how differential engagement across these circuits can modulate whether time is compressed or expanded in memory.

Disclosures: D.F. Gregory: None. **B. Tanriverdi:** None. **E. Cowan:** None. **N.L. Balderston:** None. **V.P. Murty:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.052/LBA138

Topic: H.07. Long-Term Memory

Title: Hippocampal damage is associated with deficits in social and emotional semantic knowledge

Authors: A. BOYD[1], D. TRANEL[2], *N. KLOOSTER[1];
[1]Hope Col., Holland, MI; [2]Dept Neurol, Univ. of Iowa, Iowa City, IA

Abstract: Semantic memory includes general knowledge about the world that is collected and adapted over time through learning experiences. This includes social and emotional knowledge that equips individuals with the information needed to understand, navigate, and interact with other people. It's been established that the hippocampus plays a critical role in memory acquisition. If the hippocampus is involved in enriching semantic memories over time, how does damage impact an individual's social and emotional semantic knowledge? Building on prior work, we hypothesized that social and emotional semantic knowledge would be impoverished in patients with bilateral hippocampal damage. To evaluate the relationship between such damage and social and emotional semantic knowledge, we compared semantic memory of participants with bilateral hippocampal damage (n=5) to that of a targeted brain-damaged comparison group of participants with bilateral lesions in the ventromedial prefrontal cortex (n=5), and a demographically-matched non-brain damaged comparison group (n=25). In our measures of semantic richness, target words with social meanings and emotional ratings were chosen from normed databases, and participants listed features and senses relevant to each item. Results indicate that patients with hippocampal damage performed significantly worse than both comparison groups ($p<0.001$). Patients can recognize these words, name pictures of the tangible nouns, and understand their basic meaning. The initial acquisition happened before hippocampal damage, and that information remains intact. While the patients produced some of the features and senses on demand, their knowledge is not as extensive and rich as the comparison groups'. The results support our hypothesis and suggest that the hippocampus may be critical to updating and enriching knowledge over time. The hippocampus is not typically considered a structure that supports social and emotional cognition. However, our work suggests that the hippocampus plays a crucial role in expanding the knowledge base which other cognitive processes use to support behavior. These findings have potential implications for other patient groups with hippocampal dysfunction and deficits in social and emotional behavior such as individuals with Alzheimer's disease, depression, schizophrenia, epilepsy, and autism.

Disclosures: A. Boyd: None. **D. Tranel:** None. **N. Klooster:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.053/LBA139

Topic: H.07. Long-Term Memory

Support: ERC Grant 101001121

Title: From learning to memory-guided action

Authors: *P. BÜCHEL[1,2,3], J. KLINGSPOHR[2,3], M. S. KEHL[2], B. STARESINA[2];
[1]Univ. of Bonn, Bonn, Germany; [2]Univ. of Oxford, Oxford, United Kingdom; [3]Univ. of Groningen, Groningen, Netherlands

Abstract: Learning never stops. As we navigate life, we continuously acquire and update knowledge to optimise memory-guided action, with a gradual shift from the former to the latter as we master our environment. How are these learning dynamics expressed in brain and behavioural patterns? Here, we devised a spatiotemporal image learning task (‘Memory Arena’) in which participants (n = 27) learn a set of 50 items to criterion across repeated exposure blocks. Critically, brief task-free periods between successive image presentations allowed us to assess multivariate electroencephalogram (EEG) patterns representing the previous and/or upcoming image identity as well as anticipatory eye movements towards the upcoming image location. As expected, participants eventually met the performance criterion, albeit with different learning rates. During task-free periods, we were able to readily decode representations of both previous and upcoming image identities. Importantly though, decoding strength followed opposing slopes for previous vs. upcoming images across time, with a gradual decline of evidence for the previous image and a gradual increase of evidence for the upcoming image. Moreover, the ratio of upcoming vs. previous image evidence directly followed behavioural learning rates. Finally, eye movement data revealed that participants increasingly used the task-free period to anticipate upcoming image locations, with target-precision slopes parallelling both behavioural performance measures as well as EEG decodability of the upcoming image across time. Together, these results unveil the neural and behavioural dynamics underlying the gradual transition from learning to memory-guided action.

Disclosures: P. Büchel: None. **J. Klingspohr:** None. **M.S. Kehl:** None. **B. Staresina:** None.

Late-Breaking Poster

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Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.054/LBA140

Topic: H.07. Long-Term Memory

Support: ONR N00014-22-1-2123

Title: Memory set size and delay effects on ERP measures of visual recognition memory

Authors: *I. UTOCHKIN, J. PEISO, E. K. VOGEL;
Inst. for Mind and Biol., Univ. of Chicago, Chicago, IL

Abstract: Neural correlates of recognition memory, an ability to distinguish between previously experienced and new events, include specific event-related potential (ERP) markers referred to as ERP old/new effects. They include an earlier mid-frontal negativity (FN400), and a later posterior complex (LPC) presumably reflecting different aspects of recognition (e.g., familiarity vs. recollection, decision making, confidence, etc.) (Rugg & Curran, 2007). We have previously found (Utochkin et al., SfN 2023) that the ERP old/new effects were highly sensitive to the amount of information (memory set size, MSS) stored in visual memory. Our participants studied 8, 32, or, 64 sequentially presented object images and were tested with a standard old/new task when old and new items are presented one at a time and the observer has to decide whether a given item is old or new. We found that smaller MSS were correlated with larger and earlier ERP old/new effects (differences between ERP's to old and new items, both in the frontal and parietal clusters). Our new study aimed to figure out whether this effect was driven by MSS per se (factors related to the number of stored items and overall memory load) or by temporal factors such as delay between item occurrences at study and test (for example, the average delay in MSS8 was shorter than in MSS32 or 64 because both the study and test phases were also shorter). In the new experiment, participants studied lists of MSS 10 or 32. In "MSS10" blocks, memory was tested with all 10 studied items and 10 new items. In "MSS32" blocks, memory was tested either using the last 8, middle 2 studied items and 10 new items ("MSS32 - last"), or using the first 8, middle 2 studied and 10 new items ("MSS32 - first"). Therefore, "MSS32 - last" had the same study test-delay as "MSS10" but different MSS. We found the strongest ERP old/new effects in both frontal (F3, F4, Fz, Fc1, Fc2, Fc5, Fc6) and posterior (P3, P7, P4, P8, Cp1, Cp2, Pz) clusters of electrodes for "MSS10". It was followed by the "MS32-first" and then "MSS32-last" condition in the frontal cluster suggesting the *primacy* advantage. In the parietal cluster, we found no differences between the first and last tested items from MSS32. Our results suggest that MSS per se is an important determinant of ERP old/new effects, although study-test delay can further moderate its influence.

Disclosures: I. Utochkin: None. **J. Peiso:** None. **E.K. Vogel:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.055/LBA141

Topic: H.07. Long-Term Memory

Support: Rutherford Discovery Fellowship (RDF-10-UOA-024)

Title: Using cathodal transcranial direct current stimulation to investigate cerebellar contributions to autobiographical memory

Authors: *A. LI-CHAY-CHUNG[1,2,3], L. J. TIPPETT[4,5], K. D. WILSON[6], R. S. ROSENBAUM[1,2,3], D. ADDIS[3,4,7];
[1]Dept. of Psychology, [2]Ctr. for Integrative and Applied Neurosci., York Univ., Toronto, ON, Canada; [3]Rotman Res. Inst. at Baycrest Hlth. Sci., Toronto, ON, Canada; [4]Sch. of Psychology, [5]Ctr. for Brain Res., The Univ. of Auckland, Auckland, New Zealand; [6]Dept. of Psychology, Gettysburg Col., Gettysburg, PA; [7]Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada

Abstract: The cerebellum is best known for its critical role in motor control. However, increasing evidence suggests a role in non-motor, cognitive processes, including autobiographical memory (AM) for personal experiences. Specifically, fMRI in healthy adults has implicated posterior cerebellar regions Crus I/II in AM, including task-related functional connectivity with default mode network regions known to support episodic memory. Brain stimulation methods such as transcranial direct current stimulation (tDCS) have further elucidated a role for the cerebellum in cognition, but, to our knowledge, it has not yet been leveraged to investigate how the cerebellum contributes to AM. We examined the effects of cathodal tDCS on the recall of AMs. Per the traditional "anodal-excitatory, cathodal-inhibitory" assumption, we predicted that the amount of episodic content of AMs would be reduced upon applying cathodal tDCS to the cerebellum. Eighteen healthy participants (aged 18 to 24 years; 15 female, 3 male) underwent 3 sessions of 20-minute tDCS, approximately 7 days apart. Each session involved one of three stimulation conditions, counterbalanced across participants: (a) cathodal right cerebellar, (b) cathodal left dorsolateral prefrontal cortex (dlPFC), or (c) sham right cerebellar. Participants also completed a cued-recall AM task, where they viewed a cue word (e.g. "pencil") and then recalled aloud a corresponding AM for a maximum of 1 minute. Participants recalled a total of 20 different AMs in each session; we later transcribed audio-recorded AMs for analysis. We used the Automated Autobiographical Interview scoring tool to estimate the amount of episodic and non-episodic content comprising each AM. A two-way ANOVA on AM content showed a main effect of content type, with AMs comprising more episodic than non-episodic content across all stimulation conditions ($p < .001$). This effect was qualified by a significant Content Type x Stimulation interaction ($p = .039$), which revealed that during cathodal stimulation of the right cerebellum, AMs comprised less episodic and more non-episodic content relative to those recalled under cathodal left dlPFC stimulation and sham right cerebellar stimulation. These findings suggest that the right cerebellum may be particularly involved in the retrieval of the episodic relative to non-episodic details comprising AMs. Overall, this study informs our knowledge of cerebellar involvement in AM and the utility of cathodal tDCS in investigating naturalistic cognitive processes.

Disclosures: A. Li-Chay-Chung: None. **L.J. Tippett:** None. **K.D. Wilson:** None. **R.S. Rosenbaum:** None. **D. Addis:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.056/LBA142

Topic: H.07. Long-Term Memory

Support: JST ERATO (JPMJER1801)
JSPS Grants-in-Aid for Scientific Research (22K21353)
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the Institute for AI and Beyond of the University of Tokyo
the Pharmacological Research Foundation, Tokyo

Title: Neural activity in the hippocampus and prefrontal cortex of ramelteon-treated mice associated with novel object recognition memory.

Authors: *K. TAKEDA, K. WATANABE, S. IIJIMA, Y. IKEGAYA, N. MATSUMOTO; The Univ. of Tokyo, Tokyo, Japan

Abstract: Ramelteon, a drug used to treat circadian rhythm disorders, is a specific agonist for melatonin receptors, demonstrating a high affinity for MT1 and MT2 receptors. Previous research has shown that ramelteon has no significant effect on memory performance assessed by behavioral tasks with stress or rewards/punishments. However, we recently demonstrated that intraperitoneal injection of ramelteon enhances the acquisition of object recognition memory in the absence of reward or punishment. The hippocampus, prefrontal cortex (PFC), and their interactions are believed to be responsible for object recognition memory, but at the electrophysiological level, it remains unknown how neural activity in these two regions is affected by ramelteon when mice acquire object recognition memory. To explore neural correlates of this improvement in object recognition memory, we chronically implanted nichrome electrodes into the hippocampus and PFC of mice and recorded the neural activity of mice engaged in an object recognition task. In this task, the mouse was allowed to explore an open field with two identical objects for 10 min on the first day (Day 1; training session). On the next day (Day 2; test session), the mouse explored the open field with one object replaced by a novel object for 10 min. Performance in the novel object recognition task was assessed by a discrimination ratio defined as (N-F)/(N+F), where N and F represent time spent in areas around the novel and familiar objects, respectively. Using Hilbert transform, we then examined neural activity in the hippocampus and PFC in terms of the power of delta, theta, beta, low gamma, and high gamma frequency bands. We found that ramelteon increased theta and high gamma power in the hippocampus and PFC, respectively, when mice encountered novel objects. Based on these

results, we hypothesize that ramelteon improves memory performance by modulating theta oscillations in the hippocampus and high gamma oscillations in the PFC. We will further investigate (1) whether neural activity during sleep is affected by ramelteon on Days 1 and 2, and (2) whether and how neural activity in the hippocampus and PFC is coupled when mice sleep and behave on Days 1 and 2.

Disclosures: K. Takeda: None. **K. Watanabe:** None. **S. Iijima:** None. **Y. Ikegaya:** None. **N. Matsumoto:** None.

Late-Breaking Poster

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Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.057/LBA143

Topic: H.08. Learning and Memory

Support: Children's Hospital of Zhejiang University School of Medicine Pre-Research Fund (CHZJU2023YY006)

Title: Dopamine D2 Receptor Modulating mPFC-BLA Circuitry Contributes to Chronic Sleep Deprivation-Induced Memory Impairment in Mice

Authors: *J. ZHU;
Children’s Hospital, Zhejiang Univ. Sch. of Med., Hang zhou, Zhejiang province, China

Abstract: Insufficient sleep significantly affects the orchestration of neural networks, leading to cognitive impairment. However, the molecular & neural circuitry gating cognitive deficits induced by sleep deprivation remain largely unexplored. Here, we reported that a chronic sleep deprivation (CSD) model, characterized by disrupting rapid eye movement (REM) sleep & disinhibiting REM-specific dopaminergic input to the medial prefrontal cortex (mPFC), markedly impaired spatial memory assessed using the Y maze in mice. Transcriptome & immunofluorescent analysis revealed a significant increase of dopamine D2 receptor (Drd2) expression, specifically in layers II & III of the mPFC after CSD. Infusion of a Drd2 agonist into the mPFC reduced spatial memory in mice without sleep deprivation, while the Drd2 antagonist reversed the deficits caused by CSD. Furthermore, we found that Drd2 co-localized with Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) positive neurons, which projected widely to various brains including the basolateral amygdala (BLA). During novel arm exploration, a significant increase in calcium influx was observed in these CaMKIIα^{+} neurons, indicating their involvement in processing spatial memory. Optogenetic activation of CaMKIIα^{+} neurons during the task rescued memory impairment induced by CSD through enhancing output to the BLA. Additionally, stimulating these BLA-projecting neurons in the mPFC reversed memory defects induced by the Drd2 agonist. Our findings clearly demonstrated that excessive Drd2 signaling

after CSD suppresses mPFC-BLA neurotransmission during spatial memory tasks & thus leads to working memory impairment. Our work suggests a possible therapeutic value of dopamine D2 receptor antagonists relieving CSD-induced cognitive decline.

Disclosures: J. Zhu: None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.058/LBA144

Topic: H.08. Learning and Memory

Support: NSF-DRL Grant 2100137
NSF-DRL Grant 2100138

Title: Neural correlates of learning differences as determinants of design fixation

Authors: D. KIM[1], J. MILOVANOVIC[2], U. KANNENGIESSER[3], J. GERO[2], *E. CHRYSIKOU[4];
[1]Northwestern Univ., Chicago, IL; [2]Computer Sci. & Architecture, Univ. of North Carolina Charlotte, Charlotte, NC; [3]Johannes Kepler Univ. Linz, Linz, Austria; [4]Psychological & Brain Sci., Drexel Univ., Philadelphia, PA

Abstract: Past research has shown that the inclusion of pictures as examples in design problem solving fosters designers' propensity to adhere to those examples, a phenomenon known as design fixation. In this study, we examined whether individual differences in learning tendencies during concept building might underlie one's susceptibility to design fixation. We hypothesized that an exemplar-based learning approach, as reflected in brain activity patterns, would amplify the impact of the examples in design problems by heightening the prominence of specific design features over the abstract relationships that bind them. Conversely, an abstraction-based learning approach might prioritize the abstract design rules governing example designs, providing protection from adhering to specific design features of the example and thus, design fixation. To test these hypotheses, mechanical engineering students participated in two experimental sessions. The first session involved completing a learning task and multiple behavioral assessments; in the second session, they underwent a functional magnetic resonance imaging scan (fMRI), while completing learning and two design tasks using a sketching tablet compatible with the imaging environment. Participants' thought processes during task completion were captured through simultaneous verbal protocols during the scans. A classification of design events via verbal protocol analysis using the Function, Behavior, Structure (FBS) ontology for design, in conjunction with the coding of the designs produced revealed an extensive frontoparietal network of regions associated with the propensity for design fixation. We discuss the importance

of adopting a real-world, multimethod approach to quantify design fixation, learning tendencies, and individual differences through diverse neurocognitive assessments.

Disclosures: D. Kim: None. **J. Milovanovic:** None. **U. Kannengiesser:** None. **J. Gero:** None. **E. Chrysikou:** None.

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LBA008: Theme H Late-Breaking Posters

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Program #/Poster #: LBA008.059/LBA145

Topic: H.08. Learning and Memory

Support: Brain and Behavioral Research Foundation (NARSAD) Young Investigator Grant 31146
UT Southwestern Endowed Scholarship
the UT System Rising STARs Award

Title: Task learning context influences spontaneous behavior: an analysis of striatal signals

Authors: *M. KIM[1], P. GAMAGE[3], R. YANG[2], D. NAVARRO[2], D. ZHANG[4], N. LI[5];
[1]AIRC, [2]UTSW, Dallas, TX; [3]Univ. of Colombo, Colombo, Sri Lanka; [4]janelia research campus, Janelia Res. Campus, ashburn, VA; [5]Advanced Imaging Res. Ctr., UT Southwestern Med. Ctr., Dallas, TX

Abstract: Dopamine (DA) transmission and spiny projection neuron (SPN) activity are critical for learning signals in the striatum. Despite extensive research on the functional correlations among learning elements (cue, reward, and action), how these elements change within the dorsal striatum during learning remains unclear. We hypothesized that varying learning rules requiring different actions would affect both task-specific and spontaneous behaviors during intertrial intervals (ITIs).
To test this, we trained head-fixed mice to perform anticipatory licking tasks in response to visual cues through Pavlovian conditioning. Mice were then conditioned to withhold licking upon cue presentation, with rewards based on task rules. We monitored their licking patterns and simultaneously measured DA transient and SPN activity in the dorsolateral striatum (DLS) using dual-color fiber photometry. This approach allows us to explore how behavior and striatal signals adapt during learning and how striatal circuitry connects task execution to preparatory periods. We observed distinct spontaneous licking patterns during ITIs, reflecting learned behaviors of producing either a rapid sequence of licks (burst) or a single lick. During Pavlovian training, most mice reduced overall spontaneous licking during ITIs, but the frequency of long lick bursts increased compared to short bursts as learning progressed. This ratio was disrupted by the introduction of a no-lick rule.

To determine if DA signals in the DLS correspond to these behavioral changes, we analyzed DA transient traces aligned with the onset of spontaneous licking. The traces showed consistent negative deflections at the onset of lick bursts, with variability in timing and shape. We applied elastic shape analysis for phase-amplitude separation of DA traces and used a linear mixed-effects regression model with non-linear functions to examine how experimental parameters affect negative phasic DA dynamics. Preliminary results suggest that DA response amplitude to spontaneous licking was significantly influenced by learning type, stage, and lick burst size. While DA signals in response to cues and rewards generally show phasic excitation, we observed inhibitory patterns with spontaneous licking. This indicates that striatal DA signaling differentiates between cue- and reward-related actions and non-reward-related spontaneous actions. We plan to confirm these findings across a larger cohort and further explore the relationship between calcium activity in D1- and D2-SPN populations and DA signals.

Disclosures: M. Kim: None. **P. Gamage:** None. **R. Yang:** None. **D. Navarro:** None. **D. Zhang:** None. **N. Li:** None.

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LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.060/LBA146

Topic: H.08. Learning and Memory

Support: R01-AG082645
R01-AG063775

Title: Beta band temporal interference stimulation at striatum facilitates human habitual learning

Authors: *W. WEN[1], D. HAZEL[2], S. SCHALLIES[1], C. WANG[1], C. LIN[1], Y. HUANG[3], R. M. REINHART[1];
[1]Boston Univ., Boston, MA; [2]Dept. of Biol., Tufts Univ., Medford, MA; [3]Soterix Med., Woodbridge, NJ

Abstract: Instruction-based learning characterizes the remarkable human intelligence in acquiring new skills bypassing the need for repetitive stimulus-response mapping. This rapid learning relies on transforming the declarative instructions into an action-oriented representation, which is mediated by the frontostriatal circuit. In the present study, we designed an original rule-guided working memory (WM) task requiring learning and updating of goal sets to achieve proficiency. During the instruction phase, participants memorize the cue-task-response associations which change between blocks. During the implementation phase, participants must select the relevant cue-task associations stored in WM and execute precise motor responses. Habitual learning is assessed by measuring changes in reaction times from the first to the last

trial within each block. To facilitate habitual learning, we designed a four-electrode configuration of noninvasive temporal interference (TI) stimulation targeting the right striatum. The focality and intensity were validated by large-scale simulation on over 600 individual anatomies. Participants performed the rule-guided WM task before, during and after 30 minutes of TI stimulation. Using TI stimulation with unprecedented precision, we found that entraining striatal beta band (20Hz) rhythmics in humans significantly enhances habitual learning. This effect was noted without altering overall response speed, task switching, or rule updating, as compared to a sham stimulation group. The spatial and frequency specificity of the facilitation effect was further supported by null results in the spatial control group with 20Hz TI over the right temporal and the frequency control group with 5Hz over the right striatum. Moreover, the facilitation effect was observed to be lateralized to the right striatum, but not the left. These findings establish a causal relationship between right striatal beta dynamics and rapid instruction-based learning.

Disclosures: W. Wen: None. **D. Hazel:** None. **S. Schallies:** None. **C. Wang:** None. **C. Lin:** None. **Y. Huang:** None. **R.M. Reinhart:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.061/LBA147

Topic: H.08. Learning and Memory

Support: NIMH Grant R01 MH119179
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Kavli Foundation Postdoctoral Fellow

Title: Theta sequences in hippocampus persist during periods of immobility and predict the upcoming choice during spatial working memory

Authors: *M. WANG[1], Y. LI[1], P. EE[1], J. ZHU[1], S. LEUTGEB[1,2], J. K. LEUTGEB[1,2]; [1]Neurobio. Department, Sch. of Biol. Sci., [2]Kavli Inst. for Brain and Mind, UCSD, San Diego, CA

Abstract: Memory coding occurs during both movement and immobility in behavioral tasks. The theta rhythm (4-12 Hz) in the hippocampus is dominant during movement, coordinates place cell activity, and forms short virtual spatial paths aligned with the animal's actual trajectory ("theta sequences"). When an animal pauses, the movement-related theta rhythm is believed to dissipate in CA1, along with the related memory coding processes. It is unknown whether and how theta-related memory coding can persist during immobility. To investigate this question, we used Neuropixels probes to record laminar neural activity profiles throughout dorsal

hippocampal subregions of 4 male and 4 female rats while they performed a spatial working memory task. We did not only observe prominent theta oscillations throughout all subregions during movement, but also identified theta oscillations in the outer molecular layer of the dentate gyrus that remained detectable during pauses (running speed < 1 cm/sec), and in particular, during the period after the animals consumed a reward ("immobility theta"). Simultaneous recordings showed that theta oscillations in CA1 were not readily detectable during the same period. Current source density analysis revealed that the neuronal activity profiles during immobility theta were similar to those during movement. Furthermore, single-unit analysis showed that theta phase-locking of hippocampal neurons was as pronounced during immobility as during movement theta. We next decoded the information content of hippocampal spikes using a Bayesian probability algorithm and found theta sequences during immobility theta periods while animals paused in reward zones and at choice points in the task. In contrast to theta sequences during movement, remote locations were preferentially represented during theta sequences at pauses, and the immediate next choice of the animal was more likely to be represented than more temporally distant future choices. These novel findings indicate that theta sequences during immobility may serve as a fundamental mechanism for memory coding outside of moving periods and will provide important insights for learning and memory retention across behavioral states.

Disclosures: M. Wang: None. **Y. Li:** None. **P. Ee:** None. **J. zhu:** None. **S. Leutgeb:** None. **J.K. Leutgeb:** None.

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LBA008: Theme H Late-Breaking Posters

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Title: Single field evolution rule governs the dynamics of representational drift in mouse hippocampal dorsal CA1 region

Authors: C. CHEN[1], ***S. YAO**[1], C. MIAO[2];
[1]Peking Univ., Beijing, China; [2]Peking Univ., China, China

Abstract: How the brain reconciles dynamism with stability to balance learning and reliable memory storage has not yet been fully understood. To address the critical question, we

longitudinally recorded place cells in the hippocampal dorsal CA1 (dCA1) region over 7 to 56 days, utilizing multiple goal-oriented navigation paradigms across various complex environments. Our findings revealed that over 80% of place cells exhibit multiple place fields, demonstrating canonical statistical structures, limited relative heterogeneity in neuronal propensity, and high independence of the properties of sibling fields (i.e., place fields of the same neuron). Rich in complex evolution events involving combinations of the disappearance, the formation, and the retention of place fields, we confirmed that sibling fields evolve nearly independently with only ~5% coordination, preferring synchronized changes. Given the approximately independent evolution of individual place fields, we uncovered the Single Field Evolution Rule (SFER): the longer a field remains active, the more likely it is to continue being active; conversely, the longer a field remains inactive, the less likely it is to recover. We quantitatively described SFER in probabilistic form, suggesting the convergent dynamics of dCA1 representational drift. Mathematical modeling revealed that the SFER sufficiently demonstrates the growing stability of the dCA1 spatial representation at the population level. Based on the unique and extensive dataset rich in multi-field dCA1 place cells, our accurate measurement of drift rate and statistical estimation of SFER provide a congruent description of the dynamism-stability duality, offering compelling evidence and fresh insight into the long-term dynamics of representational drift in dCA1.

Disclosures: C. Chen: None. **S. Yao:** None. **C. Miao:** None.

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Support: NIH Grant NS086947
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Walter F. Heiligenberg Professorship

Title: Time cell sequences in the medial entorhinal cortex are prolonged by ongoing theta oscillations

Authors: Y. LI[1], J. WANG[1], W. LI[1], J. K. LEUTGEB[1,2], ***S. LEUTGEB**[1,2,3];
[1]Univ. of California San Diego, La Jolla, CA; [2]Inst. for Advanced Study, Berlin, Germany; [3]Kavli Inst. for Brain and Mind, San Diego, CA

Abstract: Cells that are sequentially active on a behavioral time scale (‘time cells’) have been proposed to support diverse cognitive functions, such as temporal discrimination and working

memory. Despite the potential importance of these cells and initial reports that hippocampal time cell sequences can span periods of up to 20 s, this finding has not been consistently confirmed. For example, sequences of hippocampal time cells were found to last no longer than ~5 s in a spatial working memory task with delay intervals of up to 60 s (Sabariego et al., Neuron, 2019, 102:1235). Because their version of the working memory task did not require movement during the delay interval, it is possible that more prolonged time cell sequences only emerge with running in a wheel or on a treadmill during the delay, which elicits sustained theta oscillations. To test this hypothesis, we trained rats in a delayed spatial alternation task that included trials with or without running on a treadmill in the delay zone. As expected, the manipulation resulted in significant differences in amplitude and duration of theta oscillations during the delay. Despite these major differences, we found that time cell sequences in the entire hippocampus (n = 123 time cells of 447 principal cells in dorsal CA1/CA3/DG, 37 of 257 in ventral CA1/CA3/DG) did not extend beyond ~5 s irrespective of the treadmill status. In contrast, time cell sequences in the dorsal medial entorhinal cortex (MEC; n = 180 time cells of 402 principal cells) were strongly dependent on theta oscillations. MEC time cell sequences lasted for only ~5 s without persistent theta (i.e., treadmill off), but for ~15 s with ongoing theta oscillations (i.e., treadmill on). Cells with time fields between 5 s and 15 s in the treadmill-on condition became broadly active or turned off in the treadmill-off condition. In addition, a high proportion of grid cells were identified as time cells, and we observed that many MEC cells, but not hippocampal cells, modulated their firing rate dependent on upcoming right or left turns. In ventral MEC (n = 119 time cells of 553 principal cells), we observed similar patterns as in dorsal MEC, but the temporal firing fields of ventral cells were generally elongated, except during the first few seconds. Taken together, these findings imply that major differences between temporal firing patterns in hippocampus and MEC emerge in theta states. In MEC, the sequential activity of cells over time, including of grid cells, depends to a much larger extent on ongoing theta oscillations. Entorhinal computations are therefore governed by oscillatory neuronal firing patterns to a larger extent than those in connected brain regions.

Disclosures: Y. Li: None. **J. Wang:** None. **W. Li:** None. **J.K. Leutgeb:** None. **S. Leutgeb:** None.

Late-Breaking Poster

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Topic: H.08. Learning and Memory

Support: Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project-ID 434434223 – SFB 1461

Title: Investigating the hippocampal circuitry in Anolis carolinensis: Structural and functional Insights into spatial information processing in the lizards' cortex

Authors: *N. RÖHRDANZ[1,2], P. MENON[2], K. BALUEVA[2], P. WULFF[2];
[1]Inst. of Physiol., Christian-Albrechts-Universität zu Kiel, Hamburg, Germany; [2]Inst. of Physiology, Univ. of Kiel, Kiel, Germany

Abstract: The lizard *Anolis carolinensis* is an interesting model organism in cognitive neuroscience as it possesses an evolutionary early three-layered hippocampal homologue. Behavioral studies suggest that lizards are able to perform similar hippocampus-dependent cognitive tasks as mammals but it is not known whether the functional organization in reptiles is the same as in mammals.To reveal hippocampal substructures in *Anolis carolinensis* , we analyzed the expression of genes known to be specifically expressed in the murine hippocampal formation and its subregions. We find a homologous region to the dentate gyrus in the lizards' medial cortex as well as homologous regions to the cornu ammonis region in the lizards dorsomedial to dorsal cortex.We investigated the participation of hippocampal substructures in processing spatial input using immediate early gene imaging in *Anolis carolinensis*. After exposure to a novel context, we find an increase in active cells especially in the medial cortex. Our data support the presence of an early hippocampal structure in the cortex of *Anolis carolinensis*. This structure shares functional principles with the mammalian hippocampus. Further research combining different behavioral paradigms with immediate early imaging will help us to further probe for functional homology and identify hippocampal sub-circuits in the lizard.

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Late-Breaking Poster

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Topic: H.08. Learning and Memory

Support: NIH Grant R01 AG074339
NIH Grant 5F32AG071263-02

Title: Mnemonic Integration Within and Across Spatial Contexts in Young and Older Adults Using Desktop Virtual Reality

Authors: *J. PARK[1], T. T. TRAN[2], K. NGUYEN[2], I. SAI[3], L. MEDINA GUERRA[3], E. C. MORMINO[3], A. D. WAGNER[2];
[2]Psychology, [3]Neurol. and Neurolog. Sci., [1]Stanford Univ., Stanford, CA

Abstract: In the real world, spatial and temporal contexts provide rich details for episodic memories during both encoding and retrieval. During recall, the spatial and environmental context of an episodic memory can assist and serve as a retrieval cue (e.g., context reinstatement). Although reinstatement of the encoding context may facilitate memory retrieval in young adults, there are mixed findings in the aging literature. Some studies have shown a similar benefit of context reinstatement on retrieval in young and older adults, whereas others have shown minimal to no effect of context reinstatement in older adults. In the current experiment, we investigated whether encountering related, overlapping experiences within the same context facilitates memory integration and associative inference and whether effects of context on integration and inference interact with age. Using a desktop virtual reality paradigm, young (18-24 years old) and older (66-95 years old) adults navigated through a virtual environment that included three different contexts (a house, library, and museum). After navigating to and entering the first context, participants encoded pairs of stimuli shown on a virtual screen (referred to as AB pairs). Subsequently, they saw new overlapping pairs (i.e., BC pairs, where one item [B] was part of a previously learned pair [AB]). Critically, overlapping pairs were encountered either in the same context as the original AB pairs or in a different context. We hypothesized that when overlapping events are encountered in the same context, the spatial context would assist in memory integration and associative inference. In comparison, when overlapping events are encountered in different contexts, the context may differentiate the two related memories, decreasing memory integration. To test memory integration, participants performed a surprise associative inference test in a new context. As predicted, preliminary findings suggest that young adults show increased memory integration and associative inference for related events (AB, BC) learned within the same context compared to across different contexts. These findings suggest that context reinstatement during encoding subsequently benefits memory integration and associative inference at test. In comparison, older adults did not demonstrate this contextual reinstatement benefit, showing no difference in associative inference performance between pairs learned within the same vs. different spatial contexts. These findings should motivate future studies aimed at understanding the mechanisms that lead to a reduced benefit of contextual reinstatement in older adults compared to young adults.

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Program #/Poster #: LBA008.066/LBA152

Topic: H.08. Learning and Memory

Support: Alzheimer's Association Research Fellowship AARFD-22-972811

Title: Ventral hippocampus neurons encode meal-related memory

Authors: *L. DECARIE-SPAIN, S. E. KANOSKI;
USC, Los Angeles, CA

Abstract: The ability to encode and retrieve meal-related information is critical to efficiently guide energy acquisition and consumption, yet the underlying neural processes remain elusive. We set to illustrate the activity dynamics of ventral hippocampus (HPCv) neurons during meal consumption and characterize the profile and function of HPCv neurons engaged by eating in adult male Sprague-Dawley rats. Fiber photometry-based recording of dynamic bulk HPCv calcium-dependent activity during meal consumption (n=6) revealed dynamic increases in activity between eating bouts, the magnitude of which predicts subsequent performance in a meal location memory task. To evaluate a possible functional connection between HPCv neurons engaged by eating and meal-related memory, rats underwent targeted recombination in active populations (TRAP)-mediated ablation of HPCv neurons responsive to fasting ('Fasted'; n=10), meal consumption ('Fed'; n=11), or exposure to predator urine ('Coyote'; n=7). Ablation of HPCv meal-responsive neurons (Fed) impaired meal location memory without influencing food motivation or spatial memory for escape location. To identify the projection profile of HPCv meal-responsive neurons, a tamoxifen-inducible Fos-driven Cre-recombinase virus was paired with a Cre-dependent fluorescent tracer. Presence of axonal projections from the HPCv to the lateral hypothalamus (LHA) was specific to rats from the Fed (n=4) and not Fasted (n=5) group. Retrograde tracing confirmed that the majority HPCv◊LHA neurons express cFos following meal consumption (n=4). In rats expressing inhibitory chemogenetic receptors (hM4Di) in HPCv◊LHA neurons, infusion of clozapine-N-oxide (n=7), but not its vehicle (n=6), impaired meal location memory and decreased inter-meal intervals. [4] Finally, to characterize the genetic profile of HPCv meal-responsive neurons, the HPCv was harvested in the Fed (n=6) or Fasted (n=6) state for single-nucleus RNA sequencing. HPCv meal-responsive neurons are enriched in the serotonin receptor type 2a (Htr2a), and HPCv infusion of the Htr2a antagonist M100907 (n=7) impaired meal location memory and decreased inter-meal intervals. Collective results identify a population of HPCv neurons that dynamically respond during eating to encode meal-related memories.

Disclosures: L. Decarie-Spain: None. **S.E. Kanoski:** None.

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Topic: H.08. Learning and Memory

Support: NIH-NCCIH AT010903

Title: Exposure to chronic light cycle disruption impairs memory and hippocampus in adolescent mice

Authors: *A. BHAN[1], P. BONILLA VILLAMIL[2], A. SHANKS[2], A. PORCU[2];
[1]Dept. of drug discovery and biomedical sciences, [2]Dept. of Drug Discovery and Biomed. Sci., Univ. of South Carolina, Columbia, SC

Abstract: Currently, more than 80% of the global population experiences light-polluted skies, with China, India, and the United States ranking among the top three affected countries. Recent studies have linked these altered light environments to increased cognitive impairments in both adolescents and adults. The hippocampus, particularly the dentate gyrus (DG), not only plays a pivotal role in memory but also serves as a subordinate circadian oscillator. Over 10% of genes and proteins in this region exhibit circadian fluctuations and are associated with changes in synaptic and neuronal excitability. However, the impact of altered light environments of the DG during adolescence remains largely unexplored. To start addressing this gap, we exposed adolescent mice to either a light cycle disruption (LCD) paradigm involving 19 hours of light and 5 hours of darkness (19L:5D) for 5 days, followed by 12 hours of light and 12 hours of darkness (12L:12D) for 2 days, over a 4-week period or to a control condition of consistent 12L:12D for 7 days. In this model, adolescent mice were exposed to LED light during the dark phase, thereby extending light exposure for 5 out of 7 days. Subsequently, mice underwent novel-object recognition (NOR) test, and their brains were processed for circadian rhythms analysis and neurogenesis. We found that mice exposed to LCD exhibited reduced exploration time with the novel object and increased exploration time with the familiar object compared to the control group. Furthermore, we observed a phase advance in neuronal activity rhythms within the granule layer of the DG, along with changes in doublecortin expression, a marker for neurogenesis, indicating neuronal network alterations induced by aberrant light exposure. Given that G-protein coupled inwardly rectifying (GIRK) regulates neuronal activity rhythm in the DG, we also analyzed GIRK expression patterns at 4 different time points in mice exposed to LCD and control condition. Our data suggests that LCD may impair memory through alterations in neuronal physiology and activity in the DG. Further exploration of the molecular mechanisms regulating memory deficits induced by aberrant light exposure holds promising avenues for developing targeted interventions to mitigate the cognitive impairments associated with disrupted light environments.

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JSPS 21H05674
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Takeda Science Foundation
Uehara Memorial Foundation
The Mitsubishi Foundation

Title: Adult-born neuron reactivation in REM sleep for memory consolidation

Authors: *M. SAKAGUCHI[1], S. SRINIVASAN[1], I. KOYANAGI[1], P. VERGARA[1], Y. WANG[1], A. OHBA[1], T. NAOI[1], K. E. VOGT[1], Y. CHERASSE[1], N. KUTSUMURA[1], T. SAKURAI[2], T. TEZUKA[3];
[1]WPI-IIIS, Ibaraki, Japan; [2]Inst. of Med., [3]Fac. of Engineering, Information and Systems, Univ. of Tsukuba, Ibaraki, Japan

Abstract: Our comprehension of memory consolidation is still incomplete due to its prolonged and multifaceted nature. Prior research suggests that synchronizing memory reactivation with theta oscillation during rapid eye movement (REM) sleep is essential for this process. Notably, robust theta oscillations are observed in the dentate gyrus of the hippocampus, where a small population of its principal neurons continues to be generated in adulthood. These adult-born neurons are crucial in modulating hippocampal circuitry to support various memory functions. However, the correlation between their information content and its causality for memory-related behavior remains unknown. In this study, we utilized genetic tracing and optogenetic silencing to demonstrate that reactivation of adult-born neuron memory ensembles, consisting of approximately five neurons, during REM sleep is necessary for fear memory consolidation. Additionally, we discovered that a specific phase of theta oscillation during REM sleep provides a critical time window for synchronized adult-born neuron activity to consolidate associative fear memory. These findings offer causal evidence that the reactivation of adult-born neuron memory ensembles during REM sleep is essential for associative memory consolidation. Overall, this study provides mechanistic insights into how new neurons integrate into functional circuitry in the adult brain.
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Title: Chemogenetic silencing of dentate gyrus excitatory cells post-encoding disrupts memory consolidation.

Authors: *K. O. MCDONALD[1], A. S. PRABHU[2], R. G. DAY[3], S. J. ATON[4];
[1]Mol. Cell. and Developmental Biol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [3]Mol. Cell. and Developmental Biol., [2]Univ. of Michigan, Ann Arbor, MI; [4]Molecular, Cellular, and Developmental Biol., Univ. of Mchigan, Ann Arbor, MI

Abstract: Chemogenetic silencing of dentate gyrus excitatory cells post-encoding disrupts memory consolidation.
Katherine O. McDonald[1], Aditi S. Prabhu[1], Russell Day[1], Sara J. Aton[1]
[1]University of Michigan, Ann Arbor, Michigan
The dentate gyrus of the mammalian hippocampus plays an important role in memory encoding and recall. When this region is experimentally lesioned prior to learning, memories fail to encode properly. Additionally, memory deficits can also be observed when dentate gyrus excitatory granule cells are optogenetically inactivated during recall tests. While it is postulated that the dentate gyrus plays a role in memory consolidation, the period between memory encoding and recall, the role of this structure during this memory-stabilization period remains unclear. The necessity of the dentate gyrus in memory consolidation is debated and yet to be proven. In our present research, we chemogenetically inhibited excitatory cells within the mouse dentate gyrus immediately following training on one of two learning paradigms: object location memory and contextual fear memory. In both experiments, animals were administered compound 21 immediately following training to target the period of memory consolidation. Experimental animals showed a reduction in object location memory performance as well as a trend for reduced contextual fear memory recall. These data suggest that activity of excitatory dentate gyrus cells during the first few hours following learning may be necessary for proper memory consolidation for the first time. Because experimental sleep deprivation, which disrupts consolidation of both contextual fear and object location memories, suppresses activity in this same cell population, this further suggests a plausible mechanism for deprivation-induced memory disruption.

Disclosures: K.O. McDonald: None. **A.S. Prabhu:** None. **R.G. Day:** None. **S.J. Aton:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.070/LBA156

Topic: H.08. Learning and Memory

Support: SFB1280

Title: Representational dynamics during acquisition and extinction of human fear memories

Authors: *D. PACHECO[1], A. BOUYEURE[2], G. JACOB[1], K. LEHONGRE[3], V. LAMBRECQ[4], V. NAVARRO[5], L. SHEN[6], J. YANG[6], B. HAN[7], Q. CHEN[6], N. AXMACHER[1];
[1]Ruhr Univ. Bochum, Bochum, Germany; [2]Univ. Paris-Descartes UMR1129, Gif Sur Yvette Cedex, France; [3]INSERM, Paris, France; [4]INSERM, PARIS, France; [5]Neurol., INSERM, Paris, France; [6]South China Normal Univ., Guangdong, China; [7]South China Normal Univ., Guangzhou, China

Abstract: While numerous imaging studies have investigated the brain regions supporting the acquisition and extinction of fear, the electrophysiological basis of these processes is much less known. Here we used intracranial EEG (iEEG) recordings in epilepsy patients (N = 40) implanted in several brain regions pertaining to the fear learning and extinction network, including the amygdala, hippocampus, and prefrontal cortex (PFC), as well as in various occipital-temporal areas relevant for processing of sensory stimulus features. Patients performed an extinction learning paradigm with phases of acquisition and extinction. We observed distinct neurophysiological signatures of fear extinction in the amygdala, with CS- items showing increased theta power as compared to CS+ items. We applied Representational Similarity Analyses (RSA) in order to assess representations of cues and contexts during the acquisition and extinction periods. Results revealed that the stability of item representations was stronger for CS+ as compared to CS- items in the lateral temporal cortex during extinction. This effect was observed during the presentation of the cue, and overlapped in time with a context-specific signal originating in the PFC. Critically, we observed that this contextual signal preceded in time and correlated across trials with item stability in the amygdala. Taken together, these results demonstrate distinct representational dynamics of cues and contexts during the extinction of fear memories in the human brain.

Disclosures: D. Pacheco: None. **A. Bouyeure:** None. **G. Jacob:** None. **K. Lehongre:** None. **V. Lambrecq:** None. **V. Navarro:** None. **L. Shen:** None. **J. Yang:** None. **B. Han:** None. **Q. Chen:** None. **N. Axmacher:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.071/LBA157

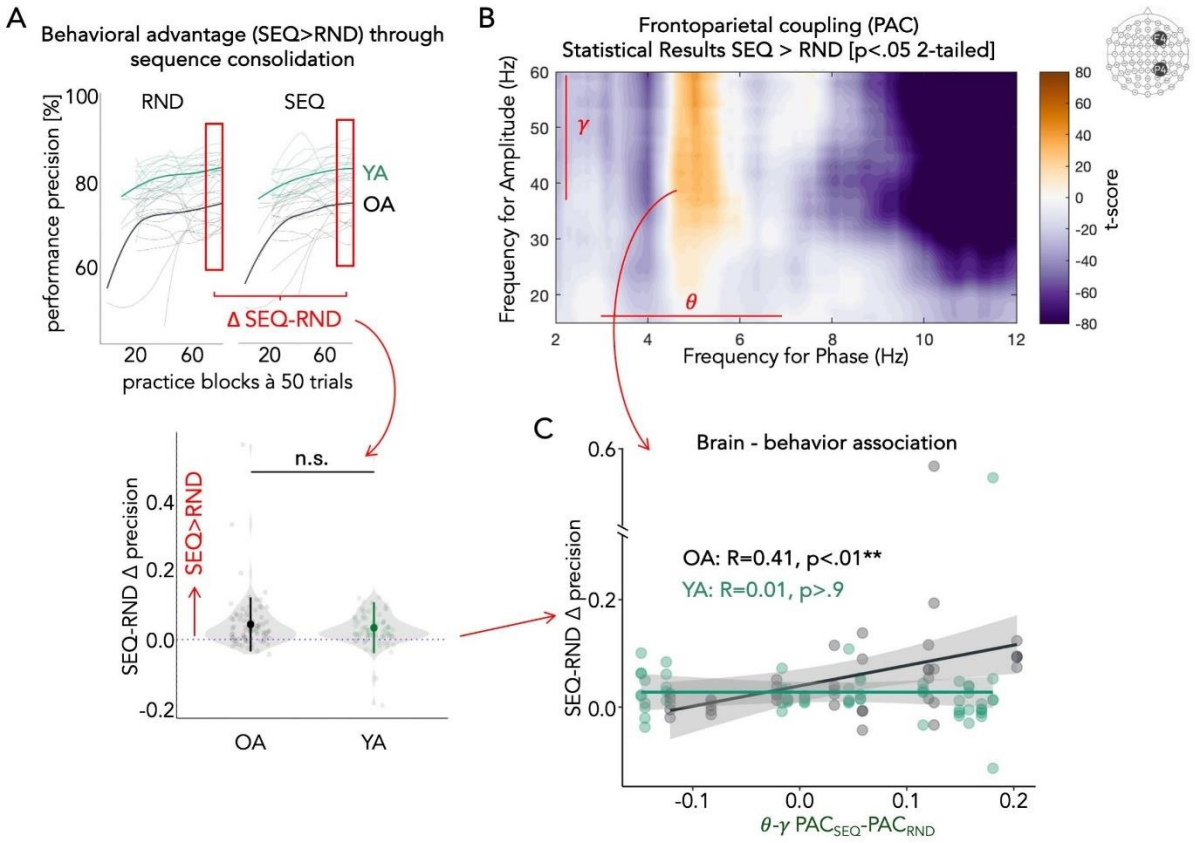
Topic: H.08. Learning and Memory

Support: seed funding under NIH Grant UL1 TR001450

Title: Older brains rely on stronger frontoparietal coupling to retrieve sequence memory after long-term consolidation.

Authors: *K.-F. HEISE[1], D. E. ARIAS[1], I. DICKENS[1], C. FINETTO[2];
[2]Hlth. Sci. & Res., [1]Med. Univ. of South Carolina, Charleston, SC

Abstract: As we age, efficiently processing and maintaining memories becomes more difficult. We here asked the question of whether declining precision in the coupling of neural oscillations within and across brain regions may be one target mechanism underlying declining age-related deficits in memory function. Healthy young (YA n=16, 18-39 years) and older adults (OA n = 19, 61-76 years) practiced an online variant of an established sequence learning task over consecutive days until a plateau in performance precision was achieved before electroencephalography (EEG) was recorded during task practice. In this task, sequential information was provided implicitly interleaved with random key presses through visual cues associated with 1-2 simultaneous keypresses on a standard computer keyboard. Learning, i.e., change in temporal and spatial precision of sequential key presses across task practice, was monitored in real-time to identify an advanced level of consolidation here defined on an individual basis with an asymptotic exponential function fitted to single-trial performance. On average, participants practiced the 4-element sequence 203 (YA 150-250, OA 100-300) times over ~4 days. Despite overall lower performance precision in older as compared to young, both groups showed comparable behavioral advantage of sequence over random performance (Fig. 1A). Task-based EEG recording at plateau revealed that sequence compared to random anticipation (SEQ>RND) was paralleled by significantly higher phase-amplitude coupling (PAC) between right frontal theta (3-7Hz) and parietal gamma (40-60Hz) frequency oscillations across both age groups (Fig. 1B). Despite comparable levels of sequence consolidation, older adults benefitted more from stronger frontoparietal theta-gamma coupling (Fig. 1C), i.e., relatively stronger coupling in SEQ compared to RND performance was associated with relatively higher precision for the same contrast. Therefore, we propose frontoparietal theta-gamma coupling as a potential compensatory mechanism to retain memory function in older age.



Disclosures: K. Heise: None. **D.E. Arias:** None. **I. Dickens:** None. **C. Finetto:** None.
Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

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Program #/Poster #: LBA008.072/LBA158

Topic: H.08. Learning and Memory

Support: Simons Collaboration on Plasticity and the Aging Brain

Title: Nominating the calcium channel Cav3.2 as a mediator of memory acquisition from patch-sequencing of hippocampal CA1 cells in a genetically diverse mouse population

Authors: *J. ALGOO[1], M. BERCHULSKI[3], T. ZHAO[3], A. R. OUELLETTE[3], G. K. FROHOCK[4], J. GRASSMANN[4], W. F. FLYNN[4], C. C. KACZOROWSKI[5], V. MENON[2], K. O'CONNELL[3];
[1]Cellular, Molecular, and Biomed. Studies, [2]Neurol., Columbia Univ., New York, NY; [4]The Single Cell Biol. Lab., [3]The Jackson Lab., Bar Harbor, ME; [5]Neurol., The Univ. of Michigan, Ann Arbor, MI

Abstract: Linking gene expression to electrophysiology (ephys) at the cellular level, and ultimately translating these profiles to behavioral phenotypes is a challenging endeavor. Using patch-sequencing (patch-seq) alongside a contextual fear conditioning paradigm (CFC), we have nominated a gene, Cav3.2, for its effects on memory acquisition, modulated through changes in action potential threshold.
We performed patch-seq on 47 CA1 and subiculum cells from 5 - 7 month old HET3 mice. This diversity model consists of genetically unique individuals of a reproducible population that originates from 4 inbred strains. The mice underwent a CFC paradigm, and were assigned to low, medium, or high performance labels for 3 cognitive performance metrics. Two metrics related to memory acquisition during training, time freezing after the last shock during acquisition (CFA) and slope of freezing over all shocks; one related to memory recall, CFM, measured as the percent of time spent freezing during the testing trial.
For targeted analysis we selected ion channels known to be expressed in the hippocampus and modeled ion channel gene expression as a function of each behavioral performance metric. Expression levels of the Cav3.2 gene were identified as being significantly different ($p < 0.05$) between CA1 cells derived from high and low performing groups when using the CFA metric. Multiple comparison correction was performed using the false discovery rate (fdr) method. We also performed correlation analysis to evaluate how changes in electrophysiological characteristics differ between performance groups. Action potential threshold (AP), was significant for differences between low and high performing CFA mice. We then evaluated the association between Cav3.2 expression and AP, and found a significant correlation.
Cav3.2 has previously been implicated in short-term memory acquisition in a study that found providing a T-type calcium channel antagonist leads to higher acquisition in a CFC paradigm in rats.[1] The current work provides additional context. We show that this association occurs across species in mice; low transcriptome levels of this gene are associated with higher memory acquisition; variation in levels of this channel occur naturally in a genetically diverse population; and, alterations in levels of this channel's transcripts are associated with phenotypic effects on behavior and specific ephys properties.
[1]Marks, W. N., Zabder, N. K., Snutch, T. P., & Howland, J. G. (2020). T-type calcium channels regulate the acquisition and recall of conditioned fear in male, Wistar rats. Behavioural Brain Research, 393, 112747.

Disclosures: J. Algoo: None. **M. Berchulski:** None. **T. Zhao:** None. **A.R. Ouellette:** None. **G.K. Frohock:** None. **J. Grassmann:** None. **W.F. Flynn:** None. **C.C. Kaczorowski:** None. **V. Menon:** None. **K. O'Connell:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.073/LBA159

Topic: H.08. Learning and Memory

Support: NSERC Discovery Grant RGPIN-2017-06753, RGPIN-2024-0588
Canada Foundation for Innovation and Ontario Research Fund 36601

Title: BDNF genetic polymorphism interacts with menstrual cycle phase to predict rule-plus-exception category learning

Authors: *M. PEROVIC[1], J. HOU[2], S. BHATTARAI[2], C. HAN[2], Y. CHEN[2], M. L. MACK[2];
[1]Univ. of Toronoto, Toronto, ON, Canada; [2]Univ. of Toronto, Toronto, ON, Canada

Abstract: Both brain-derived neurotrophic factor (BDNF) and ovarian hormones have established effects on neuroplasticity, learning and memory. Critically, ovarian hormones modulate BDNF expression across the menstrual cycle and its animal analogues. In order to examine the effects of this complex interaction on cognition, we use BDNF genetic polymorphism as an estimate of participants' baseline BDNF availability and study their performance on a rule-plus-exception category learning task at two points in the menstrual cycle. We find that, while Met homozygotes show advantages during the early follicular phase (typically characterized by low levels of ovarian hormones), Val homozygotes outperform them in the late follicular phase (typically characterized by high estradiol), indicating nuanced, genotype- and menstrual cycle-specific effects on category learning ability. These results provide the first evidence of BDNF genotype interacting with the menstrual cycle to predict cognitive performance in women and deepen our understanding of menstrual cycle-dependent changes in memory and learning. Notably, both BDNF and ovarian hormones have major effects on the hippocampus, and the category learning task we use, which necessitates memory integration and differentiation, is significantly associated with hippocampal processes. As such our findings are of interest to neuroscientists broadly interested in hippocampus and its role in learning.

Disclosures: M. Perovic: None. **J. Hou:** None. **S. Bhattarai:** None. **C. Han:** None. **Y. Chen:** None. **M.L. Mack:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.074/LBA160

Topic: H.08. Learning and Memory

Support: NSF Grant 0963581

Title: The Relationship between Physiological Arousal and Memory Encoding of Negative Stimuli in Young and Middle-aged Adults

Authors: *S. KAFAFI[1], X. NIU[1], M. UTAYDE[2], K. SANDERS[2], E. A. KENSINGER[3], J. PAYNE[2];
[2]Psychology, [1]Univ. of Notre Dame, Notre Dame, IN; [3]Psychology and Neurosci., Boston Col., Chestnut Hill, MA

Abstract: Emotionally negative experiences are generally more memorable than neutral ones, partly due to the activation of the central noradrenergic system, particularly within the amygdala, during negative emotion encoding. This activation, originating from the norepinephrine-releasing locus coeruleus in the brain stem, marks negative events as goal-relevant by inducing physiological arousal responses such as elevated heart rate and sweating. This study investigates how objective measures of physiological arousal during encoding influence memory performance for negative and neutral scene components across young and middle-aged adults. Higher skin conductance response amplitude in response to negative scenes was linked to poorer memory performance for negative compared to neutral objects, while greater heart rate deceleration for negative scenes predicted better memory performance for negative objects. Both younger and middle-aged adults exhibited higher false alarm rates for negative scenes compared to neutral scenes, indicating a greater tendency to incorrectly remember negative stimuli. However, middle-aged adults showed a more pronounced increase in false alarm rates for negative scenes, suggesting a heightened susceptibility to memory errors for emotionally negative information with age. Together, these findings suggest physiological arousal may have an overgeneralizing effect during the encoding of negative memories, and this effect becomes more prominent with increasing age.

Disclosures: S. Kafafi: None. **X. Niu:** None. **M. Utayde:** None. **K. Sanders:** None. **E.A. Kensinger:** None. **J. Payne:** None.

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Program #/Poster #: LBA008.075/LBA161

Topic: H.08. Learning and Memory

Support: Israel Science foundation (ISF) 2937-21
Human Frontier Science Program (HFSP) RGP0042/2019

Title: The independent evolution of the octopus vertical lobe highlights universal principles of associative learning networks

Authors: *B. HOCHNER[1], I. KATZ[2], F. BIDEL[3], Y. MEIROVITCH[4], D. BOLIGIN[5], N. NESHER[6], T. SHOMRAT[7];
[1]Dept of Neurobiology, Hebrew Univ., Jerusalem, Israel; [2]Hebrew Univ. of Jerusalem,

Jerusalem, Israel; [3]Dept. of neurobiology, Hebrew Univ., Jerusalem, Israel; [4]Harvard Univ., Cambridge, MA; [5]Deprtment of neurobiology Hebrew university, Jerusalem, Israel; [6]Fac. For Marine Sciences, Ruppin Academic Cente, Michmoret, Israel; [7]Marine Sci., The faculty of Marine Sciences, Ruppin Academic Cen, Michmoret, Israel

Abstract: The discovery of activity-dependent long-term potentiation (LTP) in the vertical lobe (VL) of *Octopus vulgaris* has indicated that the octopus VL and mammalian hippocampus share not only anatomical features as suggested by J.Z Young but also the cellular process believed to mediate learning and memory, thus suggesting the independent evolutionary convergence of similar cellular mechanism. However, like the mossy fibers-to-CA3 pyramidal cell synapses, the textbook example of non-associative LTP, the VL LTP, that occurs at the synapses between the inputs pathway and the amacrine interneurons (AMs), was found to be also NMDA-independent and presynaptically expressed. These two properties are inconsistent with the canonical associative Hebbian LTP in the hippocampal CA1 region. Here, we integrate results that show that LTP expression and maintenance are mediated by persistent activation of NO-synthase in the postsynaptic AM interneurons and that LTP expression is mediated through NO retrogradely facilitating presynaptic transmitter release (Stern-Mentch et al. 2022; Turchetti-Maia et al. 2018). We suggest that mechanistically, the NO system in the VL provides an alternative solution to that of the NMDA receptor in the hippocampus.Moreover, our recent connectome results (Bidel & Meirovitch et al. 2023) contributed morphological support to this idea as they show that the majority of the AMs are simple (SAMs) each receiving only a single synaptic input. As this monosynaptic connection undergoes LTP, it implies that each SAM is analogous to a dendritic spine, which in CA1 ensures the fundamental Hebbian properties - synaptic *specificity* and synaptic *associativity*. How can associativity be achieved among coactivated SAMs? The connectome results revealed reciprocal connections between the SAMs and serotonergic processes. Such interconnections resemble the 5-HT-mediated heterosynaptic facilitation of the sensory-to-motoneuron synapse of the defensive reflex of *Aplysia*. Indeed, preliminary results suggest that the 5-HT-dependent PKC cascade, which mediates 5-HT-induced synaptic dishabituation in *Aplysia* (Ghirardi et al. 1992), is used in the VL to mediate LTP induction. Based on these findings, we are testing the working hypothesis that synaptic associativity in the VL is mediated by volume transmission of 5-HT and/or NO among the coactivated SAMs. This integrative assessment of the past and recent results supports the idea that the evolution of cognitive abilities in an advanced mollusk has converged into morphological and molecular properties that provide the biological properties essential for associative learning networks.

Disclosures: B. Hochner: None. **I. Katz:** None. **F. Bidel:** None. **Y. Meirovitch:** None. **D. Boligin:** None. **N. Nesher:** None. **T. Shomrat:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.076/LBA162

Topic: H.08. Learning and Memory

Support: Project K3-F-995/001-2021

Title: Pharmacological study of kynurenic acid synthesis in Helix pomatia snail in vitro

Authors: *H. BARAN;
Karl Landsteiner Res. Inst. Mauer, Amstetten-Mauer, Austria

Abstract: Kynurenic acid (KYNA), a tryptophan metabolite along the kynurenine pathway, is an endogenous antagonist of glutamate ionotropic excitatory amino acid (EAA) receptors and the nicotinic acetylcholinergic subtype α7 receptor (nAChR). The involvement of KYNA in various pathological conditions and aging is significant. Increased KYNA levels correlate with dementia and cognitive impairment. Recently, we have demonstrated the presence of the enzymes kynurenine aminotransferases I, II and III, which synthesize KYNA, in different organs of the snail *Helix pomatia*, i.e. in the heart, liver and brain (Kronsteiner et al., Cell Physiol Biochem 2023;57:279-97). We were interested to investigate the effect of anti-dementia drugs, i.e. cerebrolysin and D-cycloserine, on KYNA synthesis in snail liver homogenate in an *in vitro* study. Snails *Helix pomatia* (obtained from Gugumuck, Vienna Snail Manufacturer, Austria) with an average age of 7 years were used. The age of the snails was determined according to the Age Rating Scale. The snails were killed, the liver was dissected and stored at -40^{o}C until the measurement of the enzyme activity of KAT I and KAT II. Study performed according to the Austrian Ethical Code. Different doses of cerebrolysin (1, 5, 10, 15 µl) and D-cycloserine (50, 100, 200, 400, 800 µM) were used in the incubation mixture of the experiment. L-kynurenine (50, 100, 200, 400, 800 µM) was used to confirm the formation of KYNA under experimental conditions. KYNA was measured by high performance liquid chromatography. The number of data was between 4 and 9 for each treatment. The results are expressed as the mean ± standard error of the mean. One-way ANOVA analysis and Student's t-test were used. Analysis of liver KAT I and II activities in the presence of different doses of L-kynurenine revealed a dose-dependent increase in KYNA formation in an *in vitro* study. In contrast, cerebrolysin and D-cycloserine dose-dependently and significantly decreased KYNA formation in snail liver homogenate. KYNA synthesis in liver homogenate from the snail Helix Pomatia was significantly and dose-dependently increased in the presence of the bioprecursor L-kynurenine. The significant effect of anti-dementia drugs on KATs activities to reduce KYNA formation in liver homogenate of snail Helix Pomatia is similar to the effect published in other species, i.e. rat and human, at least in an *in vitro* study. Pharmacological study in an *in vivo* on the KYNA modulation in the snail Helix Pomatia is of particular importance.

Disclosures: H. Baran: None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Program #/Poster #: LBA008.077/LBA163

Topic: H.08. Learning and Memory

Support: Korea Goverment NRF RS-2024-00335928

Title: Pavlovian conditioning of a model spiking neural network for discriminating spatio-temporal sensory inputs having short time intervals

Authors: *K. LEE;
Korea Univ., Seoul, Korea, Republic of

Abstract: The brain's remarkable ability to discern sequences of events unfolding within the fast timescale of milli- and tens of milli-seconds, as required in tasks such as precise timing in sports and music, continues to be a subject of active investigation. In this study, as a proof of concept, we suggest and explore a temporally Pavlovian conditioned Izhikevich model neural network as a potential mechanism for enabling this capability. Through a series of numerical simulations and comprehensive analyses, we present compelling evidence that this conditioned network effectively discriminates various doublets and triplets of sequential input pulses, each characterized by distinct millisecond order time intervals. A crucial insight emerging from our findings is the formation of a feed-forward network during the learning process, wherein temporal sensory information is mapped into specific topographic patterns. Subsequently, in the decoding phase within the read-out stage, discrimination is achieved based on the relative shape and degree of shift in the spiking rate profile of a population burst triggered by a given input. We propose that this mechanism extends beyond the simple spatiotemporal input sequences and may have broader implications for time perception and cognitive processing in real-world scenarios where precise timing plays a pivotal role.

Disclosures: K. Lee: None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Program #/Poster #: LBA008.078/LBA164

Topic: H.08. Learning and Memory

Support: NRF of Korea grant RS-2024-00349515
NRF of Korea grant RS-2024-00435727
NRF of Korea grant RS-2023-00265406
Creative-Pioneering Researchers Program through Seoul National University

Title: Similarity in brain activity dynamics across individuals during navigation and its prediction of spatial memory performance

Authors: *J. LIM, S.-E. PARK, S.-H. LEE, S. LEE;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Spatial navigation and learning are dynamic information processing tasks involving multiple events, such as making turns and encountering or passing landmarks. Therefore, brain activity must correspond to the changing cognitive functions and demands over the course of the event. We hypothesized that such dynamic neural processing may reflect the successful encoding of a navigational episode.To study activity dynamics during navigation, we had 76 participants (42 females; average age 36.5, SD 16.4) share the same navigation experience by watching 24 different 1-minute-long first-person view navigation videos in the scanner. At the end of each video, they answered a spatial memory question involving the identification of their traveled path or destination on a map. Canonical activity dynamics were defined by averaged activity dynamics across participants for each brain region. By comparing the similarity between an individual's dynamics and the canonical dynamics, we assessed the degree of shared dynamics across individuals for each brain region and investigated its association with individual spatial memory performance.The similarity between individual and canonical dynamics was strongest in the visual areas in the occipital lobe, and the parietal (e.g. precuneous), frontal (premotor cortex) as well as medial temporal lobe (parahippocampus). We also found that informative navigational events such as turns or landmarks contributed to the canonical dynamics of many brain regions. Next, we found that individuals whose activity dynamics were well-aligned with canonical dynamics in the medial temporal lobe performed better on subsequent Path and destination questions, and that age-dependent spatial memory decline was partly mediated by desynchronization with canonical dynamics in the medial temporal lobe.

Disclosures: J. Lim: None. **S. Park:** None. **S. Lee:** None. **S. Lee:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

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Program #/Poster #: LBA008.079/LBA165

Topic: H.09. Spatial Navigation

Support: NIH RF1AG078736-01
Packard Fellowship for Science and Engineering

Title: Development of goal-selective disinhibition in hippocampus

Authors: *X. ZHENG[1], N. JEONG[5], A. L. PAULSON[2], S. M. PRINCE[6], V. NGUYEN[3], S. THOMAS[7], C. GILPIN[8], M. GOODSON[4], A. C. SINGER[9];

[1]Georgia Inst. of Technol., Atlanta, GA; [2]Georgia Inst. of Technol., Cary, NC; [3]Georgia Inst. of Technol., Senoia, GA; [4]Biomed. Engin., Georgia Inst. of Technol., Atlanta, GA; [5]Goals Unhindered, LLC, Atlanta, GA; [6]Emory Univ., Atlanta, GA; [7]Univ. of Virginia, Charlottesville, VA; [8]Abbott, Atlanta, GA; [9]Coulter Dept. of Biomed. Engin., Georgia Inst. of Technol. & Emory Univ., Atlanta, GA

Abstract: Remembering important locations relies on the hippocampus, where excitatory pyramidal cells represent spatial context. These pyramidal cells are strongly regulated by interneurons. While previous studies focused on interneurons' general regulatory functions, we discovered inhibitory activity plays a key role in spatial memory formation of reward locations. Specifically, parvalbumin-positive (PV) interneurons, which directly inhibit pyramidal cells, reduce spiking activity around reward locations. This inhibitory reduction cannot be fully explained by changes in speed or licking behavior. Optogenetically disrupting decreases in inhibitory activity at reward locations impedes learning, indicating this disinhibition is necessary for remembering goal locations. However, whether selective disinhibition occurs around generally salient locations, and how disinhibition develops during learning remain unclear. Here, we address these key questions. We analyzed PV interneuron activity as head-fixed mice performed a Y-maze decision task in a virtual environment (n = 7 male C57BL/6J mice, 4.5-7 mo. old). Before animals reached two possible goal arms, a visual cue was presented to indicate which arm would be rewarded. A reward was provided immediately after animal enters the correct arm. We assessed single-unit activity of PV interneurons and controlled for effects of speed and licking. We observed a significant reduction in PV interneuron activity around reward locations compared to baseline activity. There was not such decrease around the visual cue that indicates which arm is correct even though this cue is highly salient. These results show that this spatial-selective disinhibition is not related to salient cues generally and is rather specific to reward and goal locations. To characterize the development of disinhibition, we assessed trial-by-trial PV activity as mice learned new reward locations in novel environments (n = 7 male C57BL/6J mice, 3.5-5 mo. old). Within a single day, PV activity develops from initially no decrease around reward locations, to a significant decrease after the reward, to a significant decrease when approaching and at the reward locations. This result indicates a shift in disinhibition from representing the receipt of rewards to anticipating the upcoming rewards. Together, our results demonstrate how hippocampal inhibitory activity develops to encode and predict reward locations. This goal-selective disinhibition that predicts reward has important implications for how animals learn locations that lead to reward.

Disclosures: X. Zheng: None. **N. Jeong:** None. **A.L. Paulson:** None. **S.M. Prince:** None. **V. Nguyen:** None. **S. Thomas:** None. **C. Gilpin:** None. **M. Goodson:** None. **A.C. Singer:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.080/LBA166

Topic: H.09. Spatial Navigation

Support: Howard Hughes Medical Institute

Title: Organization of task elements into functional modules in prefrontal cortex

Authors: *C. BÖHM[1,2], A. K. LEE[3,2];
[1]Charité Universitätsmedizin Berlin, Berlin, Germany; [2]Janelia Res. Campus, Ashburn, VA; [3]BIDMC / HHMI, Boston, MA

Abstract: Prefrontal cortex (PFC) is critically important for the organisation and execution of flexible behavior, including sensory integration, decision making, and cognitive control. In particular, its functions are believed to be supported by networks of cells representing information that is currently relevant for the execution of the task at hand. This information can include sensory or behavioral variables, such as specific motor actions, and more abstract information, such as task-relevant categories, task phase or rules.
Despite the well-recognized role of PFC in flexible behavior, the organization of these different types of information and learned concepts, and how they are flexibly accessed during task execution, is not fully understood. In a multi-phase spatial working memory task that required rats to navigate flexibly from one of three starts to one of three goals via unpredictable routes, we found that the representation of task elements were structured according to the task's logic. This structure reflected both the meaning of task elements and the mutual relationships between categories of task elements. Key locations, actions and task phase dependent direction of movement were organized into functional motifs that collectively reflected the key conceptual elements of the task. Additionally, the structured representation of task elements was supported, at least in part, by functional preferences of subsets of cells. The structured representation of task elements in PFC might provide the animal with a cohesive understanding of a task, facilitate the correct succession of behaviors according to task phase and, together with the nonrandom selectivity of individual cells, may enable modularized computation across different behaviors and contexts.

Disclosures: C. Böhm: None. **A.K. Lee:** None.

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Topic: H.09. Spatial Navigation

Support: POSCO TJ Park Foundation

the National Research Foundation of Korea RS-2023-00211417, RS- 2021-R1A4A2001803

Title: Novelty triggers time-dependent theta oscillatory dynamics in hippocampal-cortical-midbrain circuitry

Authors: *A. J. PARK;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Rapid adaptation to novel environment is crucial for survival, and this ability is impaired in many neuropsychiatric disorders. Understanding neural adaptation to novelty exposure therefore has therapeutic implications. Here, we found that novelty induces time-dependent theta (4-12Hz) oscillatory dynamics in brain circuits including the medial prefrontal cortex (mPFC), ventral hippocampus (vHPC), and ventral tegmental area (VTA), but not dorsal hippocampus (dHPC), as mice adapt to a novel environment. Local field potential (LFP) recordings were performed while mice were freely behaving in a novel or a familiar arena for 10 minutes. Initially, mice exhibited increased exploratory behavior upon exposure to novelty, which gradually decreased to levels observed in mice exposed to the familiar arena. Over the same time course, the mPFC, vHPC, and VTA displayed progressively increasing theta power. Additionally, theta coherence and theta phase synchrony measures demonstrated that the connectivity between these areas was initially weakened and then gradually strengthened to the level observed in the familiar group. Conversely, mice exposed to the familiar arena showed steady and consistent behavior as well as theta dynamics in all areas. Treatment with a dopamine D1-receptor (D1R) antagonist in the vHPC disrupted neurophysiological adaptation to novelty specifically in the vHPC-mPFC and vHPC-VTA circuits, without affecting behavior. Thus, novelty induces distinct theta dynamics that are not readily dictated by behavior in the mPFC, vHPC, and VTA circuits, a process mediated by D1Rs in the vHPC.

Disclosures: A.J. Park: None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.082/LBA168

Topic: H.09. Spatial Navigation

Support: National Science and Technology Innovation 2030 Major Program 2022ZD0205000
National Natural Science Foundation of China 32371076
The Lingang Lab LG202105-01-08

Title: Opposing gradients between recognition and navigation along the primate hippocampal long axis

Authors: X. XU, K. DU, ***D. MAO**;
Inst. of Neuroscience, Chinese Acad. of Sci., Shanghai, China

Abstract: The hippocampus plays a critical role in both recognition memory and spatial navigation. However, for a long time, independent studies of these functions have not been able to answer the mechanism by which the hippocampus plays both roles. Thus, the aim of the present study is to investigate whether recognition memory and navigation share a common circuit or have independent circuits within the hippocampus. Using macaque monkeys as subjects, we adopted a multi-task paradigm: a visual paired comparison (VPC) task followed by a free foraging (FF) task in a single session to probe recognition memory and spatial navigation, respectively. This design allowed us to record from the identical group of neurons and examine how the neural representations change across cognitive tasks. Considering the difference in the connections between the anterior and posterior portions of the hippocampus, we implanted 128 chronic electrodes along the hippocampal longitudinal axis. In the VPC task, we identified 22.5% of neurons showing a significant correlation between firing rate modulation and recognition performance**.** In the FF task, we found that neurons encode diverse spatial variables, and most exhibit conjunctive encoding that aligns with previous reports. When looking at the common neurons recorded in both tasks, 50.3% of neurons were selective to only one of these two tasks, and only 11.1% were tuned to both tasks. Further, the proportions of neurons tuned to the VPC task increased along the posterior-to-anterior axis, whereas those tuned to the FF task showed an opposite gradient. These results suggest that the hippocampus exerts memory and navigation functions through two groups of less-overlapping neurons. The anterior part of the hippocampus is more involved in recognition memory, while the posterior part plays a more significant role in navigation.

Disclosures: X. Xu: None. **K. Du:** None. **D. Mao:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.083/LBA169

Topic: H.09. Spatial Navigation

Support: NIH 4R01NS121764-02

Title: Influences of spatial versus visual inputs on activity in retrosplenial cortex

Authors: *Z. NAVRATILOVA[1], D. BANERJEE[1], J. ZHANG[2], S. P. GANDHI[3], B. L. MCNAUGHTON[4];

[1]Univ. of California Irvine, Irvine, CA; [2]Neurobio., Univ. of California, Irvine, Irvine, CA; [3]Neurobio. and Behavior, Univ. of California, Irvine, CA; [4]Neurobio. and Behavior, The Univ. of California Irvine, Irvine, CA

Abstract: Semantic memory and abstraction of knowledge from experience are thought to involve communication between the hippocampus and neocortex. The hippocampus encodes novel episodes using sparse and orthogonal neural representations, which are often correlated with spatial location. Recent studies have shown that several neocortical areas, including the retrosplenial cortex (RSC), and primary visual cortex (V1) of mice contain similar neural coding correlated to spatial location in one-dimensional environments. This spatial coding depends on an intact hippocampus, at the time of learning. To understand the contributions of visual and spatial (distance) cues to this neural activity, we dissociated visual cues from space by shuffling the position of some visual cues on each trial. We used 2-photon imaging to simultaneously study activity in RSC, and V1, and in separate mice in the hippocampus (CA1). We found that in all three areas, spatial information was degraded in the portion of the novel environment containing unstable cues. Many V1 neurons expressed reliable activity near certain visual cues. A few neurons (~5%) in RSC, and none in CA1 expressed activity near the location-varying visual cues. To elucidate the role of memory on the activity of CA1 and RSC neurons, we also exposed the mice to environments with stable cues for several days, before implementing the shuffling procedure. In these learned environments, population activity in CA1, RSC, and V1 continued to express spatial information after the landmarks were dissociated from position. However, on the single cell level, more CA1 neurons were active at consistent positions than in RSC or V1, where equal numbers of neurons were consistently active near specific cues as at consistent locations. In summary, in a novel environment, V1 neurons were most likely to fire at consistent visual cues, irrespective of position. Fewer RSC neurons did the same. In a learned environment, spatial location influenced the activity in all three brain regions, reducing the number of V1 neurons that fired at consistent cues and increasing their position selectivity, but CA1 was the most position selective. RSC was influenced both by visual and spatial cues, showing activity somewhere between CA1 and V1.

Disclosures: Z. Navratilova: None. **D. Banerjee:** None. **J. Zhang:** None. **S.P. Gandhi:** None. **B.L. McNaughton:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.084/LBA170

Topic: H.09. Spatial Navigation

Support: Marga und Walter Boll-Stiftung 210-05. 01-21

Title: The age-related decay of wayfinding skills is strategy-specific

Authors: *J.-Y. HUANG[1], D. MEMMERT[1], O. ONUR[2], O. L. BOCK[1];
[1]German Sport Univ. Cologne, Cologne, Germany; [2]Univ. Hosp. Cologne, Koln, Germany

Abstract: Literature proposes five cognitive strategies that travelers use for decision making at intersections. Here we investigate whether those strategies are differentially affected in older age. Using a within-person design, young and older adults navigated five virtual mazes, each requiring a different decision-making strategy. Data confirmed an age-related decay of wayfinding accuracy in all mazes. This decay was small for the beacon and for the relative location strategy, but was pronounced for the serial order, associative cue and cognitive map strategy. Contrary to literature, the decay was not larger for the cognitive map strategy than for the serial order and the associative cue strategy. However, the decay was substantially larger if cognitive map formation was tested outside a wayfinding context. We further found an age-related decay in the acquisition of incidental spatial knowledge when wayfinding by the cognitive map strategy, but not when wayfinding by one of the other strategies. We conclude that our older adults compensated their deficits in cognitive map formation by exploiting auxiliary wayfinding cues, such as their momentary position with respect to the outer walls of the virtual maze. The additional computational demand of this compensation could explain the age-related decay in the acquisition of incidental knowledge.

Disclosures: J. Huang: None. **D. Memmert:** None. **O. Onur:** None. **O.L. Bock:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.085/LBA171

Topic: H.09. Spatial Navigation

Title: Anterodorsal thalamus histamine signaling modulates object location memory via histamine H3 receptors

Authors: *Z. FANG;
Zhejiang Univ., Hangzhou, China

Abstract: The histaminergic (HA) system has long been considered to be associated with learning and memory, fulfilling its functions mainly through the activation of both H1R, H2R and H3R. By whole-brain mapping of histaminergic projections in mouse brain, we find dense histaminergic projections to the anterodorsal thalamus (AD). AD contains a large proportion of head direction cells and has recently been identified as a critical nucleus in episodic memory regulation. However, the precise role of this histaminergic projection remains to be elucidated. By employing optogenetic technique, we found that TMN-AD histaminergic circuit

bidirectionally modulates object location memory (OLM) but not other forms of memory including contextual fear memory and novel object recognition. Interestingly, histamine H3 receptor (H3R) but not H1R or H2R express densely in AD shown by fluorescence in situ hybridization (FISH). Therefore, we selectively delete H3R in AD by bilaterally injecting AAV-syn-cre-GFP into AD in $Hrh3^{fl/fl}$ mice and found that OLM was impaired. By contrast, selective depletion of H1R in AD fails to affect OLM. Taken all, evidence so far indicate that AD-projecting histaminergic circuit mediating object location memory via downstream H3R-dependent signaling in AD glutamatergic neurons.

Disclosures: Z. Fang: None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.086/LBA172

Topic: H.10. Human Learning and Cognition

Title: Investigating Neural Dynamics of a Naturalistic Memory Task in sEEG

Authors: *P. WEGER;
Maastricht Univ., Maastricht, Netherlands

Abstract: Given the limitations of conventional therapies for memory impairment, cognitive Brain- Computer Interfaces (BCIs) show promise in alleviating early symptoms of memory decline through targeted, real-time interventions. However, studying memory processes is typically done through constrained experimental designs with limited real-world applicability, underscoring the need for more natural tasks with undefined periods of memory formation and retrieval.
To study these natural memory processes, we recorded stereotactic electroencephalography (sEEG) in six epilepsy patients while they played the card game Memory (also known as Concentration). The game introduces variable periods of memory encoding and decoding, incorporating aspects of short-term memory, working memory, and attention. We collected data from 676 channels across cortical and subcortical structures, including 29 electrodes in the hippocampus and 12 electrodes in the prefrontal cortex.
We identified Local Field Potentials (LFPs) in various frequency bands that correlated with game success and card familiarity. Decoding these events across participants and anatomical regions yielded performance metrics significantly above chance level for subsets of individuals and cortical areas. Elevated beta activity in the Angular Gyrus (AG) and Supramarginal Gyrus (SMG) could be identified in one participant when recognizing previously seen cards, indicating active engagement in visual memory processing.
Our findings support the feasibility of decoding memory-related LFPs using a naturalistic task

setup. This establishes a basis for further exploration of the neural mechanisms underlying natural memory processing and the development of cognitive BCIs for treating memory impairments.

Disclosures: P. Weger: None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.087/LBA173

Topic: H.10. Human Learning and Cognition

Title: Child Development Evaluation in Preschoolers: A Study Case of Mexico

Authors: *I. MORENO-VITE[1], R. BALTAZAR TELLEZ[1], J. HERNÁNDEZ-HERNÁNDEZ[3], J. ARIAS-RICO[4], E. RAMÍREZ MORENO[2], E. CANO VALDEZ[5];
[1]Univ. Autónoma del Estado de Hidalgo, Pachuca de Soto, Mexico; [2]Univ. Autónoma del Estado de Hidalgo, Pachuca, Hidalgo, Mexico; [3]Univ. Autónoma del Estado de Hidalgo, México, México, Mexico; [4]Inst. de Ciencias de la Salud, Univ. Autonoma Del Estado De Hidalgo, Pachuca, Mexico; [5]UNIVERSIDAD AUTONOMA DEL ESTADO DE HIDALGO, Estado de México, Mexico

Abstract: The National Institute of Public Health (INSP) estimates that early childhood development in Mexico occupies the 81% national range. Early stimulation guarantees the optimal increase in cognitive, linguistic, motor, and affective skills and functions, which increases the child's visual-motor development, creativity, and imagination in the first five years of his life. The general objective of this research was to assess the child's development in preschoolers. The research consisted of a quasi-experimental study with a focus on the independent and observational variables. A pretest identified and classified the level of Neurodevelopment. Each child participant in the research received an individual assessment using the Child Development Evaluation Test (EDI). EDI evaluates five areas of development: Gross motor skills, fine motor skills, language, social skills, and knowledge. Methodologically, the Child Development Evaluation (EDI) test was analyzed and formed part of a screening tool designed to detect problems in children's Neurodevelopment. The nursing staff applied the test to 26 preschool children from 3 to 4 years old in an educational institution, following the bioethical principles and protecting the autonomy and rights of the participating subjects. EDI test scores were analyzed using frequencies and percentages in the SPSS V-25 software. The results were generated by summarizing the items included in each area. This research applied a first phase, providing a data analysis pretest. Subsequently, the study applied didactic and playful activities with each child to strengthen the areas of more lag regarding their development; these interventions conformed to the study's second phase. This research's third phase consisted of a

post-test by applying the EDI test again. Results revealed that 85% of the preschoolers achieved normal development during the pretest (first phase). Its development level increased to around 94% in the third evaluation phase. 93% reported prayer during the initial assessment phase, while the prayer level decreased to 84% in the third evaluation phase. Furthermore, 10% was at risk of delay during the first evaluation phase, while during the third phase, the percentage decreased. These differences between the pretest and post-test of the intervention were statistically significant ($p \leq 0.05$).This study shows the impact of interventions on stimulated children, where it was possible to modify their level of development. Further discussions show that early stimulation must be promoted during the first years of life to contribute to and enhance optimal development in physical, intellectual, and psychosocial skills.

Disclosures: I. Moreno-Vite: None. **R. Baltazar Tellez:** None. **J. Hernández-Hernández:** None. **J. Arias-Rico:** None. **E. Ramírez Moreno:** None. **E. Cano Valdez:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.088/LBA174

Topic: H.10. Human Learning and Cognition

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CAPES 88887.671450/2022-00

Title: Tracking dependencies on past events employing the goalkeeper game: an EEG study

Authors: *P. CABRAL PASSOS[1], P. AZEVEDO[2], J. E. GARCÍA[3], C. VARGAS[4];
[1]Univ. of São Paulo, Ribeirão Preto, Brazil; [2]Physiol., Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [3]Statistics Dept. of the Mathematics, Statistics and Scientific Computation, Unicamp, Campinas, Brazil; [4]Neurobio. Dept., Inst. of Biophysics Carlos Chagas Filho of the Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil

Abstract: The statistical brain conjecture states that behavior is guided by statistical inference. To address this conjecture, we employed the Goalkeeper Game (GG, https://game.numec.prp.usp.br/). Acting as a goalkeeper, the participant is asked to predict kicks in a sequence of penalties while his/her electroencephalographic (EEG) activity is recorded. The sequence of kicks of the penalty taker is generated by a probabilistic context tree model, a mathematical object used to generate, compress and model stochastic sequences. A Context Tree

(CT) statistical model selection algorithm is then employed to summarize the relationship between the sequence of kicks and the sequence of EEGs preceding the response choices in the GG. The algorithm returns a context tree that matches (or not) the kicker's tree. If so, the EEG segments recorded from the goalkeeper during the game should have the same dependencies on the past as those of the kicker's sequence. Eleven right-handed subjects (3 F, 23 &pm 9.91 yrs) participated in the study (ethics approval: CAEE 69431623.2.0000.5407). The kicker shooted, in each trial, to the left-0, center-1 or right-2, totalizing 1500 trials (3 blocks of 500 trials). The goalkeeper informed his/her prediction choice by pressing buttons mapped to the numbers 0, 1 and 2 on the keyboard (CEDRUS RB-840). Each button was mapped to a unique right hand finger. For EEG analysis we considered the 300ms interval preceding the button press. Raw EEGs (32 elec., avg ref., ActicHamp, 2.5kHz) were filtered at 1Hz and decomposed (ICA). The ICLabel (Swartz Center for Comp. Neurosci.) was then used for artifact removal. The resulting EEG was downsampled (1024 Hz) and low-passed at 45 Hz (4th-order butterworth). The CT algorithm starts from a maximum tree containing subsequences in the sequence of kicks which are represented with 0, 1 and 2. Then, each branch is visited. A branch is composed of at least a pair of subsequences of the same size that differ by one element. The EEGs associated with each pair of the branch are compared using the projective method (Hernàndez et al., 2021). If differences are found ($p < 0.05$) the branch is maintained in the estimated tree, otherwise it is pruned. After the context tree estimation, a distance (Balding et al., 2009) was calculated from the estimated trees to the penalty taker tree. Group analysis revealed that the distance between the kicker's context tree model and that of the goalkeepers reduced significantly from the 2nd to the 3rd block ($p < 0.05$) only for the frontal electrodes Fp1 and Fz. These results suggest that the EEG signals recorded in frontal regions of the brain track the dependencies of the past displayed in the penalty taker sequence.

Disclosures: P. Cabral Passos: None. **P. Azevedo:** None. **J.E. García:** None. **C. Vargas:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.089/LBA175

Topic: H.10. Human Learning and Cognition

Title: Early motor learning micro-offline gains do not rely on hippocampal-dependent processes

Authors: *N. AHMED, T. SURESH, S. J. HUSSAIN, M. FREEDBERG;
Univ. of Texas at Austin, Austin, TX

Abstract: In motor learning, micro-offline gains (MOGS) are improvements in performance that occur during brief rest periods between practice trials, facilitating rapid consolidation and

stabilization of motor memory. While motor learning primarily engages cerebral regions, including the basal ganglia, cerebellum and motor cortex, recent studies suggest that MOGS may be dependent on the hippocampus, an area that is most commonly associated with episodic memory. However, the involvement and necessity of the hippocampus for MOGS is still not established. To determine whether the hippocampus plays a role in MOGS, we tested whether replacing rest periods with a hippocampal-dependent task (i.e., episodic memory encoding) would significantly alter MOGS. We predicted that, if MOGS rely on hippocampal-dependent processes, MOGS should be significantly reduced when participants perform an episodic memory task in lieu of a rest period. Furthermore, we predict that the ability to recall those episodic memories after motor learning should be negatively correlated with MOGS. Forty-four healthy participants performed an explicit sequence learning task, which involved typing a sequence of keypresses on a response box as rapidly and accurately as possible for ten seconds on each trial using their non-dominant hand. Our experiment included three groups that differed only in whether they rested (REST), encoded episodic memories (ENC), or compared the similarity of two words (SIM) during the rest periods. The ENC and SIM groups were both exposed to the same stimuli (pairs of words) but only differed in their task demands. While episodic memory encoding is hippocampal-dependent, making semantic comparisons relies significantly less on the hippocampus. Thus, we expected the ENC group to show significantly smaller MOGS than the REST and SIM groups. After motor learning acquisition (~35 minutes later), participants in the ENC group were asked to recall as many word pairs as possible. A one-way ANOVA comparing MOGS during the first 11 trials (early learning) did not reveal evidence of group differences in MOGS. A planned t-test between the REST and ENC groups and between the ENC and SIM groups was also statistically insignificant. We also did not observe a significant correlation between episodic memory performance and MOGS in the ENC group. Our results do not support the idea that MOGS are dependent on hippocampal processes or that inter-trial rest period is important for the development of micro-offline gains. Thus, although our experiment revealed negative results, we propose that while MOGS may involve hippocampal activity, they are not dependent on hippocampal processes.

Disclosures: N. Ahmed: None. **T. Suresh:** None. **S.J. Hussain:** None. **M. Freedberg:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Topic: H.10. Human Learning and Cognition

Support: R21AG072673 and R01NS119468 (to AMB)
Hewitt Foundation (to DZ)

Title: Autoencoder models of human graph learning reveal that sparse and dense representations differentially support planning and recall

Authors: *E. DINH[1], D. ZHOU[1], J. GUO[1], S. M. NOH[1], K. COOPER[2], A. BORNSTEIN[1]; [1]Cognitive Sci., [2]Neurobio. & Behavior, UCI, Irvine, CA

Abstract: Humans can learn complex task structure to infer how to efficiently reach their goals. This learned structure must be stored in memory. Previous work has shown that interventions which give experience more order ("blocked") or randomization ("intermixed") can aid or hinder learning of task structure and thus planning, depending on whether training is properly matched to memory encoding abilities. However, it is not fully understood how the interventions alter the learned representations to do so. Memory representations that are sparser and more distributed could be more efficient and robust to interference. This led prior work to hypothesize that high memory precision allows for sparser and more distributed memory representations. Furthermore, the intermixed sequence may lead to more distributed representations, whereas the blocked sequence leads to localized representations. Here we test these hypotheses using a neural network model.Participants implicitly learned complex associative structures in a latent learning and inference experiment (Noh, Cooper, Stark, Bornstein 2024). A blocked or intermixed sequence of shuffled node pairs was generated from a graph which contained 12 nodes and 16 edges. Later, participants used learned structure to judge relative distances from a source node to target nodes. Finally, participants were asked to draw the underlying graph.Autoencoders, neural networks which learn to represent inputs as compressed representations, were trained to simulate learning under the blocked or intermixed sequence. Hidden layer width was varied to reflect people with differing memory capacities.We measured how distributed representations were by calculating the entropy of the reconstructed graph's edge weights. We found that internal representations become more distributed with greater memory capacity ($\beta = 0.02$, $p = 1.21 \times 10{-}13$) and for the intermixed condition ($\beta = 0.39$, $p = 2 \times 10{-}16$). Next, we measured sparsity from the weighted degree of the representation. Representations exhibited lower degree (more sparse) with higher memory capacity ($\beta = -0.05$, $p = 0.002$), and for the intermixed condition compared to the blocked condition ($\beta = -3.07$, $p = 2 \times 10{-}16$). Critically, these representations reproduced two kinds of task behavior: Shortest-path judgments were improved when condition and memory capacities were matched (low-blocked, high-intermixed) relative to mismatched, and graph reconstruction accuracy was greater for blocked.These results suggest that representational form adjusts to memory capacity and is further shaped by training structure, explaining differences in planning across individuals and conditions.

Disclosures: E. Dinh: None. **D. Zhou:** None. **J. Guo:** None. **S.M. Noh:** None. **K. Cooper:** None. **A. Bornstein:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.091/Web Only

Topic: H.10. Human Learning and Cognition

Support: JSPS KAKENHI Grant Number 21K18028
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JSPS KAKENHI Grant Number 20H03794

Title: Selective Effect of Multiple Hippocampal Transection on Prospective Temporal Estimation with No Effect on Temporal Reproduction

Authors: *Y. ONUKI, K. IBAYASHI, Y. ISHISHITA, K. OHTANI, N. KUNII, K. KAWAI; Jichi Med. Univ., Shimotsuke, Japan

Abstract: Multiple hippocampal transection is a neurosurgical procedure aimed at treating drug-resistant temporal epilepsy by cutting the longitudinal fibers within the hippocampus responsible for the propagation of epileptic seizures, while preserving the transverse fibers to maintain memory function. The hippocampus is known to be involved not only in memory formation but also temporal information processing. However, detailed investigations into temporal processing have been limited due to constrains in neurosurgical approaches. This study aims to explore the impact of MHT on temporal processing functions, specifically rospective temporal estimation and temporal reproduction. Prospective temporal estimation involves predicting the time needed for a future event, while temporal reproduction requires generating a time interval matching the duration of a presented stimulus. To investigate these functions, we developed tasks for both. The prospective temporal estimation task had patients estimate the time for all dots to disappear from a visual stimulus within a 5-11 second range. In the temporal reproduction task, patients reproduced the time interval of a presented visual cue, also within the 5-11 second range. We measured the behavioral changes of the prospective temporal estimation and temporal reproduction tasks in patients (n=6) who underwent multiple hippocampal transection at the three time points: pre-surgery, 1 month post-surgery, and 6 months post-surgery. In the prospective temporal estimation task, we found at postoperative periods, the estimated times were delayed by approximately 1 second relative to the accurate duration for visual stimuli requiring estimation of less than 10 seconds. Conversely, for visual stimuli requiring time estimation exceeding 10 seconds, the estimated times were approximately 1 second shorter than the accurate duration. In the temporal production task, patients at postoperative periods successfully reproduced the temporal interval of presented cues regardless of a variety of temporal intervals. The results suggest that the longitudinal fibers within the hippocampal circuits play a role in the prospective temporal estimation, a function related to temporal planning for future events from the visual cue. These circuits may not, however, be involved in the working memory of temporal information. Further studies are warranted to examine the distinct functional roles of the anterior and posterior hippocampal areas and the potential interactions between the hippocampus and the cerebral cortex in forming prospective temporal estimations.

Disclosures: Y. Onuki: None. **K. Ibayashi:** None. **Y. Ishishita:** None. **K. ohtani:** None. **N. Kunii:** None. **K. Kawai:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Program #/Poster #: LBA008.092/LBA177

Topic: H.10. Human Learning and Cognition

Support: Norman Prince Neurosciences Institute

Title: Interval timing dysregulation in essential tremor

Authors: *T. ULLRICH[1], S. LEE[2], W. F. ASAAD[2];
[1]Brown Univ., Westford, MA; [2]Neurosurg., Brown Univ., Providence, RI

Abstract: The cerebellum is implicated in timing behavior and has a putative role in essential tremor (ET) pathophysiology. In order to evaluate whether people with ET show any deficits in timing, we enrolled patients considering surgical treatment for medication-refractory ET (n=67, preoperative group) and age-matched controls (n=6) in a behavioral study evaluating the ability to reproduce time intervals in the 500-1500 ms range. We repeated the study for ET patients who received high-intensity focused ultrasound treatment (n=7, postoperative group) for ablation of the ventral intermediate nucleus (VIM), which receives input from the cerebellum, in order to assess the importance of the VIM in timing. Both ET groups exhibited significantly decreased accuracy and precision compared to controls (Mann-Whitney U and Levene tests). The imprecision manifested primarily at the shortest intervals, which attenuated the characteristic effect of scalar variability that defines increased variability for longer time intervals. Prior work has indicated that reproduction times are biased towards the mean of prior observed intervals. In our study, ET subjects demonstrated a stronger bias after presentation of a short interval than controls did, although this effect was deemed insignificant following false discovery rate adjustment. However, in the preoperative group, the bias was significantly amplified in trials following an early response, only if feedback was given (Mann-Whitney U test). This effect may or may not be isolated to the preoperative group, as the same feedback analysis is inconclusive for the postoperative and control groups, pending further data. These results suggest that ET patients were systematically more variable at time interval reproduction, which is best explained by a particular deficit in reproducing shorter intervals. We also enrolled ET patients undergoing deep brain stimulation electrode implantation for the VIM (n=12) and recorded intracranially while they completed the behavioral task. We utilized a semi-automated spike sorting pipeline to isolate single-unit activity. Current efforts are ongoing to characterize timing-related dynamics in the VIM.

Disclosures: T. Ullrich: None. **S. Lee:** None. **W.F. Asaad:** None.

Late-Breaking Poster

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Topic: H.10. Human Learning and Cognition

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National Research, Development and Innovation Office 2019-2.1.7-ERA-NET-2022-00038

Title: Direct in vivo identification of Hebbian networks in humans with a novel three-dimensional laminar electrode array

Authors: R. G. AVERKIN, S. BORDÉ, G. MOLNAR, P. BARZÓ, ***G. TAMAS**;
Univ. of Szeged, Szeged, Hungary

Abstract: We pioneered functional assessment of human synaptic function in acute brain slices with multiple patch-clamp recordings and showed that individual neurons can trigger sequences of polysynaptic events. Single neuron-activated groups of cells resembled the so-called functional assemblies proposed as building blocks of higher-order cognitive representations by D. Hebb. These synaptic event series were composed of motifs alternating glutamatergic and GABAergic postsynaptic potentials and required selective spike-to-spike coupling from pyramidal cells to GABAergic interneurons. We developed novel three-dimensional, high-density electrode arrays for human in vivo recordings. The maximal vertical density of recording sites (30 µm) is similar to the density of human neurons in the cortex, the minimal lateral spacing of shanks in the array is 200 µm. Our electrode arrays contain a scalable number of recording sites, can span all layers of the cortex if needed and allow quick manual surgical placement and incorporation into standard intracranial EEG grids useful in mapping recording sites relative to epileptic foci and/or propagating network oscillations. We successfully implanted several prototypes of the novel electrode arrays in combination with standard intracranial EEG grids for 7 to 11 days in human patients. Our recordings with the 3D array confirmed the strong power for low- and middle-frequency bands in supragranular layers compared to infragranular layers. We performed in vitro targeted patch clamp experiments in the neighborhood of in vivo electrode tracks in brain slices with the full anatomical recovery of the patched cells. Analysis of human in vivo recordings using the new microelectrode arrays allowed us to identify monosynaptically coupled human neurons in vivo. Moreover, these in vivo recordings confirmed the existence of reliable, monosynaptic human pyramidal cell-to-interneuron spike-to-spike coupling with up to 83% reliability and relatively weak pyramid to pyramid spike-to-spike coupling with <5% reliability. We conclude that the novel 3D high-density electrode array allows the identification of Hebbian firing sequences involving closely located pyramidal cells and interneurons with timeframes corresponding to high frequency cortical motifs in the human cortex.

Disclosures: R.G. Averkin: None. **S. Bordé:** None. **G. Molnar:** None. **P. Barzó:** None. **G. Tamas:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.094/LBA179

Topic: H.10. Human Learning and Cognition

Support: U01NS117839
K99NS126233

Title: Prefrontal and medial temporal neurons encode ordinal information of event sequences in humans

Authors: *E. PAVARINO[1], J. ZHENG[2], I. SKELIN[3], M. YEBRA[4], M. L. DARWIN[6], C. REED[7], S. K. KALIA[8], T. A. VALIANTE[3], D. KRAMER[9], J. A. THOMPSON[10], A. N. MAMELAK[11], G. KREIMAN[12], U. RUTISHAUSER[5];
[1]Harvard Univ., Boston, MA; [2]Neurolog. Surgery and Biomed. Engin., Univ. of California Davis, Davis, CA; [3]Univ. Hlth. Network, Toronto, ON, Canada; [4]Neurosurg., [5]Dept. of Neurosurgery, AHSP #6432, Cedars-Sinai Med. Ctr., Los Angeles, CA; [6]Neurosurg., CU Anschutz Med. Campus, Aurora, CO; [7]Cedars Sinai, Los Angeles, CA; [8]Toronto Western Res. Inst., Toronto, ON, Canada; [9]Univ. of Colorado Sch. of Med., Aurora, CO; [10]Neurosurg., Univ. of Colorado, AMC, Aurora, CO; [11]Cedars Sinai Med. Ctr., Los Angeles, CA; [12]Harvard Med. Sch., Boston, MA

Abstract: Humans remember episodic events as discrete units, yet how these memories are integrated into a chronological continuum remains unknown. While prefrontal and medial temporal regions are implicated in temporal recall, the specific neural mechanisms underlying this process in humans are unclear. We investigated this question by recording single-neuron activity and local field potentials in 23 drug-resistant epilepsy patients as they watched a custom-shot set of stimuli consistent of 25 video clips, each composed of four sequenced everyday events of variable length. Participants' memory was tested with scene recognition and temporal order discrimination tasks. We recorded 1014 single units across patients. We identified "order-selective neurons" (OSNs) in the hippocampus (12% of hippocampal population), amygdala (13%), and orbitofrontal cortex (10%) that responded selectively to specific event orders, regardless of event content and event absolute time occurrence. At a population level, we discovered that event order was linearly decodable from neural activity alone, with OSNs being the major contributing features. Removing OSNs from the pseudopopulation reduced decoding accuracy to chance levels, highlighting their crucial role for temporal information encoding. Trial-averaged PCA population trajectories in time revealed significant neural state-space shifts

corresponding to different event orders. At the mesoscale, theta oscillations increased in power along event sequences, with OSNs exhibiting theta phase precession. These findings reveal a neural mechanism for encoding event order in human episodic memory, demonstrating how event structure sculpts neural dynamics in medial temporal and orbitofrontal regions. This work provides insight into how the brain weaves discrete episodic events into a coherent temporal narrative, advancing our understanding of human episodic memory formation.

Disclosures: E. Pavarino: None. **J. Zheng:** None. **I. Skelin:** None. **M. Yebra:** None. **M.L. Darwin:** None. **C. Reed:** None. **S.K. Kalia:** None. **T.A. Valiante:** None. **D. Kramer:** None. **J.A. Thompson:** None. **A.N. Mamelak:** None. **G. Kreiman:** None. **U. Rutishauser:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.095/LBA180

Topic: H.11. Language

Support: Institutional funds from Penn State College of Medicine

Title: Sound symbolism for concrete, but not abstract, semantic domains is preserved in people with aphasia

Authors: *J. DORSI[1], C. SANDBERG[2], S. A. LACEY[3], L. NYGAARD[5], K. SATHIAN[4]; [1]Pennstate Col. of Med., Hershey, PA; [2]The Pennsylvania State Univ., University Park, PA; [4]Dept. of Neurol., [3]Penn State Col. of Med., Hershey, PA; [5]Psychology, Emory Univ., Atlanta, GA

Abstract: Speech sounds map onto certain domains of meaning, in a phenomenon termed sound symbolism. For example, the pseudowords ‘bouba’ and ‘kiki’ are associated with rounded and pointed shapes, respectively. Aphasia is a condition, often caused by a stroke, that impairs the understanding and/or production of words. Only two studies have investigated sound symbolism in people with aphasia (PWA), one showing that onomatopoeia facilitates performance by PWA on tasks relying on phonological-to-semantic connections (Meteyard et al., Neuropsychologia, 2015), and the other that sound-to-shape mapping for pseudowords is not as good in PWA as in neurologically intact people (NIP; Ammon et al., Cortex, 1977). Both studies suggest that sound-symbolic language may be preserved in aphasia, but onomatopoeia and shape both relate to concrete domains of meaning. PWA, like NIP, have better comprehension of concrete than abstract words (Alyahya et al., NeuroImage: Clinical, 2018). It is important to determine the extent to which sound-symbolic language is preserved in PWA, since this represents a potential rehabilitation avenue. Here, we compared sound symbolism for a concrete (shape) and an

abstract (valence) domain in 10 PWA and 10 age- and gender-matched NIP. We used a two-alternative forced-choice task (2AFC) in which participants classified auditory pseudowords as sounding either rounded or pointed (shape), and either good or bad (valence). 40 pseudowords were chosen for each domain from the highest-rated items in a prior study (Matthews et al., Soc Neurosci Abstr 2021, P883.07), evenly split between the two alternatives in each domain. ANOVA showed a main effect of domain in which accuracy was higher for the concrete (shape) than the abstract (valence) domain, and a main effect of group in which the PWA were less accurate than the NIP. Although the domain by group interaction was not significant, PWA classified pseudowords significantly above chance levels for shape but not valence, suggesting that sound symbolism for concrete, but not abstract, domains is preserved in aphasia. These results clarify the extent to which sound symbolism may be preserved in aphasia, and therefore help to shape potential rehabilitation approaches. Our ongoing work seeks to replicate these findings using different concrete and abstract domains and using other test paradigms such as ratings; and to extend this work to real words.

Disclosures: J. Dorsi: None. **C. Sandberg:** None. **S.A. Lacey:** None. **L. Nygaard:** None. **K. Sathian:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.096/LBA181

Topic: H.11. Language

Support: JSPS KAKEN 22K15628

Title: Decreased functional connectivity within the frontal language network in cerebellar mutism.

Authors: *K. IBAYASHI[1], Y. ONUKI[2], N. KUNII[4], K. KAWAI[3];
[2]Dept. of Neurosurg., [1]Jichi Med. Univ., Shimotsuke, Japan; [3]Dept. of Neurosurg., Jichi Med. Univ., Tokyo, Japan; [4]Dept. of Neurosurgery, Jichi Med. Univ., Shimotsuke, Japan

Abstract: *Background:* Cerebellar mutism is characterized by impaired speech production, volitional movement, and emotional regulation following posterior fossa surgery, most commonly for medulloblastoma. Its occurrence is approximately 30%, and most cases recover the ability to speak after weeks to months from surgery. The neuropathophysiological basis of cerebellar mutism remains understudied. *Case Presentation:* A 12-year-old male underwent gross total removal of medulloblastoma. Although postoperative MRI revealed no evidence of parenchymal damage, cerebellar mutism was evident immediately after surgery. Language-task-induced BOLD-fMRI response was recorded both at the symptomatic phase, and also at the

recovered phase. *Methods:* The language task was a word repetition task, which required the subject to covertly repeat the word presented through earphones, both at postoperative-week 4 (symptomatic phase) and week 34 (recovered phase). Functional connectivity was computed using Pearson's correlation coefficient, between the statistically extracted 7 language-related ROIs. Analysis was then focused on differences between symptomatic and recovered phases. *Results:*The results indicated that connections between; bilateral SMA and right IFG (pars triangularis and opercularis), left IFG (pars triangularis) and right IFG (pars triangularis/opercularis), and right MFG and right IFG (pars triangularis) decreased during the symptomatic phase of cerebellar mutism compared to the recovered phase. *Discussion:* Our results showed that the internal connectivity of the frontal language network decreased during the symptomatic phase of cerebellar mutism. The causal mechanism through which cerebellar pathology impacts the frontal language network remains elusive and requires further study.

Disclosures: K. Ibayashi: None. **Y. Onuki:** None. **N. Kunii:** None. **K. Kawai:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.097/LBA182

Topic: H.11. Language

Support: Weill Neurohub
Chan Zuckerberg Biohub

Title: Linking speech perception to production in single neurons of human precentral gyrus

Authors: *D. XU[1], J. E. CHUNG[2], A. SILVA[2], Q. R. GREICIUS[2], Y. ZHANG[2], M. K. LEONARD[2], E. F. CHANG[2];
[1]Neurolog. Surgery, Univ. of California, San Fransisco, San Francisco, CA; [2]Neurolog. Surgery, Univ. of California, San Francisco, San Francisco, CA

Abstract: Speech perception and production are deeply interconnected aspects of human language. The mechanisms that enable us to link a sequence of speech elements from perception to production remains unknown. Here, we used Neuropixels multielectrode array recordings throughout the speech cortical areas while participants performed a delayed speech repetition task. Single neuron activity was observed. We discovered "mirror" neurons in human precentral gyrus (PrCG) that are transiently activated after perceiving specific speech content during listening and before producing the same content during speaking. Another group called "bridge" neurons maintain elevated firing between the same speech content in perception and production, bridging over the delay period. These neurons link and transform speech elements parallel in time and for various sentences. Unsupervised population analysis reveals sustained and

orthogonal dynamics for different sentences only in middle PrCG. With characteristics of a premotor region, PrCG neurons preferentially encode specific phonemic sequences. These results reveal the role of PrCG neurons in linking specific contents from perception to production across the sensorimotor transformation of speech.

Disclosures: D. Xu: None. **J.E. Chung:** None. **A. Silva:** None. **Q.R. Greicius:** None. **Y. Zhang:** None. **M.K. Leonard:** None. **E.F. Chang:** None.

Late-Breaking Poster

LBA008: Theme H Late-Breaking Posters

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Topic: H.11. Language

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NSF Grant BCS-1 349 042
Center for Visual Science P30 EY001319

Title: Language-specific functional diaschisis: glioma infiltration of posterior perisylvian language areas disrupts functional responses in the left precentral gyrus

Authors: *W. BURNS[1], E. STRAWDERMAN[1], W. H. PILCHER[1], B. MAHON[1,2], F. GARCEA[1];
[1]Univ. of Rochester Med. Ctr., Rochester, NY; [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The left ventral precentral gyrus plays a key role in higher level cognitive functions, including speech motor planning. Dual route models of language propose that the left precentral gyrus receives input from the left inferior frontal gyrus to support laryngeal motor control for language production, as well as from the dorsal language pathway via the arcuate fasciculus. The dorsal language pathway underlies auditory-to-motor integration and is a key pathway supporting repetition of auditorily presented words. We hypothesized that lesions to the dorsal language pathway will disrupt functional neural responses in the left ventral precentral gyrus when participants repeat sentences. Moreover, we hypothesized this effect will be specific to the domain of language, such that lesions to the dorsal language pathway should have no effect upon neural processing in the left ventral precentral gyrus when participants hum short melodies. In our study, 56 pre-surgical participants with lesions distributed throughout the left hemisphere performed a language and music repetition task while undergoing functional MRI. On every trial, they were presented with a sentence (“the boy stopped to tie his shoes”) or piano melody; they were instructed to listen to and repeat the stimulus after a rehearsal period of 12 - 20

seconds. Overall, both language and music repetition elicited increased blood oxygen level-dependent (BOLD) signal in the left ventral precentral gyrus. We then tested if participants with lesions to the dorsal language pathway reduced BOLD responses specifically for language repetition - but not melody repetition - in the left precentral gyrus. Consistent with that hypothesis, lesions to the left supramarginal gyrus, the left ventral postcentral gyrus, the left posterior superior temporal gyrus, and the underlying white matter caused weaker BOLD responses in the left ventral precentral gyrus during sentence repetition. When the analysis was repeated with data from the melody repetition condition, we found no relation between BOLD responses in the left ventral precentral gyrus and lesion damage to those sites. Our results provide causal evidence that lesions to the dorsal language pathway exert a domain-specific reduction upon processing in the left ventral precentral gyrus. These findings indicate that auditory-to-motor integration processes that come by way of the dorsal language pathway provide key inputs to speech motor planning in the left ventral precentral gyrus.

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LBA008: Theme H Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: LBA008.099/LBA184

Topic: H.11. Language

Title: The importance of sentence structure: testing models of sentence meaning using representational similarity analysis of an fMRI reading task

Authors: *J. FODOR;
The Univ. of Melbourne, Melbourne, Australia

Abstract: How is sentence meaning encoded and processed in the brain? This study seeks to address this question by testing a range of computational models of sentence meaning using functional magnetic resonance imaging (fMRI). This work extends upon previous research in two main ways. First, this study analyses a more diverse mixture of sixteen different models, including word embeddings, transformers, syntactic parsing methods, and hybrid neurosymbolic architectures. Second, to control for the confound of lexical similarity, a set of sentence stimuli was developed in which various semantic roles (verb, agent, patient, etc) are interchanged (e.g. ‘The lobbyist wrote to the politician about the reporter’ becomes ‘The reporter wrote to the lobbyist about the politician’). Data collection involved participants reading 108 sentences while undergoing 7T fMRI scanning. Data were preprocessed using fMRIprep, with activation maps for each sentence estimated using GLMSingle. Representational Similarity Analysis (RSA) was used to assess the fit between each computational model and the fMRI activation. To determine

which brain regions encoded sentence information, voxelwise searchlight RSA analysis was also conducted. Searchlight results show sentence information is encoded in the medial frontal and inferior frontal gyrus, anterior and posterior temporal lobe, angular gyrus, posterior cingulate cortex, precuneus, and visual cortex. RSA results show that most models achieve correlations of between 0.02-0.20 with fMRI data. Surprisingly, there is no consistent relationship between model complexity and performance, with state-of-the-art transformers often performing similarly or even worse than simpler architectures. Furthermore, while models that ignore word order performed very poorly on sentences involving word interchanges, significant improvement was achieved by augmenting such models with information about semantic roles. These results highlight the critical role of sentence structure in semantic representation, and raise questions regarding whether transformers always represent sentence meaning in a comparable manner to the brain.

Disclosures: J. Fodor: None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.001/LBA1

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Using in situ hybridization with AMPIVIEW™ LoopRNA™ probes to evaluate spatial distribution of a long non-coding RNA in rodent brain

Authors: *G. HEINRICH[1], N. CHANDEL[2], F. MAZZONI[2], J. COLEMAN[2];
[1]Enzo Life Sci., Chapel Hill, NC; [2]Enzo Life Sci., Farmingdale, NY

Abstract: Introduction: Investigators are increasingly focused on long non-coding RNAs (lncRNAs) as epigenetic regulators, biomarkers, and therapeutic targets. Dysregulated expressions of lncRNAs are implicated in multiple disease etiologies, including cancers and neurodegenerative disorders. Because lncRNAs form a distinct class of molecules that do not translate into proteins, they are best detected *in situ* with purpose-designed molecular probes using techniques and tools that are still being optimized to identify and spatially characterize them in their native tissues and subcellular locations. The ability to delineate different properties, including stability, tissue specificity, and association with regulatory and effector transcripts and proteins, is crucial to understanding their biology, and to evaluating the efficacy of emerging therapies and diagnostic platforms. The non-coding RNA activated by DNA damage (*Norad*) is lncRNA required for genome stability and is unusual among lncRNAs in its high degree of expression and sequence conservation across mammalian species. Its dysregulation has been established in neuroblastoma and in murine brain injury models. **Methods:** In this study, we used AMPIVIEW™ RNA probes, powered by Enzo's LoopRNA™ ISH technology, to specifically

target the lncRNA *Norad* and its downstream target *Wnt5a*. Expression levels and spatial localization of selected targets were determined by *in situ* hybridization (ISH) in murine brain tissue samples. **Results**: We detect robust expression via chromogenic or fluorescent staining of the lncRNA *Norad* in both rat and mouse brain. We place this expression in the spatial context of the tissue with other associated targets along the Wnt signaling pathway. **Conclusion**: AMPIVIEW™ RNA probes specifically detect expression of the lncRNA *Norad* in fixed rodent brain tissue sections and can be used to characterize its spatial patterning across tissue architecture in the context of other important regulatory and associated factors. Our results highlight the power of ISH and the flexibility of AMPIVIEW™ and LoopRNA™ technology to detect multiple different types of RNA targets.

Disclosures: G. Heinrich: A. Employment/Salary (full or part-time):; Enzo Life Sciences. **N. Chandel:** A. Employment/Salary (full or part-time):; Enzo Life Sciences. **F. Mazzoni:** A. Employment/Salary (full or part-time):; Enzo Life Sciences. **J. Coleman:** A. Employment/Salary (full or part-time):; Enzo Life Sciences.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.002/LBA2

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Cross-site validation of mAb-based huntingtin quantification assays

Authors: *Y. ZHANG[1], V. PAHLOW[1], C. FRYE[1], X.-X. LIN[2], I. ANGULO[3], D. MACDONALD[4], T. CUSTER[1], Z. ALI[1];
[1]Charles River Labs, Skokie, IL; [2]Charles River Labs, Leiden, Netherlands; [3]Charles River Labs, Colmenar Viejo, Spain; [4]CHDI Management, Inc., Los Angeles, CA

Abstract: Cross-site validation of mAb-based huntingtin quantification assays
Yilin Zhang[1], Vanessa Pahlow[1], Carol Frye[1], Xin-Xuan Lin[2], Ivan Angulo[2], Zahida Ali[1], Douglas Macdonald[3], T. Corey Custer[1]1 Charles River, Skokie, IL, USA 2 Charles River, Leiden, NL 3 CHDI Management, Inc., The Company that Manages the Scientific Activities of CHDI Foundation, Inc, Los Angeles, CA, USA
AbstractHuntington's disease (HD) is caused by an expansion of the CAG repeat sequence in the huntingtin gene which produces an expanded polyglutamine (polyQ) domain resulting in the mutant huntingtin protein (mHTT). Sensitive, reliable, and readily accessible assays that enable the detection of the mHTT protein, as well as other huntingtin (HTT) variants, in HD animal models is key for pre-clinical HD programs. Previously, we have described selective assays that measure HTT proteins on the electrochemiluminescence Meso Scale Discovery (MSD) detection platform using either polyclonal or monoclonal antibodies. Now, we further validate the assays

across laboratory sites for both rodent and non-human primate model biosamples. Using seventy-two zQ175Q mouse model cortex tissues, we could detect mHTT level changes in heterozygous versus homozygous zQ175Q when compared to wild type murine HTT in both polyQ-length dependent and independent assays. We also expanded our HTT detection platform to non-human primate (NHP) biosamples, using thirty-five brain tissue samples from six regions from 5 NHP subjects. The cross-site verification in both animal models was conducted by comparing the limit of detection (LoD), lower limit of quantification (LLoQ), dynamic range, and precision. Additionally, correlation coefficient analysis demonstrated the studies performed in geographically distinct laboratories are reliable. Overall, these robust and sensitive MSD-based assays add a powerful platform to the HD research community to assess HTT levels and test novel HTT-directed therapeutics in rodent and NHP models.
Key words: Huntington's disease (HD), huntingtin (HTT), Meso Scale Discovery (MSD), Cross-site validation.

Disclosures: Y. Zhang: None. **V. Pahlow:** None. **C. Frye:** None. **X. Lin:** None. **I. Angulo:** None. **D. Macdonald:** None. **T. Custer:** None. **Z. Ali:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.003/LBA3

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Defense Threat Reduction Agency (DTRA) CB11092

Title: Evaluating airway responsiveness: leveraging a novel assay for assessing functional response in precision-cut lung slices (PCLS) from a humanized mouse model

Authors: *J. SHERLOCK[1,2], S. COE[1,2];
[1]USAMRICD, Gunpowder, MD; [2]ORISE, Oak Ridge, TN

Abstract: Organophosphorus nerve agent (OPNA) poisoning leads to a cholinergic crisis resulting in difficulty breathing, seizures, and death due to the inhibition of acetylcholinesterase (AChE). This process can be reversed with the use of reactivators which interact with the inhibited enzyme, releasing the bound OPNA from the active site. A genetically modified mouse strain was developed to address both the inherent resistance to intoxication afforded by serum carboxylesterase (CaE) and the varied reactivation potential of species-specific AChE. These goals were achieved by incorporating a loss of expression mutation of CaE (KO) as well as the alteration of the protein coding sequence of the AChE loci (KI) to express the human enzyme homolog. The strain combining both the knock in and knock out (KIKO) modifications presents an opportunity to evaluate compounds that interact with AChE in a humanized model. To

confirm that the KIKO mouse accurately models the human response, direct comparison of tissue functionality as it relates to reactivation potential is required. In this study, precision-cut lung slices (PCLS) will be used as a comparative *ex vivo* model to visualize lung function and quantitate reactivation after exposure to OPNAs. These slices maintain the complexity of lung tissue, allowing for the study of airway function. Previous studies have utilized PCLS to demonstrate airway responsiveness, providing a system to test therapeutics for OPNA exposure. This study aims to develop an assay by measuring inhibition and reactivation as a function of airway response in KIKO lung tissues. PCLS samples will demonstrate airway contraction when exposed to OP and reversal of contraction when administered a reactivator, analyzed via brightfield microscopy. In the future, we anticipate that the functional reactivation of KIKO tissue will be compared to human tissue and presented as an adjunct for *in vivo* testing of OPNA reactivators.

Disclosures: J. Sherlock: None. **S. Coe:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.004/LBA4

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: An Optimized Fluorescent 9-plex Spatial Proteomics Workflow with Spectral Unmixing to Identify Cell Types in the Brain

Authors: *D. NIELL, N. MOONEY, K. HAMILTON;
Thermo Fisher Scientific, Eugene, OR

Abstract: Fluorescent localization of biomarkers markers can enable detailed identification of cell types within the brain. The ability to uniquely identify cell types increases greatly with the number of biomarkers that can be used concurrently. Spatial proteomic workflows have been enhanced through the integration of enzyme-activated amplification reagents in combination with fluorescent spectral unmixing. These advancements offer several benefits, including the simultaneous detection of up to 8 biomarkers within a single tissue section. In comparison, traditional immunohistochemistry (IHC) approaches have limitations in terms of resolving spectrally distinct signals for a limited number of targets. To address this challenge, we have developed a multiplex spatial IHC workflow that incorporates spectral unmixing. By optimizing spatial amplification reagents in conjunction with a spectral imager and subsequent single-cell analysis, we can enable a more comprehensive investigation of cell types in complex tissues like the brain using a single sample. A key innovation in our workflow is the integration of spectral unmixing, which enables the separation of overlapping spectral signatures and the accurate identification of 8 individual biomarkers. Using a spatial imaging system to generate high-

resolution images of whole tissue sections combined with quantitative image analysis software, we can measure the spatial distribution of distinct cell populations based on the identified biomarkers. This allows for the specific localization of neuronal and glial subpopulations, as well as proliferating cells and disease markers, within a single tissue slice. These results highlight the advantages of using a spectrally unmixed 9-plex sample analysis (8 biomarkers and a nuclear counterstain) to investigate the spatial relationships between cell types in the brain. This technology has the potential to advance our understanding of the complex cellular dynamics and interactions within the brain, paving the way for further discoveries in neuroscience research and potentially contributing to the development of targeted therapies for neurological disorders.

Disclosures: D. Niell: A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **N. Mooney:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **K. Hamilton:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.005/LBA5

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: 1NIH NIAA 1R01AA027808-01A1
HiREC-NIMHDS21MD001830

Title: Characterization of B6.129-Ctnnb1^{tm2Kem}/KnwJ during extinction learning after binge-like alcohol exposure

Authors: *P. A. COLON RIVERA[1], A. RIVAS JIMENEZ[2], C. VELAZQUEZ-MARRERO[3]; [1]Biol., Univ. of Puerto Rico, Cayey, Puerto Rico; [2]Univ. Of Puerto Rico Anat. and Neurobio. Grad. Program, Morovis, Puerto Rico; [3]Inst. of Neurobio., Univ. of Puerto Rico Med. Sci. Campus/ Inst. of Neurobio., San Juan, PR

Abstract: The expression of β-catenin, as part of the canonical Wnt-signaling pathway, plays a fundamental role in cell processes such as proliferation, differentiation, and homeostasis. The availability of conditional knockouts (K.O.) allow for local and temporal specificity without interrupting normal developmental processes. We will use the B6.129-Ctnnb1^{tm2Kem}/KnwJ conditional transgenic K.O. strain in a C57 background, to examine the role of β-catenin in alcohol-related behavioral paradigms. Previous work in our lab has shown the importance of Wnt/β-catenin signaling on the development of alcohol molecular tolerance associated with increased voluntary alcohol consumption and extinction learning. Our overarching hypothesis is that activation of the Wnt/β-catenin signaling has a pivotal role in mediating contextual fear extinction deficit induced by alcohol. Validation of a local K.O. of β-catenin in key brain regions

such as the basal lateral amygdala (BLA) on a transgenic model, will allow us to determine its role in alcohol extinction deficits. The induction of Cre-recombinase by pENN.AAV.CamKII.HI.GFP-Cre.WPRE.SV40 (AAV-Cre) as compared to the control AAV-GFP will be outlined; validating positioning, viral expansion, and quantifying GFP luminescence. Further determination of specific knockdown via immuno-histological quantification of β-catenin will be performed on coronal slices using cryo-preserved tissue samples. The implementation of this genetic model will conclusively determine the role of Wnt/β-catenin, allowing for novel targets and therapeutic approaches in the development of prevention and treatment alternatives for anxiety disorders associated with binge-alcohol drinking.

Disclosures: P.A. Colon Rivera: None. **A. Rivas Jimenez:** None. **C. Velazquez-Marrero:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

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Program #/Poster #: LBA009.006/LBA6

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: W. M. Keck Award KF-05617242

Title: Assessing feasibility of tracking expression of AAV cargos in living mice with bioluminescent reporters

Authors: *M. TOLEDANO[1], C. CALLICOATTE[1], K. LE[2], M. METCALFE[1], A. LUPTAK[3], J. PRESCHER[4], O. STEWARD[5];
[1]Anat. and Neurobio., [2]Med. Scientist Training Program, [3]Pharmaceut. Sci., [4]Chem., Univ. of California, Irvine, Irvine, CA; [5]Reeve-Irvine Res. Ctr., Univ. of California, Irvine, Irvine CA, CA

Abstract: Viral vector delivery of genetic cargos is a powerful tool for discovery and translational science. However, applications require extensive optimization for timing and dosing, which creates high-cost bottlenecks because current assays of cargo expression require postmortem assessments of multiple animals at multiple time points. To overcome this bottleneck, we are testing approaches using bioluminescent reporters that allow serial tracking of adeno-associated virus (AAV) cargo expression in living rodents. Bioluminescence is generated through an enzyme, luciferase, acting on luciferin substrates. Viral vectors expressing luciferase can be injected into the brain and luminescence can be detected in living animals through the skull and scalp using an in vivo imaging system (IVIS). Here, we report studies assessing the ability of luminescence to quantitatively track AAV cargo expression over time after injections

of AAV into the sensorimotor cortex. Our previous studies reveal that bioluminescence detected by IVIS from equivalent doses of AAV expressing firefly luciferase (fLuc) varies across animals by orders of magnitude, but luminescent signal within individual animals is consistent over time. To determine the reasons for high inter-animal variability, we injected AAV expressing luciferase and an HA tag into the sensorimotor cortex of mice, and assessed: 1) variability of expression of HA and fLuc across animals by immunohistochemistry (IHC) using automated thresholding algorithms for image analysis; 2) the relationship between bioluminescent signal and AAV DNA levels by qPCR; 3) feasibility of tracking timing of cargos that are expressed transiently. IHC assessments of cargo expression revealed a strong relationship between numbers of transduced neurons and total fLuc (r^2=0.9784), with intra-animal variability consistent with expression of other AAV cargos such as GFP. The relationship between luminescence and AAV-derived fLuc transgene copies present in the injection site determined by qPCR from dissected brain samples was relatively weak (r^2 =0.3067). Preliminary studies indicate feasibility of quantitatively tracking timing (onset and cessation) of expression of cargos that are expressed transiently in individual mice. Together, our data suggests the following: 1) high variability of luminescence does not reflect high variability of transduction or AAV-driven fLuc expression; 2) IHC provides a more reliable measure of extent of transduction than qPCR from dissected samples; and 3) it is feasible to quantitatively track timing (onset and cessation) of expression of cargos that are expressed transiently in individual mice.

Disclosures: M. Toledano: None. **C. Callicoatte:** None. **K. Le:** None. **M. Metcalfe:** None. **A. Luptak:** None. **J. Prescher:** None. **O. Steward:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OS is a co-founder, scientific advisor, and has economic interests in the company Axonis Inc, which is developing novel therapies for spinal cord injury and other neurological disorders..

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.007/LBA7

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: China Postdoctoral Innovation Talent Support Program
China Postdoctoral Science Foundation Program
National Natural Science Foundation of China

Title: Optimization of Miniature Base Editing Systems and Application in Snijders Blok-Campeau Syndrome

Authors: *W. LI, T.-L. CHENG;
Inst. for Translational Brain Sci., Fudan Univ., Shanghai, China

Abstract: Snijders Blok-Campeau Syndrome, a rare hereditary brain disorder caused by *CHD3* gene mutations, is clinically characterized by intellectual developmental delay and symptoms associated with autism. Currently, effective clinical treatment options are lacking. Gene editing technology has witnessed rapid advancements in recent years, demonstrating significant potential for accurately rectifying pathogenic mutations in the genome. This holds immense promise for treating rare genetic diseases. However, the clinical application of gene editing technologyfaces a crucial challenge: the large size of Cas endonuclease proteins hinders efficient packaging and poses difficulties in in vivo delivery.This work is dedicated to the development and optimization of a novel miniature base editing system. The goal is to provide new tools for the precise repair of *CHD3* gene mutations, explore potential therapeutic strategies, and offer innovative approaches to treating rare genetic brain diseases. The initial phase involves the screening of Cas endonuclease and deaminase components from various species to develop and optimize miniature base editors. The aim is to enhance base editing efficiency, widen the activity window, and minimize off-target risks. Subsequently, different combinations of sgRNA-miniature base editors will be screened in vitro. The work will conclude by exploring the application of the miniature base editing system in gene therapy using a mouse model of Snijders Blok-Campeau Syndrome.

Disclosures: W. Li: A. Employment/Salary (full or part-time):; Fudan 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.; Shanghai Jiaotong University. **T. Cheng:** A. Employment/Salary (full or part-time):; Fudan 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.; Shanghai Jiaotong University.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.008/LBA8

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Israel Science Foundation grants 2958/21 and 3363/21
Israel Ministry of Science grant 2180
BrightFocus Foundation grant 929965

Title: Multiplexed super-resolved characterization of intact brain organoids using expansion sequencing

Authors: A. GLICK[1], N. FELDMAN[1], K. WARSHAWSKY[2], G. VATINE[2], *S. ALON[1];
[1]Fac. of Engin., Bar Ilan Univ., Ramat Gan, Israel; [2]Ben-Gurion Univ., Beersheba, Israel

Abstract: Brain organoids are three-dimensional (3D) structures, mainly derived from pluripotent stem cells, that aim to mimic key aspects of human brain development. They have emerged as a key tool in neuroscience research, providing unparalleled opportunities to model neurodevelopmental processes, study complex brain disorders, and test potential therapeutic interventions in a controlled and physiologically relevant environment. However, until now it has been challenging to perform multiplexed imaging of RNA in intact brain organoids with single cell resolution, and almost impossible to do so with subcellular resolution. This difficulty arises from the fact that common spatial transcriptomics technologies can only be applied to thin tissue sections (~10 micrometers) whereas organoids are typically more than 100 micrometers thick. One can choose to prepare sections from intact organoids, but this will not capture the organoid complex 3D structure. Here we demonstrate the first multiplexed super-resolved characterization of intact brain organoids. Our technology is a modified version of expansion sequencing (ExSeq; Alon et al., Science 2021, Vol 371, Issue 6528), which enables highly multiplexed mapping of RNAs of thick tissues with nanoscale resolution. Performing ExSeq on patient-derived induced pluripotent stem cells (iPSC) differentiated into cortical organoids, allows us to examine: (1) the content of cells inside the intact organoids while preserving morphological cues and the identity of proximal cells; and (2) nanoscale RNA distribution within neurites from single cells. In addition, we extended ExSeq to allow multiple cycles of antibodies staining on expanded organoids. This allows us to combine genomics and protein staining via image analysis, and provides a deep characterization of intact brain organoids.

Disclosures: A. Glick: None. **N. Feldman:** None. **K. Warshawsky:** None. **G. Vatine:** None. **S. Alon:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.009/LBA9

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Investigating Ancestral Genetic Factors in Children with ADHD

Authors: *Z. AGHA[1], J. B. WILLIAMS[2];
[1]Dept. of Psychiatry, SUNY Univ. at Buffalo, Buffalo, NY; [2]Dept. of Psychiatry, Jacob Sch. of Med. and Biomed. Sciences, Univ. At Buffalo, Buffalo, NY

Abstract: Title: Investigating Ancestral Genetic Factors in Children with ADHD Zehra Agha[1], Jamal B. Williams[11]Department of Psychiatry, State University of New York at Buffalo,

Jacobs School ofMedicine and Biomedical Sciences, Buffalo, NY 14203, USA.**Abstract**Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorderaffecting ~12% of school-aged children in the US. Recent studies suggest that geneticsrepresents more than 80% of the risk of ADHD, yet which genetic contributions areresponsible for ADHD has not been fully elucidated. Specifically, although commonvariants have been identified in large-scale analysis, rare variants associated with ADHDare far less known. Furthermore, the majority of what we understand about thesecontributions is derived from those of European descent. Therefore, the need for in-depthgenetic analysis of non-European ancestry is needed. In this study, we compare commonand rare variants between European American and African American children betweenthe ages of 9-10 years old from the Adolescent Brain Cognitive Development cohort. Indoing so, we perform comparative polygenic risk analysis between European and AfricanAmericans with and without ADHD. We also investigated protein truncating variants(PTVs) between the two groups, with a pLI ³ 0.9, in which we identified 26,075 PTVs in9,810 different genes in African American cases, with 153 variants being de novo. Incomparison, the burden of variants in the same 9,810 genes among the European caseswas 25786. Notably, there was a complete overlap in the genes impacted by differentvariants between African American and European American cases. Lastly, our study alsodemonstrates distinct differences in copy number variants between ancestral groups. Ourresearch not only highlights novel genetic contributions to ADHD but also highlightsancestral differences between European and African Americans.

Disclosures: Z. Agha: None. **J.B. Williams:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.010/LBA10

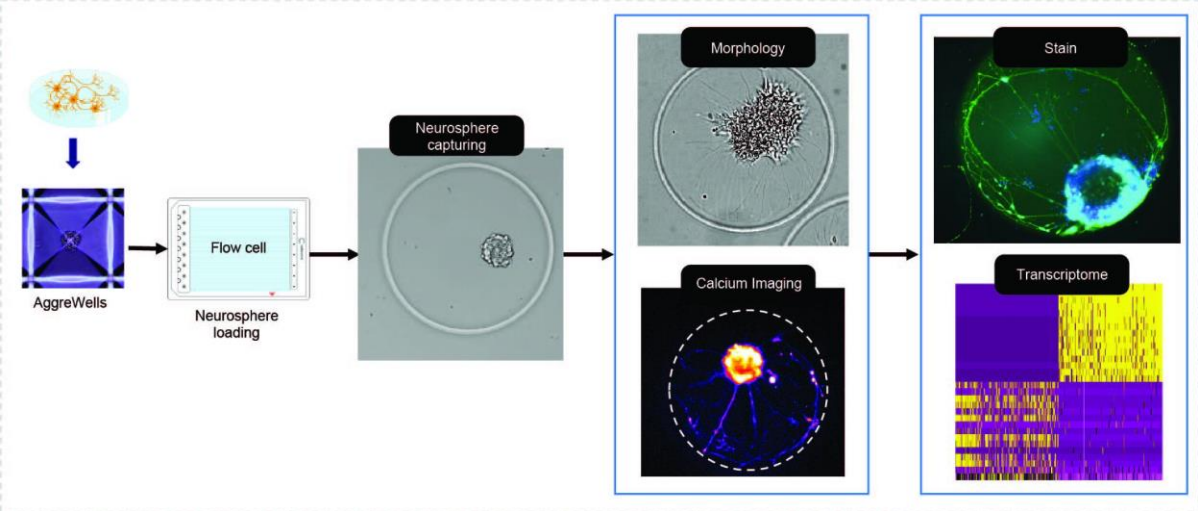
Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Novel system for culturing and analyzing single neurospheres for high-scale study of physiological-relevant neuronal functions and transcriptomes

Authors: *N. H. ELDER[1], O. VILA[3], S. FARAHVASHI[3], G. SCHROTH[3], M. RONAGHI[3], F. FATTAHI[2];
[2]Cell. and Mol. Pharmacol., [1]Univ. of California San Francisco, San Francisco, CA; [3]Cellanome, Foster City, CA

Abstract: We present an innovative technology that encapsulates and maintains human neurospheres for extended periods to investigate the dynamics of axon growth, network formation, synapse development, and neurodegeneration. This system enables precise manipulation, imaging, and profiling of individual neurospheres, thus opening new research

avenues to study neuron-target interactions, axogenesis, neurodegeneration, and neuronal physiology at an unprecedented resolution. Traditional molecular and functional assays often involve disruptive processes such as cell dissociation, droplet encapsulation, or flow-based microfluidics, which perturb neurons and alter their physiological state, reducing the reliability of biological findings. Furthermore, these methods do not permit the study of live neurons within functional networks, limiting the potential for multi-modal assays that correlate dynamic physiological properties with molecular profiles. Our platform addresses these challenges by enabling the comprehensive study of individual neurospheres, either in isolation or in networks. To achieve this goal, we generated neurospheres from 17-day old V2a interneurons derived from human pluripotent stem cells. Groups of 100 or 200 neurons were aggregated in AggreWells for 2 days before being transferred to our flow cells. Our novel technology then captures individual neurospheres in, customizable, biocompatible compartments enabling longitudinal monitoring over days to weeks. Throughout this period, multi-modal analysis can be conducted on the same neurosphere by integrating morphology, function, and transcriptomic data through live imaging and barcoded library generation for RNA-sequencing. By preserving the integrity and function of neurospheres, this technology enables large scale and in-depth assessment of neuronal functions such as synapse formation and axon growth in response to various perturbations. Our goal is to leverage this system to perform high throughput multimodal screens to advance our understanding of neural degeneration and repair.



Disclosures: **N.H. Elder:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Cellanome. **O. Vila:** A. Employment/Salary (full or part-time):; Cellanome. **S. Farahvashi:** A. Employment/Salary (full or part-time):; Cellanome. **G. Schroth:** A. Employment/Salary (full or part-time):; Cellanome. **M. Ronaghi:** A. Employment/Salary (full or part-time):; Cellanome. **F. Fattahi:** F. Consulting Fees (e.g., advisory boards); Cellanome.
Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.011/LBA11

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Spatial multiomic assay for studying interneuron heterogeneity in the brain

Authors: *C. ZHOU[1], **D. WAKHLOO**[2], A. DIKSHIT[2], L.-C. WANG[2];
[1]R&D, ACDbio/Bio-techne, Newark, CA; [2]ACDbio/Bio-Techne, Newark, CA

Abstract: Interneurons are a diverse group of inhibitory neurons that play an essential role in maintaining the delicate balance and function of neural circuits within the brain. Any disruptions of the balance between excitatory and inhibitory signals can lead to complex neurological disorders, age-related cognitive decline, and psychiatric disorders. Neurological and aging-related disorders lead to structural and functional changes, such as alterations in synaptic plasticity, neurotransmitter levels, and neural connectivity. Interneurons, particularly within the hippocampus, the cortex, and the striatum, are integral to memory formation, learning, and sensory processing. Therefore, valuable insights can be gained from understanding the interneuron diversity in the brain. To enable optimum protein detection with RNA, we have developed a new protease-free workflow for the RNAscope™ Multiplex Fluorescent V2 assay that can detect up to 4 RNA targets with proteins. This assay utilizes a TSA-based amplification strategy that boosts the signal for both RNA and protein targets. We utilized 3 RNA probes against three widely studied interneuron types: *Pvalb* for Parvalbumin neurons, *Vip* for Vasoactive Intestinal Peptide, and *Sst* for Somatostatin interneurons. An antibody against NeuN was used to stain the nuclei of all mature neurons. We used these markers to examine the interneuron diversity in the aging brain and Parkinson disease mouse brain. RNAscope™ Multiplex Fluorescent V2 assay offers a powerful technique for studying cellular diversity by visualizing target RNAs with protein markers in brain tissue sections. The protease-free workflow enables optimal protein detection by preserving antigen integrity and tissue morphology. This multiomic workflow valuable insights required to study complex tissues like the brain and aids in understanding interneuron heterogeneity at different ages and in various neurological disorders.

Disclosures: C. Zhou: A. Employment/Salary (full or part-time):; Author is full time employee of Bio-techne/ACDbio. **D. Wakhloo:** A. Employment/Salary (full or part-time):; Author is full time employee of Bio-techne/ACDbio. **A. Dikshit:** A. Employment/Salary (full or part-time):; Author is full time employee of Bio-techne/ACDbio. **L. wang:** A. Employment/Salary (full or part-time):; Author is full time employee of Bio-techne/ACDbio.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.012/LBA12

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH R01 HG011864
1R01NS121223

Title: Ribo-stamp - a new method for measuring translation in neurons at single-cell and isoform resolution.

Authors: *F. ZAMPA[1], S. L. SISON[2], G. LIPPI[3], G. W. YEO[4];
[1]Dorris Neurosci. Dept., Scripps Res. Inst., San Diego, CA; [2]Neurosci., Univ. of California San Diego, San Diego, CA; [3]Neurosci., The Scripps Res. Inst., La Jolla, CA; [4]Mass Inst. Tech., Cambridge, MA

Abstract: A detailed census of the identity and function of brain cell types is necessary to understand the complex biology of cognition and behavior. Single cell RNA-sequencing (scRNA-seq) is used to map single-cell transcriptomes as proxies of functional states. Still, transcriptomic profiles do not capture post-transcriptional regulatory mechanisms, a concern for neuronal cells which heavily rely on translational controls in response to activity. Recent single-cell mRNA translation profiling methods have significantly advanced the field but currently exhibit limitations in scalability, or do not enable concurrent translation and transcriptome profiling. Generally, these technologies also require highly specialized technical expertise, which has hindered their widespread adoption. To overcome these limitations, we have developed the Ribosome Surveying Targets by Antibody-free Mutation Profiling (Ribo-STAMP) technology. In Ribo-STAMP, a fusion of the cytidine deaminase APOBEC1 with a ribosomal protein is expressed in cells, resulting in cytosine into uracil (C-to-U) edits that permanently mark translated mRNAs and that are identified by standard RNA-seq analyses using mutation-aware transcript mapping algorithms. Here, we establish the utility of Ribo-STAMP for neuroscience research. We validate Ribo-STAMP in primary cultures, by profiling the neuronal transcriptome and translatome in response to BDNF stimulation. We further combine Ribo-STAMP with scRNA-seq to study translation efficiency in mouse hippocampus cell types. Leveraging short- and long-read RNA sequencing, we uncover cell-type specific transcription-independent translation programs, down to RNA isoforms resolution. Intriguingly, we also identify global and gene-specific translation rates differences among hippocampal principal cells that are modulated by neuronal activity. Results from this study indicate that Ribo-STAMP can be used for RNA translation mapping, as well as for measuring neuronal stimulation-induced translation. Understanding changes of translational profiles of brain cell types at baseline and after neuronal activity will provide insights into how the brain functions in a healthy state and how it may go awry during disease.

Disclosures: F. Zampa: None. **S.L. Sison:** None. **G. Lippi:** None. **G.W. Yeo:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.013/LBA13

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Highly multiplexed immunofluorescence imaging of human and murine brain tissues

Authors: X. MESHIK, M. INGALLS, A. NORTHCUTT, *O. BRAUBACH;
Canopy Biosci. - A Bruker Co., St. Louis, MO

Abstract: Neuronal and glial cell types can be characterized using cellular morphology, molecular expression profile, excitability, spatial context, or some combination of these parameters. Multiplex immunofluorescence imaging (mIF) introduces new opportunities to further elucidate the molecular and cellular diversity of brain cells by providing *in situ* biomarker expression detection with high plexity while maintaining single-cell and subcellular resolution. Here, we present a quantitative spatial biology solution to study fresh frozen and FFPE tissue samples of human and animal origin using the CellScape Precise Spatial Multiplexing platform. Tissues are mounted on standard microscope slides and then enclosed in microfluidic chambers for immediate use or long-term storage. Staining and imaging are then conducted automatically, on-instrument and in real-time. The experiment is divided into separate iterative staining and imaging cycles, which provide the end user with the opportunity to pause and conduct inter-cycle analyses that may guide decisions on whether and how to continue each experiment. With the facilitation of cell profiling and spatial analysis in mind, we developed an antibody panel consisting of neuronal, glial, vascular, and cellular architecture markers for use in human FFPE and mouse fresh-frozen tissues. Additionally, we present staining data from the application of this panel on healthy and diseased brains, collectively demonstrating that mIF with CellScape is a reliable spatial biology solution for neuroscience research.

Disclosures: X. Meshik: A. Employment/Salary (full or part-time):; Bruker Corporation. **M. Ingalls:** A. Employment/Salary (full or part-time):; Bruker Corporation. **A. Northcutt:** A. Employment/Salary (full or part-time):; Bruker Corporation. **O. Braubach:** A. Employment/Salary (full or part-time):; Bruker Corporation.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.014/LBA14

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Automated preparation of single nuclei from FFPE samples for snRNA-Seq

Authors: *N. RAPICAVOLI[1], N. KHAN[1], N. PEREIRA[2], J. SCHIMMEL[1], R. CHALIGNE[3];
[1]S2 Genomics, Livermore, CA; [2]S2 Genomics, LIVERMORE, CA; [3]MSKCC, New York, NY

Abstract: Formalin-fixed, paraffin-embedded (FFPE) tissues are the preferred format for preserving clinical samples with an estimated 20 million samples collected each year in the United States. Until recently, FFPE tissue samples have been difficult to study by single cell RNA sequencing. Recent advances in single nuclei RNA-Seq technology have made it possible to overcome these challenges and generate high-quality gene expression data from FFPE samples at the single nuclei level. We report here the development of a fully automated workflow for the deparaffinization, rehydration and processing of FFPE slices into singulated nuclei on the Singulator 200+ Platform. Isolated nuclei are compatible with the 10x Genomics Chromuium flex assay which uses targeted probes to hybridize to RNA. Single nuclei sequencing data will be presented on the preparation and analysis of snRNASeq libraries from healthy human brain and glioblastoma samples.

Disclosures: N. Rapicavoli: A. Employment/Salary (full or part-time):; S2 Genomics. **N. Khan:** A. Employment/Salary (full or part-time):; S2 Genomics. **N. Pereira:** A. Employment/Salary (full or part-time):; S2 Genomics. **J. Schimmel:** A. Employment/Salary (full or part-time):; S2 Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); S2 Genomics. **R. Chaligne:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.015/LBA15

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Integration of combinatorial barcoding with spatial barcoding for single-cell RNA-sequencing application provides high-quality, high-resolution spatial transcriptome data in brain tissue

Authors: *V. TRAN[1], S. MARRUJO[2], J. WILHELMY[3], C. CHANG[4], W. WANG[3], J. PANGALLO[2], C. FAN[4], G. GEISS[2];
[1]Parse Biosci., Shoreline, WA; [2]Parse Biosci., Seattle, WA; [3]Curio Biosci., Palo Alto, WA; [4]Curio Biosci., Palo Alto, CA

Abstract: *Transcriptomic data is quintessentially valuable in single-cell analysis to determine cell identity and gene expression. However, during the course of sample processing, cells are dissociated and spatial information is lost. As a result, the nuances of cell interactions and*

organization are not captured. This is especially important in studies of primary tissues such as the brain that rely on cell-to-cell communication for functionality. Gathering single-cell information at scale is another challenge in the field. By combining the combinatorial barcoding technology of Parse's Evercode barcodes and Curio Trekker spatial nuclei tags, transcriptomic and spatial information is seamlessly co-captured for single-cell analysis.To demonstrate compatibility of the two technologies, frozen nuclei of brain sections were spatially tagged with the Curio Trekker platform. The same brain sections were subsequently dissociated and the nuclei were fixed and stored using the Parse Nuclei Fixation Kit. Frozen nuclei were thawed and processed through a custom Evercode barcoding workflow. The resulting libraries contained both transcriptomic and spatial information, with shared barcodes as the cell identifier. Trekker barcodes were enriched and sequenced alongside a corresponding transcriptome library, and through parallel pipelines the data were subsequently integrated. The results yielded both high-quality metrics of transcriptome data and high confidence of spatial assignments for samples of P1 mouse brain. At a sequencing depth of 20,000 reads/cell, we detected ~2,000 genes/cell and >60% nuclei were spatially assigned. This results in a high-quality dataset containing detailed gene expression profile for individual nucleus in its spatial context, allowing for robust analysis of cell-cell interaction.Together the technologies of combinatorial barcoding and spatial resolution will lead to unprecedented scaling that will resolve new biological insights in the field of neuroscience and beyond.

Disclosures: **V. Tran:** A. Employment/Salary (full or part-time):; Parse Biosciences. **S. Marrujo:** A. Employment/Salary (full or part-time):; Parse Biosciences. **J. Wilhelmy:** A. Employment/Salary (full or part-time):; Curio Bioscience. **C. Chang:** A. Employment/Salary (full or part-time):; Curio Bioscience. **W. Wang:** A. Employment/Salary (full or part-time):; Curio Bioscience. **J. Pangallo:** A. Employment/Salary (full or part-time):; Parse Biosciences. **C. Fan:** A. Employment/Salary (full or part-time):; Curio Bioscience. **G. Geiss:** A. Employment/Salary (full or part-time):; Parse Biosciences.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.016/LBA16

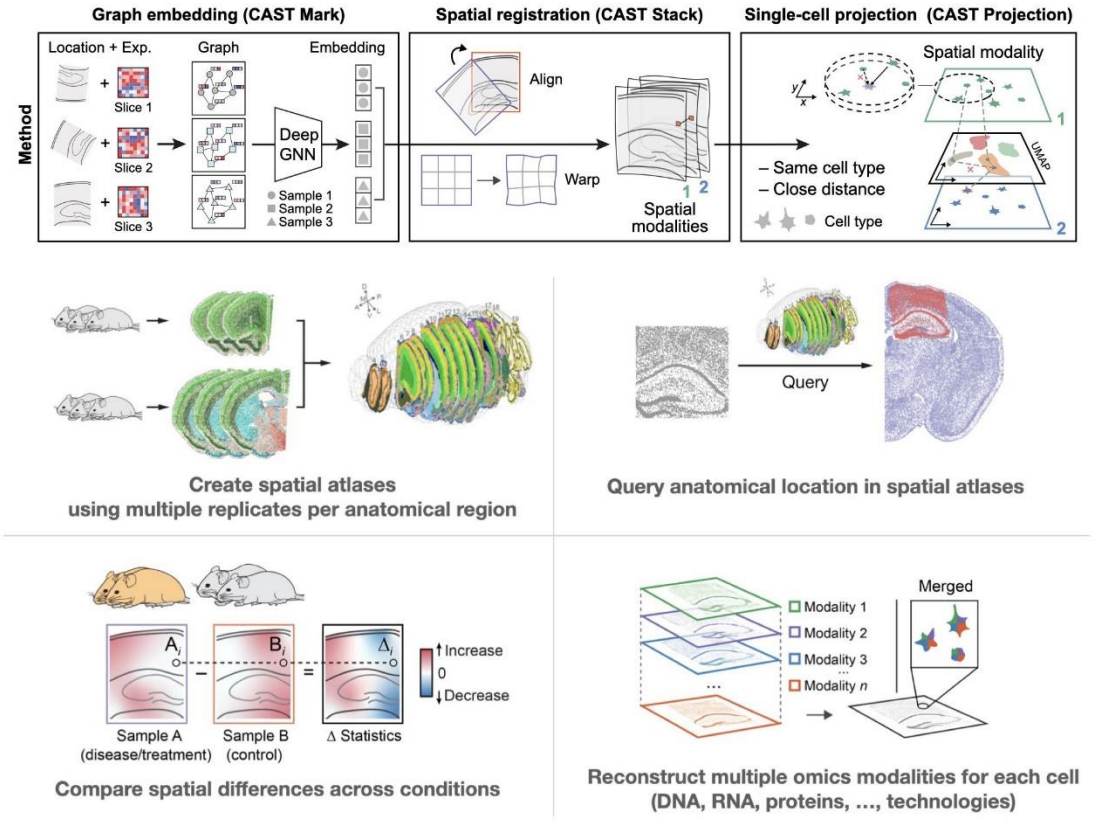
Topic: I.02. Systems Biology and Bioinformatics

Support: NIH DP2 New Innovator Award 1DP2GM146245
NIH BRAIN CONNECTS UM1 NS132173
Thomas D. and Virginia W. Cabot Professorship
Edward Scolnick Professorship
Ono Pharma Breakthrough Science Initiative Award
Merkin Institute Fellowship

Title: Search and match across spatial omics data of the brain at single-cell resolution

Authors: *S. LUO[1,2], Z. TANG[1,2], X. WANG[1,2];
[1]Stanley Ctr. for Psychiatric Res., Broad Inst., Cambridge, MA; [2]Dept. of Chem., MIT, Cambridge, MA

Abstract: Spatial omics technologies characterize molecular properties of the brain with spatial information, but integrating and comparing spatial data across different technologies and modalities is challenging. A comparative analysis tool that can search, match, and visualize both similarities and differences of molecular features in space across multiple samples is lacking. To address this, we introduce CAST (Cross-sample Alignment of SpaTial omics), a deep graph neural network (GNN)-based method enabling spatial-to-spatial searching and matching at the single-cell level. CAST aligns brain samples based on intrinsic similarities of spatial molecular features and reconstructs spatially resolved single-cell multi-omic profiles. CAST further allows spatially resolved differential analysis (ΔAnalysis) to pinpoint and visualize disease-associated molecular pathways and cell-cell interactions in Alzheimer's disease samples, and single-cell relative translational efficiency (scRTE) profiling to reveal variations in translational control across cell types and brain regions. CAST serves as an integrative framework for seamless single-cell spatial data searching and matching across technologies, modalities, and sample conditions.



Disclosures: S. Luo: None. **Z. Tang:** None. **X. Wang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stellaromics Inc..

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.017/LBA17

Topic: I.02. Systems Biology and Bioinformatics

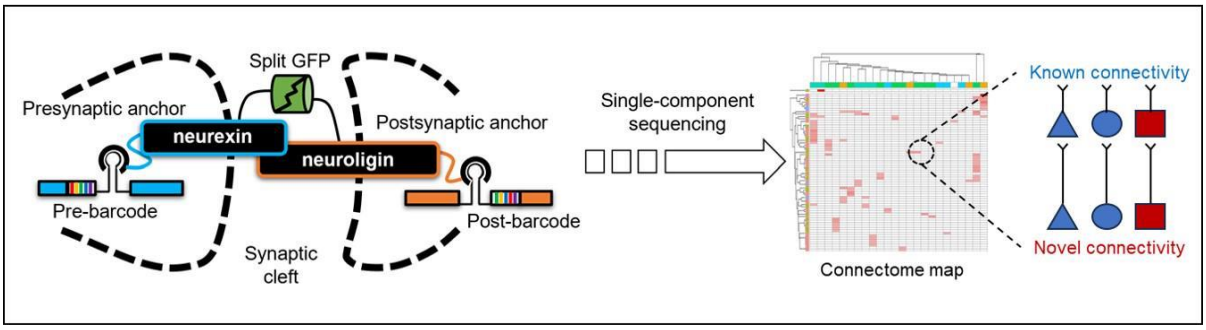
Support: Wu Tsai Neurosciences Institute Interdisciplinary Scholar Award
Stanford ChEM-H Postdocs at the Interface Seed Grant
Life Sciences Research Foundation Shurl and Kay Curci Foundation Fellowship

Title: Connectome-seq: High-Throughput Mapping of Brain-Wide Neural Circuits at Single-Cell Resolution

Authors: *B. ZHAO[1,2], A. ISAKOVA[2], M. WAGNER[3], Y. WU[2], A. Y. TING[2], L. LUO[2]; [1]Univ. of Illinois Urbana Champaign, Urbana, IL; [2]Stanford Univ., Stanford, CA; [3]NIH, Bethesda, MD

Abstract: Deciphering the complex wiring of the mammalian brain is crucial for understanding neural information processing and the basis of neurological disorders. However, with an estimated 86 billion neurons and up to 1000 trillion synapses in a single human brain, comprehensive mapping of mammalian neuronal connections using traditional imaging-based methods remains a formidable challenge. We present connectome-seq, a novel high-throughput sequencing approach for large-scale reconstruction of neuronal connectivity at single-cell resolution. This method uses unique molecular barcodes to label individual neurons and their synaptic connections, enabling efficient decoding of the brain's wiring diagram through massively parallel sequencing. Connectome-seq employs a split reporter system that anchors RNA barcodes at synapses upon assembly of engineered pre- and post-synaptic components. Optimized AAV vectors enable efficient in vivo delivery across diverse neuronal populations. A custom biochemical workflow isolates intact, barcoded synaptic terminals (synaptosomes) and enriches transgene-expressing subpopulations using immunostaining and fluorescence-activated sorting. Using 10X Genomics platform, parallel sequencing of single synaptosomes and nuclei allows detection of synaptic barcodes and cell type-specific markers. A computational pipeline then matches barcodes to infer synaptic connections. We benchmarked this approach in the mouse pontocerebellar circuit, recapitulating known connectivity while uncovering novel connections, with validation by viral tracing. By providing a high-throughput, high-resolution view of synaptic connectivity, connectome-seq promises to transform our understanding of neural circuit organization and plasticity. This technology opens new avenues for investigating

how brain wiring changes during learning or in neurodegenerative diseases, potentially guiding novel therapeutic strategies for neurological disorders.



Disclosures: B. Zhao: None. **A. Isakova:** None. **M. Wagner:** None. **Y. Wu:** None. **A.Y. Ting:** None. **L. Luo:** None.
Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.018/LBA18

Topic: I.03. Anatomical Methods

Support: NRF South Africa support for rated researchers
IUCN Kate Sanderson Bequest grant

Title: Detection of nanoplastics in the brain of dolphins (Tursiops aduncus)

Authors: *D. LANG;
Univ. Cape Town, Cape Town, South Africa

Abstract: An estimated 4.8 to 12.7 million metric tons of plastic waste are entering the sea every year, and the trend is rising. A particular threat on aquatic animals is posed by nanoplastics (NP) particles, which are small enough to cross biological barriers and could thereby reach the brain and cause harm. NPs either directly enter the sea or arise from breakdown of larger plastic fragments through UV radiation, mechanical abrasion and other environmental effects. Studies on phytoplankton, crustaceans, gastropods and fishes showed effects on fitness, brain metabolism and inflammation of organisms after plastic ingestion. By accumulation through the food chain, particularly high amounts of plastic are expected in predators like dolphins. The detection and localization of NP in complex brain tissue remains methodologically challenging. Here, the establishment of an imaging-based method to detect NP particles in the brain of dolphins is described, using hyperspectral, confocal Raman imaging on sections of preserved brain tissue of *Tursiops aduncus* and comparing the resulting spectra with reference spectra for various plastic polymers. Preliminary results suggest presence of polyethylene and polyamide

NP in the sampled brain tissue with a high probability. This method holds immense potential for reliable detection of polymers in brain tissue. Further studies on the subcellular localization of NP and their potential effects on the brains of dolphins and other marine predators are required but considering published pathophysiological effects of NP in other organisms, it appears reasonable to speculate that NP accumulation in the brain might cause physiological and/or behavioural abnormalities in marine mammals.

Disclosures: D. Lang: None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.019/LBA19

Topic: I.03. Anatomical Methods

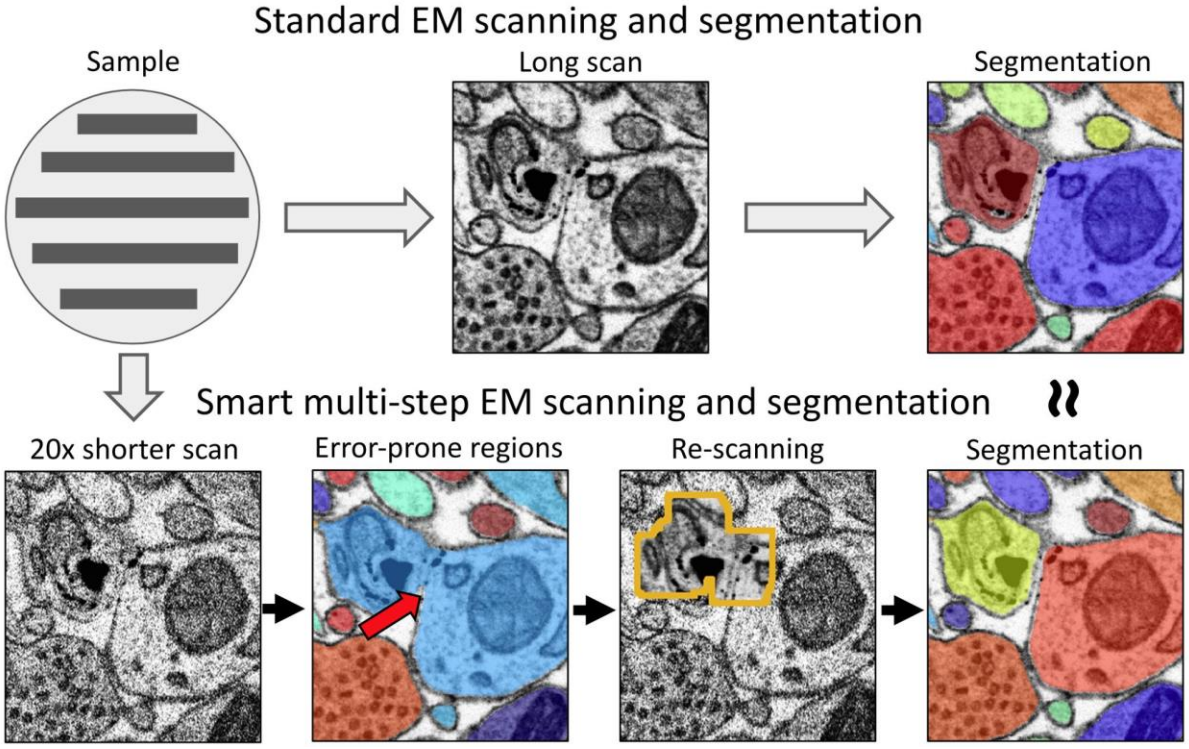
Support: U01NS132158

Title: SmartEM: machine-learning guided electron microscopy

Authors: *Y. MEIROVITCH[1], C. PARK[2], S. SAWMYA[6], Y. LI[3], I. S. CHANDOK[4], T. ATHEY[7], D. XENES[9], H. MARTINEZ[11], C. A. BISHOP[10], P. POTOCEK[12], L. MI[13], J. MATELSKY[8], N. KARLUPIA[5], Y. WU[3], D. R. BERGER[5], R. SCHALEK[3], M. PEEMEN[12], H. PFISTER[3], B. A. WESTER[14], R. SCHOENMAKERS[12], N. SHAVIT[6], A. D. SAMUEL[2], J. W. LICHTMAN[3];
[1]Ctr. for Brain Sci., [2]Physics, [3]Harvard Univ., Cambridge, MA; [4]Physics, Harvard Univ., Somerville, MA; [5]Mol. and Cell. Biol., Harvard Univ., Cambridge, MA; [6]CSAIL, MIT, Cambridge, MA; [7]Biomed. Engin., [8]Johns Hopkins Univ., Baltimore, MD; [9]Res. and Exploratory Develop., [10]research and exploratory development, Johns Hopkins Univ. Applied Physics Lab., Laurel, MD; [11]Johns Hopkins Applied Physics Lab., Laurel, MD; [12]Thermo Fisher Scientific, Eindhoven, Netherlands; [13]Allen Inst. for Brain Sci., Allen Inst., REDMOND, WA; [14]Res. and Exploratory Develop., JHU-Applied Physics Lab., Laurel, MD

Abstract: One way electron microscopy (EM) has advanced neuroscience is by enabling detailed mapping of neural connections. However, long imaging and limited access to high-throughput multi-beam systems hinder its utility for many labs. We have addressed these challenges by integrating machine learning (ML) into the image acquisition phase of more readily available single beam scanning electron microscopes (SEM) to reduce image acquisition time without sacrificing quality. We anticipate this innovation will improve accessibility to circuit reconstruction approaches.Traditionally SEMs use a uniform, prolonged dwell time - the period an electron beam spends on each pixel - so that the most challenging parts of an image are relatively noise-free. Our SmartEM approach restricts the slow scanning only to regions that

might be error prone once segmented, saving considerable time. The workflow starts with an initial rapid scan of the tissue. During image acquisition, a deep learning model, adapted to the dataset and operating in real-time, identifies regions of the very rapid initial scan prone to segmentation errors. The microscope then selectively rescans these regions slowly. The resulting heterogeneous dwell time images are then accurately segmented with a second ML algorithm to give high-quality segmentation results comparable to traditional methods. Applied to mouse cortex, SmartEM achieved segmentation accuracy comparable to traditional methods but with a 7-fold speedup. The dataset comprised 94 sections imaged at 4 nm resolution, covering a volume of 60x68x3 μm^3. We conducted a detailed spine analysis and a 3D neuronal reconstruction, revealing that ~ 65% of dendritic spines were accurately captured without split errors, comparable to recent reconstruction efforts. To enhance reproducibility and adoption, SmartEM outputs have been validated and integrated into existing EM workflows via BossDB, a public archive. We think this ML-guided real-time rescanning approach could improve other imaging modalities, including CLEM and STEM, expanding SmartEM's applicability.



Disclosures: Y. Meirovitch: None. **C. Park:** None. **S. Sawmya:** None. **Y. Li:** None. **I.S. Chandok:** None. **T. Athey:** None. **D. Xenes:** None. **H. Martinez:** None. **C.A. Bishop:** None. **P. Potocek:** None. **L. Mi:** None. **J. Matelsky:** None. **N. Karlupia:** None. **Y. Wu:** None. **D.R. Berger:** None. **R. Schalek:** None. **M. Peemen:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **H. Pfister:** None. **B.A. Wester:** None. **R. Schoenmakers:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **N. Shavit:** None. **A.D. Samuel:** None. **J.W. Lichtman:** None.
Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.020/LBA20

Topic: I.03. Anatomical Methods

Support: Cleveland Clinic's LRI Shared Laboratory Resources Division

Title: Automated Volume Electron Microscopy for Neuroscience

Authors: E. K. BENSON[1], G. J. KIDD[2], ***S. GOODMAN**[3];
[1]3D Ultrastructural Imaging & Computation Core, Lerner Institute, Cleveland Clin., Cleveland, OH; [2]Lerner Inst., Cleveland, OH; [3]Univ. of Wisconsin, Madison, WI

Abstract: Volume Electron Microscopy (vEM) with its 100 um^3 and larger datasets is ideal for neuroscience. vEM includes serial block-face scanning EM (SBEM), FIB-SEM, and array tomography. While vEM imaging is automated, manual specimen prep of neurological specimens is a 4-5-day process of tedious error-prone reagent exchanges (fixatives, labels, stains, solvents, resins) that may not provide the consistency required for artificial intelligence image segmentation (AI) and quantification that is practically essential. The 3DEM Core provides state-of-the-art vEM project development, specimen prep, imaging, and analysis using open-source (e.g. Image J, Python/TensorFlow) and parallelized analysis for high throughput and Deep-Learning applications. The Core specializes in automated SBEM imaging and analysis of brain, neural tissues, organoids, cell pellets, and cell cultures. The Core automates specimen prep with the mPrep ASP-1000 (ASP, Automated Specimen Processor) to provide repeatability, speed, minimize reagent consumption, cut hands-on effort, and provide reproducibility for reliable feature identification and AI segmentation. ASP prep quality was validated by comparing cortex from the same prefusion-fixed rat brain prepared in a 4-day manual process to an 8-hr ASP-prep. Manual and ASP specimens yielded comparable 3D perspective projections, staining, infiltration, sectioning, and statistically identical measures of axon sizes, myelin thickness, and G-ratios. The Core has developed automated AI image analyses including non-linear 3D measures of internodal myelination of large-diameter motor axons, and an assay of peripheral nerve axon diameters, myelin thickness, and integrity/pathology using 2D section scanning: 3 peripheral nerve segments (different experimental conditions) are mounted in a mPrep/s capsule with a fiduciary thread. These are then vEM-prepared and embedded in the capsule. Semithin sections on coverslips are then Ur and Pb batch stained and imaged with a Sigma VP or Teneo SEM with low kV backscattered electron detectors (Gatan, ThermoFisher respectively). Scripted imaging (Gatan Digital Micrograph) enables 30+ samples to be imaged at 20 nm/pixel in 1 hour. This provides automated quantitative axon pathology from multiple experimental conditions to assess therapeutics. The ASP also enables vEM prep of in vitro 2D cell cultures, 3D organoids, and cell pellets. With ASP processing, the 3DEM core now employs a 3-step automated

workflow comprising specimen prep, imaging, and concluding with deep-learning AI analysis. With this automated workflow, Core scientists now can focus on human-only knowledge tasks.

Disclosures: E.K. Benson: None. **G.J. Kidd:** None. **S. Goodman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Microscopy Innovations LLC.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

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Topic: I.03. Anatomical Methods

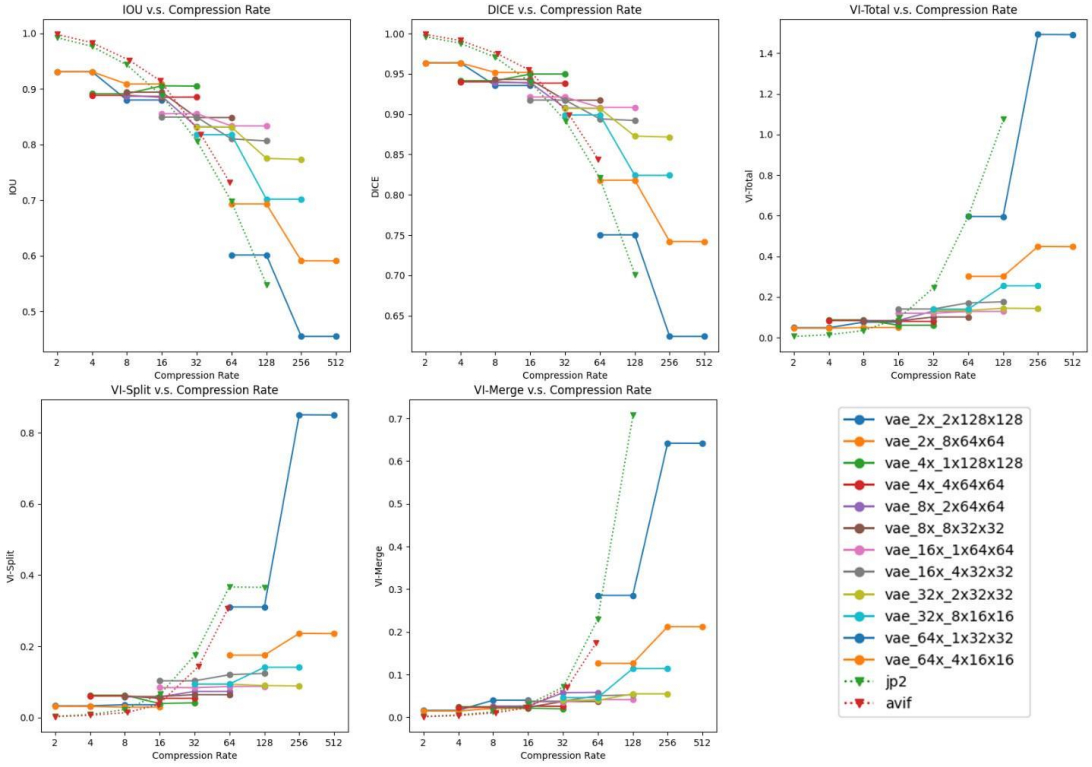
Support: NIH Cooperative Agreement U01NS132158
NSF grant NCS-FO-2124179
NIH grant R01HD104969
NIH grant 5U24NS109102
NIH grant U01NS108637
NIH grant R24MH114785

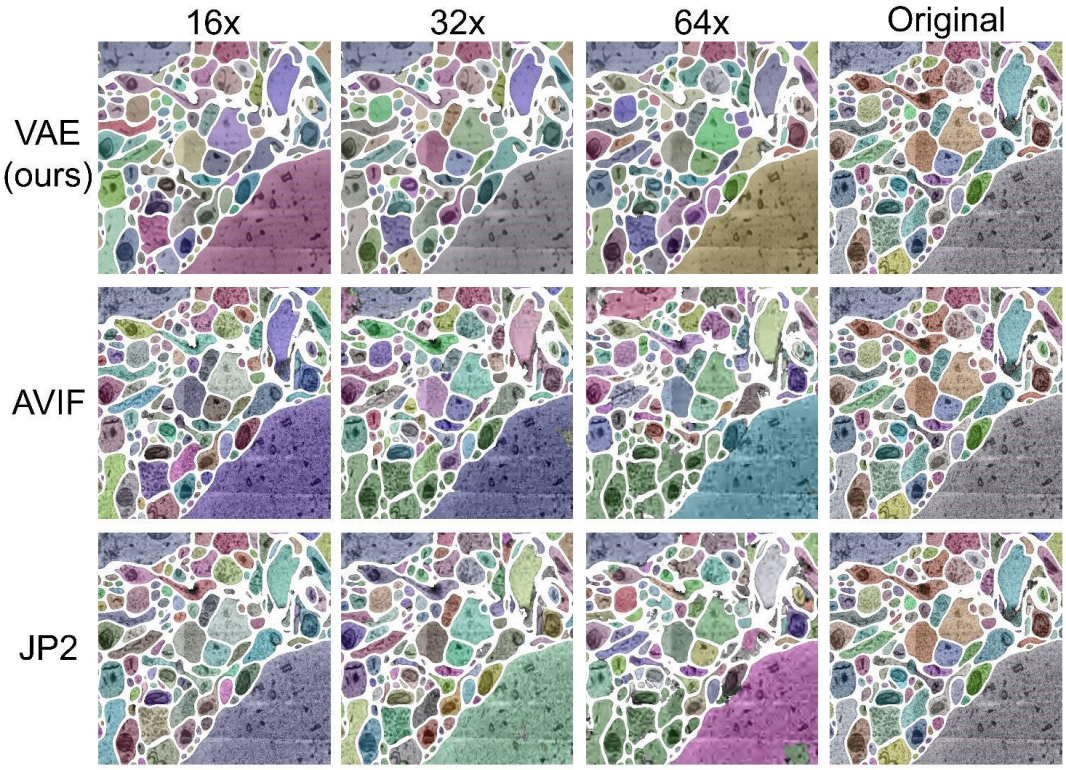
Title: Em-compressor: electron microscopy image compression in connectomics with variational autoencoders

Authors: *Y. LI[1], C. PARK[1], D. XENES[2], C. A. BISHOP[2], D. R. BERGER[1], A. D. SAMUEL[1], B. A. WESTER[2], J. W. LICHTMAN[1], H. PFISTER[1], W. LI[1], Y. MEIROVITCH[1];
[1]Harvard Univ., Cambridge, MA; [2]Johns Hopkins Univ. Applied Physics Lab., Laurel, MD

Abstract: The ongoing pursuit to map detailed brain structures at high resolution using electron microscopy (EM) has led to advancements in imaging that enable the generation of connectomic volumes that have reached the petabyte scale and are soon expected to reach the exascale for whole mouse brain collections. To tackle the high costs of managing these large-scale datasets, we have developed a data compression approach employing Variational Autoencoders (VAEs) to significantly reduce data storage requirements. Due to their ability to capture the complex patterns of EM images, our VAE models notably decrease data size while carefully preserving important image features pertinent to connectomics-based image analysis. Through a comprehensive study using human EM volumes (H01 dataset), we demonstrate how our approach can reduce data to as little as 1/128th of the original size without significantly compromising the ability to subsequently segment the data, outperforming standard data size reduction methods (see figure 1 and 2 below). This performance suggests that this method can greatly alleviate requirements for data management for connectomics applications, and enable more efficient data access and sharing. Additionally, we developed a cloud-based application

named EM-Compressor on top of this work to enable on-the-fly interactive visualization: https://em-compressor-demonstration.s3.amazonaws.com/EM-Compressor+App.mp4.





Disclosures: Y. Li: None. **C. Park:** None. **D. Xenes:** None. **C.A. Bishop:** None. **D.R. Berger:** None. **A.D. Samuel:** None. **B.A. Wester:** None. **J.W. Lichtman:** None. **H. Pfister:** None. **W. Li:** None. **Y. Meirovitch:** None.
Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.022/LBA22

Topic: I.03. Anatomical Methods

Support: NIH UM1NS132358
NIH U01NS132181
NIH R00EB023993
NIH R21HD106038
NIH R01NS128843
NIH U01MH117023
NIH P41EB030006
NIH RF1MH128969

Title: Multiscale 3D-imaging of white matter fiber orientations with polarization-sensitive optical coherence tomography and light-sheet fluorescence microscopy

Authors: *N. BLANKE[1], E. ÖZEN[2], C. CHUNG[2], M. CASPER[2], W. LI[2], W. WANG[3], C. CLICKNER[1], D. GONG[1], Z. WU[3], E. M. C. HILLMAN[2], H. WANG[1];
[1]Radiology, Massachusetts Gen. Hosp., Charlestown, MA; [2]Biomed. Engin., Columbia Univ., New York, NY; [3]Appel Alzheimer's Dis. Res. Institute, Feil Family Brain and Mind Res. Inst., Weill Cornell Med., New York, NY

Abstract: Mapping the 3D orientations of myelinated axons (fibers) across white matter is a key aspect in studying neuroanatomical connections. There is currently a need for new, high-resolution neuroimaging methods that can complement the lower-resolution, whole-brain tractography provided by leading methods in diffusion MRI (dMRI). In this work, we used two optical imaging techniques, polarization-sensitive optical coherence tomography (PS-OCT) and light-sheet fluorescence microscopy (LSFM), to perform 3D-imaging of fiber tracts in partially cleared mouse brains. Our goal was to establish a pipeline for performing PS-OCT and LSFM simultaneously on the same brain tissues, as both techniques image in a reflectance geometry and therefore can be integrated in a combined system for comparative images of fibers at different scales. However, these two modalities have different contrast mechanisms and would ordinarily require different sample preparation. For fluorescence imaging with LSFM, the sample would, ideally, be fully delipidated and optically cleared to enable the most efficient imaging of fibers across depth at the microscopic scale (~1 μm). PS-OCT, on the other hand, is a label-free technique that requires myelin structure (lipids) to be largely intact for quantifying fiber

orientations at mesoscopic resolution (~10 μm), and as a result, conventional optical clearing cannot be utilized. To accommodate PS-OCT and LSFM within the same tissues, we have developed a partial delipidation and RI-matching protocol, with mild B1n/PTxwH buffer pre-treatment followed by equilibration in iohexol to a RI tuned to myelin lipids (n ≈ 1.46). Using a GFP/RFP double positive (Thy1-GFP-M and ChAT-Cre driven tdTomato) mouse brain sample with partial clearing, which provided both fluorescent labeling of two distinct sparse neuron populations and preserved myelin structure, we show that both PS-OCT and LSFM can be used for effective 3D-imaging of fibers up to ~200 μm in depth. With the sparse neuronal labeling, LFSM can provide 3D images of individual fibers within dense white matter, where the subset of labeled axons is consistent with the overall orientation and organization of the white matter tract measured by PS-OCT. These results demonstrate a proof-of-concept for 3D-imaging of fiber tracts in mouse brain tissues, paving the way for simultaneous acquisition of PS-OCT and LSFM across larger specimens such as human or monkey brain samples in future work. Together, PS-OCT and LSFM provide complementary information at different spatial scales, and these techniques could serve to validate and enhance ex-vivo dMRI, which is limited to hundreds of microns in resolution.

Disclosures: N. Blanke: None. **E. Özen:** None. **C. Chung:** None. **M. Casper:** None. **W. Li:** None. **W. Wang:** None. **C. Clickner:** None. **D. Gong:** None. **Z. Wu:** None. **E.M.C. Hillman:** None. **H. Wang:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.023/LBA23

Topic: I.03. Anatomical Methods

Support: JSPS KAKENHI JP24H02308
JSPS KAKENHI JP24H02312
JST CREST JPMJCR2021
AMED JP23wm0525012

Title: Multiplexed mapping of mesoscopic projections with fluorescent barcode vectors and a machine learning based barcode reader

Authors: D. MORIYASU[1], S. FUJIMOTO[2], I. IMAYOSHI[3], ***T. IMAI**[1];
[2]Fac. of Med. Sci., [1]Kyushu Univ., Fukuoka, Japan; [3]Inst. For Virus Research, Kyoto Univ., Kyoto, Japan

Abstract: The brain consists of hundreds of brain regions with thousands of cell types. To understand how different brain regions interact with each other, mesoscopic maps of the

neuronal connectivity have been extensively studied in the last decade. However, the existing methods have several limitations. Whole brain imaging combined with tracer injection visualizes projections from only one region per animal. Therefore, we need to obtain data from many animals to describe a comprehensive map of the connectivity. Moreover, data obtained from multiple animals must be registered to a standard brain atlas, making it difficult to evaluate the fine-scale organization of the connectivity. Recently, RNA barcode-based tools have been developed for highly multiplexed connectivity mapping. However, this strategy cannot currently provide detailed morphological information at the whole-brain scale. To overcome these limitations, we developed a multiplexed mapping tool for mesoscopic projection named "fluorescent barcode vectors". We developed AAV vectors expressing two of seven different fluorescent proteins (XFPs), allowing the multiplexed labeling of neurons with up to 21 color combinations (fluorescent barcode vectors). When these barcode vectors were expressed in a non-overlapping manner, each XFP signal was detected in an all-or-none fashion after linear unmixing of fluorescence signals. We introduced the fluorescent barcode vectors into 10-20 cortical areas in mice. The brain slices spanning the entire brain were then imaged with fluorescence microscopy. In subcortical areas, such as the striatum and the thalamus, the axonal projections were differentially visualized with multiple fluorescent barcodes, revealing a fine and intermingled topographic organization. To facilitate automated identification of fluorescent barcode signals, we also developed a machine learning-based "barcode reader" that enables pixel classification based on color and morphological information. This barcode reader detected even single axons for each of the barcodes from densely labeled brain samples based on the limited number of training datasets. When we used this barcode reader for the 21 two-color barcodes, there was almost no pseudo-positive detection. Our fluorescent barcode vectors with the automated barcode reader provide a multiplexed mapping of mesoscopic projections with rich morphological information. Our strategy will be powerful for high-throughput mapping of mesoscopic axonal projections in mice and for applications to other animals, including primates.

Disclosures: D. Moriyasu: None. **S. Fujimoto:** None. **I. Imayoshi:** None. **T. Imai:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.024/LBA24

Topic: I.03. Anatomical Methods

Support: NIH RF1MH126706

Title: Cre Reporter Alleles vs AAVs in the Evaluation of Genetically Encoded Tags for Transneuronal Anterograde Access

Authors: *J. LAHR, T. ZAMAN, M. R. WILLIAMS;
Pediatrics and Human Develop., Michigan State Univ., Grand Rapids, MI

Abstract: To map and manipulate neural circuits, there is an unmet need for effective and non-toxic tools that enable trans-neuronal anterograde access. While some neurotropic viruses such as HSV-1 H129 enable such access, there are significant barriers to their utilization, including notable toxicity at the cell and organismal level. In contrast, some non-viral tools, such as Wheat Germ Agglutinin, suggest that genetically encoded tools (i.e. protein fusions) can spread from neuron to neuron in an anterograde direction, although the efficacy is limited. We have therefore sought to create a genetically encoded amino acid sequence, an AnteroTag, that enables fusion proteins to spread from a defined starter population into post-synaptic neurons, in the mammalian brain. Here we assay the performance of an AnteroTag variant in the cortico-ponto-cerebellar circuit of the mouse, making comparisons between the anterograde spread of a control Cre and an AnteroTagged-Cre fusion. Experiments were performed in male and female adult mice and were evaluated at multiple post-injection time points. We find that there are apparent qualitative differences in AnteroTag performance levels depending upon whether the reporter of Cre activity comes from the genome of the mouse (i.e. at the Gt(ROSA)26Sor locus), from the genome of an AAV (FLEX/DIO) Cre-reporter construct, or the interaction of both. We discuss that the efficacy of our AnteroTag system, and that of likely contemporary emerging alternatives, must be critically evaluated in the context of the controls and reporter systems being employed.

Disclosures: J. Lahr: None. **T. Zaman:** None. **M.R. Williams:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.025/LBA25

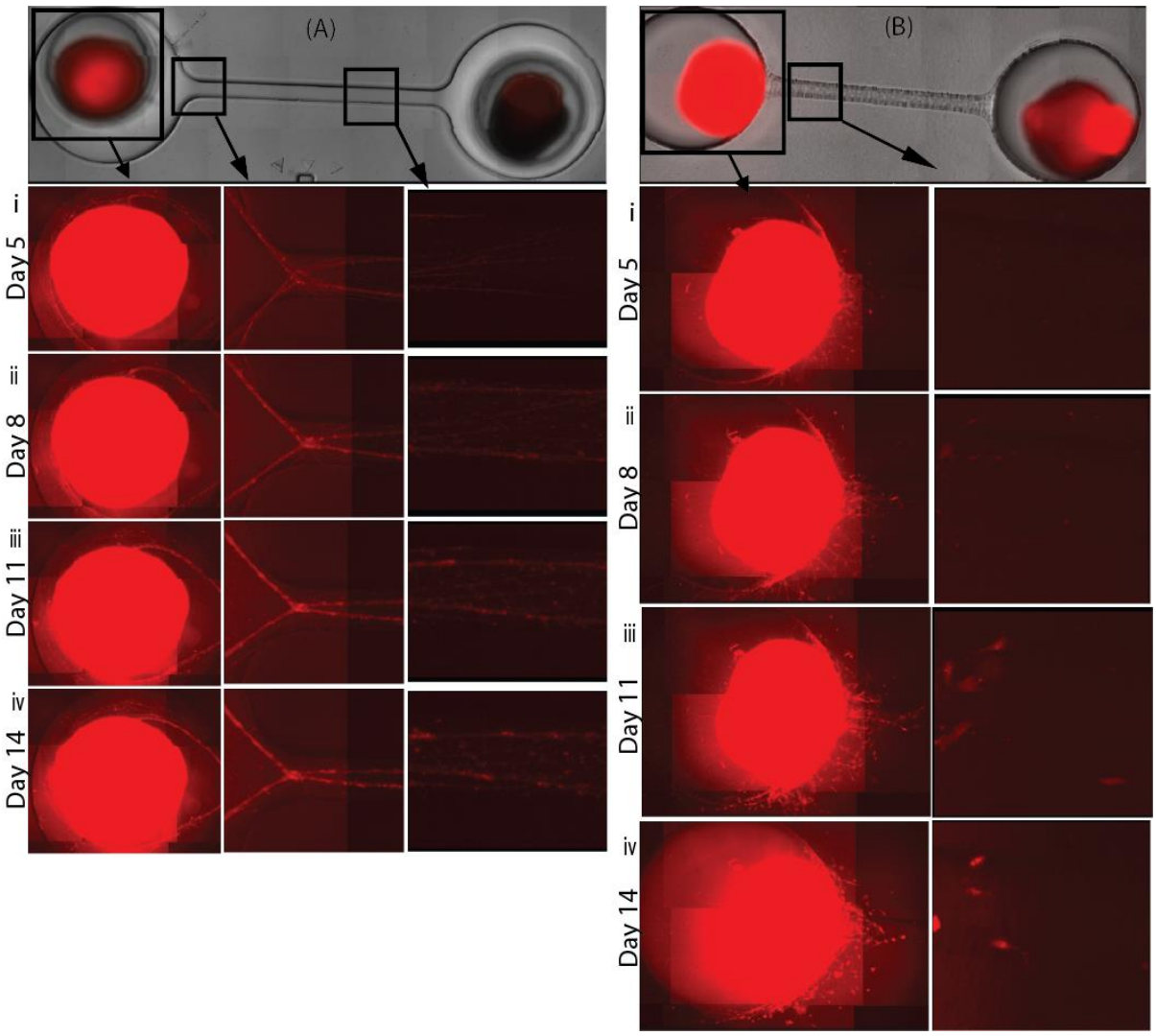
Topic: I.03. Anatomical Methods

Support: NIH Grant K12GM139185
NIH NHGRI 3RM1HG011543

Title: Unlocking Optimal Micro-Macro Fabrication Methodology for Neural Engineering: Comparative Analysis of Polydimethylsiloxane (PDMS) Molds in Neurite Outgrowth Studies

Authors: *M. MOAREFIAN[1,2,3], J. MINNICK[1,2], J. SEVETSON[1,4,3], S. SALAMA[4,3,1], M. TEODORESCU[2,3,1];
[1]UCSC Genomics Inst., Santa Cruz, CA; [2]Electrical and Computer Engin. Dept., [3]Inst. for the Biol. of Stem Cells, [4]Molecular, Cell and Developmental Biol. Dept., Univ. of California Santa Cruz, Santa Cruz, CA

Abstract: In tissue engineering, and particularly in neural engineering, understanding the impacts of master molds on neurite outgrowth within PDMS microstructures is crucial for an investigation of neuron mechanosensation. This research provides insights into optimal micro- and macro-fabrication processes for neural tissue cultures. 3D printed master molds are highly suitable for industrial scale-up fabrication, in terms of affordability and accessibility. However, they offer less precision in surface topography compared to photolithography master molds, and the layered nature of 3D printing can create microscale ridges between layers. Photolithography can be more difficult to scale due to technical complexity and material availability, but master molds can provide nanoscale features with smooth surfaces in PDMS replication. This study investigates neurite outgrowth within diverse topographical microstructures, focusing on how the master mold fabrication method affects axonal outgrowth and directionality. By examining the correlation between scaffold topography and cellular behavior, we aim to discover new ways to enhance desired neuronal network phenotypes through specific microfabrication strategies. We compared human cortical neuron axonal outgrowth and neuron mechanosensation using four different fabrication strategies over 14 days with live imaging: A. Photolithography for microstructures (channel) and stainless-steel machine inserts for macrostructures (well). B. 3D printed master-mold for both macro and microstructures. C. 3D printed molds for microstructures and stainless-steel machine inserts for macrostructures. D. Photolithography for microstructures and biopsy punching for macrostructures. Our results indicate that smoother surfaces with ridges less than 1 micron in both micro and macro structures, provided by condition A, is the best method for consistent axonal outgrowth and morphology. This method also shows the highest consistency across replicates and has the potential usage in large-scale production of microdevices.



Disclosures: M. Moarefian: None. **J. Minnick:** None. **J. Sevetson:** None. **S. Salama:** None. **M. Teodorescu:** None.
Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.026/LBA26

Topic: I.03. Anatomical Methods

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Lore McGovern
HHMI
Open Philanthropy
Lisa Yang
NIH1R01AG070831
NIH1R01MH123403

Title: Protein barcoding and highly multiplexed imaging in expansion microscopy to enable scalable optical connectomics

Authors: S. Y. PARK[1,2], K. LEEPER[1], S. TRUCKENBRODT[1], J. WINNUBST[1], J. M. MICHALSKA[1], A. SHERIDAN[1], B. AN[3], S. CHAN[1], H. G. J. DAMSTRA[1], M. WU[1], J. Y. AXUP[1], C. MAGNO[1], D. LEIBLE[3], J. KORNFELD[4], E. S. BOYDEN[3,5], S. G. RODRIQUES[2], ***A. PAYNE**[1];
[1]E11 Bio, Alameda, CA; [2]The Francis Crick Inst., London, United Kingdom; [3]McGovern Brain Inst., MIT, Cambridge, MA; [4]Max Planck Inst. for Biol. Intelligence, Planegg, Germany; [5]HHMI, Departments of Brain and Cognitive Sciences, Media Arts and Sciences, and Biol. Engineering, Ctr. for Neurobiological Engineering, Ctr. for Envrn. Hlth. Sciences, Computat. & Systems Biol. Initiative, Koch Inst., Cambridge, MA

Abstract: Circuit mapping conventionally relies on continuous neurite tracing across long distances in single-channel morphological data. This approach is vulnerable to gaps in imaging data, and is error prone, requiring extensive manual proof-reading — all making circuit mapping time- and resource-intensive, and limiting scalability.
We report Optical Connectomics, a scalable approach to single-cell circuit mapping that integrates combinatorial cell barcoding and highly multiplexed imaging. Individual cells are barcoded via stochastic AAV delivery of cell-filling protein epitopes. Barcoded cell morphology and synaptic identity are then co-detected by optical imaging using expansion microscopy and iterative antibody staining, enabling fine morphological discrimination of cell processes and precise synapse attribution.
We demonstrate this approach in mouse motor cortex and hippocampus, with more than 15 distinct protein epitopes, corresponding to at least 2^{15} possible barcodes. We found barcoding proteins could be delivered with high levels of co-infection, and observed that fusing barcode epitopes to a common scaffold protein made them distribute efficiently across the length of entire neurons, including into dendritic spines, axons, and synaptic terminals millimeters from the cell body.
To recover barcodes, we developed a multiplexing protocol compatible with hydrogel-embedded samples, comprising iterative cycles of immunostaining, imaging and signal extinction. We built a scalable image processing pipeline to stitch and register the data across imaging cycles. We found that high-dimensional barcode information at 6-fold expansion allows effective

discrimination of adjacent cells, even for the thinnest neurites, resolving ambiguities encountered when using morphological information alone. We were able to precisely attribute synaptic markers to individual pre- and post-synaptic neurites, which is necessary for recovering synaptic connectivity.
We anticipate Optical Connectomics to scale favorably towards larger, higher-dimensional datasets. Expansion microscopy allows tunable resolution and integration of molecular readouts with connectomics. Protein barcodes may complement recently proposed optical pan-protein connectomics (bioRxiv 2024.03.01.582884) by bridging spatial gaps, and barcode-based error-correction may reduce the need for proofreading. Finally, an exponentially expanding barcoding space for every added epitope tag scales towards whole mouse brain labeling, which may be possible with 30 epitopes (~1 billion unique barcodes).

Disclosures: S.Y. Park: None. **K. Leeper:** None. **S. Truckenbrodt:** None. **J. Winnubst:** None. **J.M. Michalska:** None. **A. Sheridan:** None. **B. An:** None. **S. Chan:** None. **H.G.J. Damstra:** None. **M. Wu:** None. **J.Y. Axup:** None. **C. Magno:** None. **D. Leible:** None. **J. Kornfeld:** None. **E.S. Boyden:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ESB is co-founder of a company, Expansion Technologies, that is exploring commercial applications of expansion microscopy.. **S.G. Rodriques:** None. **A. Payne:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.027/LBA27

Topic: I.04. Physiological Methods

Title: Hyperspectral fiber photometry for multiplexed neural signal imaging

Authors: *S. SUNIL[1], R. GALA[2], K. M. HAGIHARA[1], H. HOU[1], X. YIN[1], K. SVOBODA[1], K. PODGORSKI[1];
[1]Neural Dynamics, [2]Brain Sci., Allen Inst., Seattle, WA

Abstract: The brain is made up of many cell types that communicate through the release of a variety of neurotransmitters to control brain function and behavior. Genetically encoded fluorescent indicators are widely used to measure neurotransmitter release at specific locations and cell types to dissect neural circuits. However, due to technical challenges, prior work has largely been limited to studying at most two signals at once in a given brain region. To enable multiplexed fluorescent measurements across many brain areas in vivo, we developed a hyperspectral fiber photometry system. The system records spectrally resolved emission at five excitation wavelengths from optical fibers implanted into the brain. Excitation lasers are combined and shaped to illuminate a linear array of optical fibers that are coupled to different

brain areas. Emitted light is dispersed perpendicular to the fiber array using a prism. The emitted spectra are captured on a sCMOS camera. Image pixels are calibrated to wavelengths and images are interleaved according to the excitation laser. These hyperspectral measurements are then unmixed using a custom constrained non-negative matrix factorization algorithm that accounts for bound and unbound indicator states, autofluorescence, hemodynamics, and brain movement. In preliminary experiments, we have performed simultaneous measurements of dopamine, acetylcholine, and calcium in the ventral striatum of mice performing a reward-based decision-making task. Preliminary analysis reveals distinct dynamics of each of these signals modulated by behavioral states and outcomes.

Disclosures: S. Sunil: None. **R. Gala:** None. **K.M. Hagihara:** None. **H. Hou:** None. **X. Yin:** None. **K. Svoboda:** None. **K. Podgorski:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.028/LBA28

Topic: I.04. Physiological Methods

Support: K. Lisa Yang Brain-Body Center

Title: Multifunctional fiberscopes for volumetric optical imaging and neuromodulation in vivo

Authors: *T. M. CANNON[1], P. MARETICH[2], N. DRISCOLL[2], M.-J. ANTONINI[2], P. ANIKEEVA[3];
[1]MIT, Boston, MA; [3]Brain and Cognitive Sci., [2]MIT, Cambridge, MA

Abstract: Optical imaging of neural activity via fluorescent indicators offers advantages over conventional electrophysiological recording techniques, including improved spatial localization of the activity of a larger number of individual neurons, more reliable discrimination of these signals over time, and the ability to monitor specific cell types and detect neurotransmitter release. Although the continued development of miniaturized, head-mounted microscopes has enabled imaging of fluorescent indicators in behaving animals, optical components for cranial implantation (endoscopic lenses) incur more damage to surrounding tissue than slender, polymer-based fibers for photometric or electrophysiological recording. Additionally, such implants stand to benefit from the integration of multifunctional elements for chemical and electrical recording and stimulation during imaging sessions to add opportunities for precise circuit perturbation. Recently, we have expanded the capabilities of our lab's multifunctional fibers to enable photometric recordings of calcium and dopamine indicators in vivo with flexible, scalable polymer optical fibers (POF) fabricated using thermal drawing and coupled to microfluidic channels and high-performance electrodes. In addition, we demonstrate the

streamlined integration of POF bundles containing thousands of individual waveguide cores into these multifunctional devices to further enable spatially-resolved imaging of neural activity at a single-cell level. To date, we have shown that our flexible, thin (<500 micron) implants are suitable for long-term implantation in deep brain regions. We have coupled them with lightweight, detachable, 3D-printed head-mountable optics, which we have integrated with fully-untethered electronics to enable imaging during free behavior. We have also leveraged the distinct patterns of spatially-resolved light modes in individual POF bundle cores to demonstrate volumetric reconstruction of the collected optical signal. Our initial recordings have captured dopamine release along the mesolimbic pathway and calcium transients in the hypothalamus in response to rewarding and stressful stimuli, respectively. We expect that our multifunctional imaging fiberscopes will expand the existing suite of neural recording tools by potentiating detailed, minimally perturbative, and multiparametric interrogation of neural circuits in deep brain regions.

Disclosures: T.M. Cannon: None. **P. Maretich:** None. **N. Driscoll:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurobionics, Inc. **M. Antonini:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurobionics, Inc. **P. Anikeeva:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurobionics, Inc..

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.029/LBA29

Topic: I.04. Physiological Methods

Title: Insights into RNA editing in the developing brain: subcellular and spatial localization of ADAR isoforms and neuromodulatory targets in mouse brain

Authors: N. MOONEY[1], S. CLARKE[1], L. MONTOYA[1], D. NIELL[1], K. HAMILTON[1], O. GOLUB[1], ***J. ROGERS**[2];
[1]Res. & Develop., [2]R&D, Thermo Fisher Scientific, Eugene, OR

Abstract: RNA editing in the developing brain is a complex process that involves the post-transcriptional base-specific modification of RNA molecules. Adenosine deaminases acting on RNA (ADARs) modify mRNA, non-coding RNA, and microRNAs by converting adenosine (A) to inosine (I). RNA editing plays a crucial role in shaping neuronal function and development by regulating protein diversity, modulating neurotransmitter receptor function, influencing RNA stability and localization, and impacting gene expression. During neurodevelopment, the

regulation of RNA editing occurs in a cell-type specific manner. To better understand the spatial and subcellular localization of the mRNA targets and protein products of RNA editing, we are using a technique that combines multiplexed ViewRNA in-situ hybridization (RNA-ISH) with immunohistochemistry (IHC). This technique allows for the imaging of up to nine fluorescent channels at the same time, facilitating the simultaneous detection of target proteins and mRNA in both cryopreserved and FFPE embryonic and adult mouse brain. Specifically, we used four fluorophores to detect mRNA encoding three ADAR isoforms and the self-edited ADAR2 frameshift splice variant. We simultaneously used DAPI to image nuclei and immunohistochemistry to detect four fluorophore-conjugated antibodies to detect the three ADAR proteins and multiple neuromodulatory protein targets of RNA editing, including Kcna1, Cacna1d, Gabra3, and GluK2. We are using this approach to determine the distribution and developmental changes of these transcripts and protein targets in order to gain insight into the mechanisms and functional implications of RNA editing in the developing mouse brain. The simultaneous detection of these channels in single samples provides a high resolution understanding of distribution and localization. Products are for research use only and are not for use in diagnostic procedures.

Disclosures: **N. Mooney:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **S. Clarke:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **L. Montoya:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **D. Niell:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **K. Hamilton:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **O. Golub:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **J. Rogers:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.030/LBA30

Topic: I.04. Physiological Methods

Title: Decoding prospective vs. retrospective hippocampal representations of economic choice during deliberative vs. re-evaluative decisions using calcium imaging

Authors: *E. ANDRAKA[1], R. DURAND-DE CUTTOLI[2], B. M. SWEIS[3];
[2]Neurosci., [3]Psychiatry, Neurosci., [1]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Economic choices depend on action-selection systems that process value-related information from the past and present when planning for future outcomes. The hippocampus (HPC), a brain region critical for learning and memory, not only represents spatial information but supports deliberative decision making by engaging a cognitive map that serves as a substrate

for simulating potential future goals. Previous in vivo electrophysiological studies of rodents during decision-making tasks have used decoding analyses to show that HPC place cells, while exhibiting firing properties that are spatially tuned, also fire in patterns that represent non-local information. At choice points, this can decode not only prospective locations related to competing future options but also retrospective locations. While this has been heavily investigated during deliberative decisions in which animals must choose between two future locations, very little is known about how HPC systems engage re-evaluative decisions in which animals consider change-of-mind choices of past actions in light of future opportunities. Furthermore, to our knowledge, HPC mechanisms of deliberative, let alone re-evaluative, decision-making have yet to be demonstrated using calcium imaging tools. Here, we leveraged open-source Miniscope recordings of the genetically encoded calcium indicator GCaMP6f in the dorsal HPC CA1 subregion (dCA1) in freely behaving mice performing our novel neuroeconomic foraging task, Restaurant Row. On this task, mice were allotted a limited time budget to forage for their daily source of food by navigating a maze investing in rewards of varying costs (delays cued by tone pitch) and subjective value (flavors in unique spatial contexts). Importantly, decisions to accept and wait for rewards on each trial were separated into discrete stages of primary commitments and secondary re-evaluations separated in space and time. We recapitulated single-cell calcium activity patterns important for encoding spatial information as well as complex economic decision variables. Using a Bayesian decoding analysis, we uncovered reliable representations of the actual location of the animal despite fast mouse movement speeds and relatively slow kinetics of GCaMP6f. We also found nonlocal representations of previous, current, and future goal locations when mice were at different choice-points, including when animals may be engaged in prospective planning as well as re-evaluative choice algorithms. These efforts pave the way for future work leveraging single-cell calcium imaging approaches to investigate circuit mechanisms at play in dissociable decision-making processes.

Disclosures: E. Andraka: None. **R. Durand-De Cuttoli:** None. **B.M. Sweis:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.031/LBA31

Topic: I.04. Physiological Methods

Support: Beijing Municipal Science & Technology Commission Z181100001318002, Z181100001518004
National Natural Science Foundation of China 31925017)
NIH BRAIN Initiative NS103558)
Shenzhen-Hong Kong Institute of Brain Science NYKFKT2019013

STI2030-Major Projects 2022ZD0208300

Title: Monitoring anandamide (AEA) and 2-arachidonoylglycerol (2-AG) dynamics with selective endocannabinoid GRAB sensors

Authors: *R. CAI[1,2], S. CAI[1,2], A. DONG[1,2], Y. LI[1,2,3];
[1]Peking Univ., Beijing, China; [2]PKU-IDG/McGovern Inst. for Brain Res., Beijing, China; [3]Chinese Inst. for Brain Res., Beijing, China

Abstract: Endocannabinoids (eCBs), including Anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are crucial retrograde neuromodulators. Despite their implications in various biological processes, the in vivo dynamics of AEA and 2-AG remain poorly understood due to the lack of detection methods with adequate spatiotemporal resolution. Previously, our group developed an endocannabinoid sensor, $GRAB_{eCB2.0}$ (eCB2.0), by inserting a circularly permuted EGFP into the third intracellular loop of the CB1 receptor. This sensor exhibits ~300% $\Delta F/F_0$ responses to both AEA and 2-AG, enabling the monitoring of eCB dynamics in living animals. However, eCB2.0 is unable to distinguish signals contributed by AEA or 2-AG. To address this limitation, we performed structure-guided sensor engineering of eCB2.0, resulting in the development of new AEA and 2-AG selective genetically encoded eCB sensors, $GRAB_{AEA1.5}$ (AEA1.5) and $GRAB_{2\text{-}AG1.5}$ (2-AG1.5), respectively. AEA1.5 shows specific fluorescent responses to AEA with a peak $\Delta F/F_0$ exceeding 1000% and no detectable signals to 2-AG. Conversely, 2-AG1.5 displays ~600% $\Delta F/F_0$ responses to 2-AG with an apparent affinity of ~3 μM and no significant response to AEA. We then expressed these sensors in living mice and used fiber photometry to record in vivo dynamics of AEA and 2-AG during foot shock in both the NAc core and BLA, as well as during sucrose reward behaviors in the VTA. We found that only 2-AG1.5 exhibited specific time-locked signals during these behaviors. Moreover, given the significant role of eCBs in psychoactive drug addiction, we extended our investigation to record AEA and 2-AG signals in the NAc shell during the administration of nicotine and Δ9-tetrahydrocannabinol (Δ9-THC). Interestingly, AEA signals were exclusively detected during nicotine intake, while only 2-AG signals were observed during Δ9-THC administration. These findings highlight the distinct engagement of endocannabinoid signaling pathways in response to different addictive substances. In summary, our newly engineered selective endocannabinoid sensors, $GRAB_{AEA1.5}$ and $GRAB_{2\text{-}AG1.5}$, serve as robust tools for real-time monitoring of AEA and 2-AG dynamics in living animals. They provide critical insights into endocannabinoid-mediated neuromodulation, thus facilitating our understanding of the nervous system.

Disclosures: R. Cai: None. **S. Cai:** None. **A. Dong:** None. **Y. Li:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.032/LBA32

Topic: I.04. Physiological Methods

Support: NIH RF1NS113278
NIH RF1NS128611
NSF 2144138
EU Innovation Horizon 896245

Title: A novel hybrid Wireless Integrated Sensing Detector for simultaneous EEG and MRI (WISDEM)

Authors: *C. QIAN[1], Y. CHEN[2], X. YU[3];
[1]Michigan State Univ., East Lansing, MI; [2]ETH, Zurich, Switzerland; [3]Radiology, Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Concurrent recording of EEG/fMRI signals reveals cross-scale neurovascular dynamics that are crucial for elucidating fundamental linkage between function and behaviors. However, MRI scanners generate tremendous artifacts for EEG detection. Despite existing denoising methods, cabled connections to EEG receivers are susceptible to environmental fluctuations inside MRI scanners, creating baseline drifts that complicate EEG signal retrieval from the noisy background. Here, a **W**ireless **I**ntegrated **S**ensing **D**etector for simultaneous **E**EG and **M**RI (WISDEM) is developed to encode fMRI and EEG signals on distinct sidebands of the detector's oscillation carrier wave for detection by a standard MRI console over the entire duration of fMRI sequence. Local field potential (LFP) and fMRI maps are retrieved through low-pass and high-pass filtering of frequency-demodulate signals. From optogenetically-stimulated somatosensory cortex, the positive correlation between evoked LFP and fMRI signals validates strong neurovascular coupling, enabling cross-scale brain mapping with this 2-in-1 transducer as a research and diagnostic tool.

Disclosures: C. Qian: None. **Y. Chen:** None. **X. Yu:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.033/LBA33

Topic: I.04. Physiological Methods

Support: NIH grant 1ZIADA000566-12

Title: Effects of Xylazine and its Combination with Fentanyl on Locomotor activity, Brain temperature, and Brain Hypoxia

Authors: *E. A. KIYATKIN[1], **M. R. NOYA**[2], S. CHOI[3];
[1]NIH, Natl. Inst. On Drug Abuse, Baltimore, MD; [2]NIH, NIDA IRP, Baltimore, MD; [3]NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD

Abstract: Xylazine, a veterinary tranquilizer and component of general anesthesia in animals, has emerged in recent years as an adulterant in an increasing number of opioid-positive overdose deaths in the United States. Although xylazine is known to depress vital functions and cause hypotension, bradycardia, hypothermia, and respiratory depression, its exact role in modulating physiological effects of opioid drugs is largely unknown.Two technologies were used in freely moving rats. First, we used multi-site thermorecording coupled with monitoring of locomotor activity to examine basic behavioral and physiological effects of xylazine. Second, we used oxygen sensors coupled with amperometry to examine the hypoxic effects of xylazine and its mixtures with fentanyl and heroin.Intravenous (iv) xylazine at low human-relevant doses (0.33-3.0 mg/kg) dose-dependently decreased locomotor activity and induced prolonged brain and body hypothermia. At a 1 mg/kg dose, xylazine dose-dependently decreased oxygen levels in the nucleus accumbens and subcutaneous space, suggesting modest central and peripheral hypoxia. In contrast to relatively weak and prolonged effects of xylazine, iv fentanyl (20 μg/kg) induced stronger biphasic brain oxygen responses. The initial rapid and strong decrease, resulting from respiratory depression, was followed by a slower, more prolonged increase reflecting a post-hypoxic compensatory phase, with fentanyl acting much quicker than heroin. When a fentanyl+xylazine mixture was administered, it induced a response that lacked its hyperoxic phase and displayed prolonged fentanyl-induced brain hypoxia. Furthermore, the hypoxic effects of fentanyl+xylazine were only slightly attenuated by iv naloxone (0.2 mg/kg), which had previously fully blocked the effects of fentanyl and heroin.These findings suggest that xylazine exacerbates the life-threatening effects of opioids, proposing worsened brain hypoxia as the mechanism contributing to xylazine-positive opioid-overdose deaths. Supported by NIDA-IRP, NIH

Disclosures: E.A. Kiyatkin: None. **M.R. Noya:** None. **S. Choi:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.034/LBA34

Topic: I.04. Physiological Methods

Support: Swiss National Science Foundation project 205320_188910/1
ERC Advanced Grant 694829 neuroXscales

Title: Activity-dependent variability of extracellular spike shapes

Authors: *S. S. KUMAR[1], T. GÄNSWEIN[3], A. HIERLEMANN[2];
[1]Dept. Biosystems Sci. and Engin., [2]BSSE, ETH Zurich, Basel, Switzerland; [3]BSSE, Swiss Federal Inst. of Technol. Zurich, Basel 9, Switzerland

Abstract: Understanding the cooperative behavior of neuronal ensembles necessitates the simultaneous recording of electrical activity from numerous neurons. High-density microelectrode arrays (HD-MEAs) are a powerful tool for such studies, providing large-scale datasets at high spatial resolution. However, the acquired signals consist of a superposition of electrical potentials of multiple neurons near each electrode. To attribute individual spikes to their respective sources, a computational routine called spike-sorting is used. Spike-sorters typically assume the stationarity of spike shapes, or in general, the spike footprint (the distribution of the extracellular electrical potentials of the neuron across the array electrodes during spiking). However, these shapes can vary systematically depending on recent firing history, which poses a challenge for spike sorting algorithms. The impact on spike-sorting performance is difficult to characterize without reliable models of spike shape changes or simultaneous access to ground-truth spiking information. We address this challenge by proposing a detailed characterization of the variability of neuronal spike footprints using a combination of HD-MEAs and whole-cell patch clamping. Our experimental setup included a CMOS-based HD-MEA featuring 59,760 electrodes at a pitch of 13.5 µm. We studied networks of primary dissociated rat hippocampal neurons between 13 - 22 days in vitro. A neuron of interest was identified for whole-cell patch clamping in current clamp mode, and a 2,025-electrode block around it was configured for readout. Ground-truth intracellular spike times were used to reveal activity-dependent extracellular spike-shape changes and to fit multivariate composite models at selected electrodes of a given footprint. Using gridded interpolation, we generated detailed spatial maps of the model parameters across neuronal compartments, revealing clearly anisotropic tendencies in spike-shape variability. Model parameters also varied considerably across neurons, suggesting that the dynamics of a neuron’s spike-shape changes may be indicative of its biophysical properties. Additionally, specific model parameters correlated well with failure modes in spike sorting. Based on this observation, we built model-based post hoc corrective routines and demonstrated their ability to rescue missed spikes and enhance spike sorting efficacy. Our findings demonstrate that detailed characterization of spike shape variability not only improves spike sorting algorithms, but may also facilitate label-free data-based neuron-type classification.

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Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.035/LBA35

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Immediate electrophysiological and functional ultrasound imaging biomarkers after subanesthetic ketamine in rodents

Authors: *M. BERGOSH[1], E. HAKOPIAN[2], N. C. ZEPEDA[3], S. MEDVIDOVIC[3], S. IYER[7], K. LIU[4], V. N. CHRISTOPOULOS[2], D. J. LEE[3,5,6,8];
[1]Neurosci. Grad. Program, [2]Bioengineering, [3]Keck Sch. of Med. Neurolog. Surgery, [4]Keck Sch. of Med., [5]Neurorestoration Ctr., [6]Dept. of Psychiatry and Behavioral Sci., USC, Los Angeles, CA; [7]Keck Sch. of Med., Los Angeles, CA; [8]Rancho Los Amigos Natl. Rehabil. Ctr., Downey, CA

Abstract: Ketamine is an emerging therapy for treatment-resistant depression, yet our understanding of its electrophysiological and network-based mechanisms is incomplete. This study first investigates novel periodic, aperiodic, and complexity measures based on mPFC local field potential (LFP)recordings immediately after subanesthetic ketamine treatment. It then compares these findings with cerebral blood volume changes, as measured while awake and behaving via novel Functional Ultrasound Imaging (FUSI) technology. In the first part of the study, 42 male Sprague-Dawley rats were administered corticosterone (CORT) or vehicle for 21 days. Over the last 7 days, animals receiving CORT were treated intraperitoneally with 15 mg/kg ketamine or vehicle during LFP recordings; then tested across an array of behavioral tasks for 9 days. We found that an immediate increase in the aperiodic exponent ($r = -.75$, $p = .013$) and offset ($r = .78$, $p < .01$), and decrease in sample entropy ($r = -.72$, $p = .020$), correlated with behavioral improvement in the Groom Test and Forced Swim Test. We hypothesized that these electrophysiological biomarkers represented changes in the activity and connectivity of the mPFC due to ketamine treatment. In the second part of the experiment, we investigated this by implanting a novel FUSI mount in 16 male rats, then recording either coronally or sagittally during three 1-hour long sessions separated by a week. The animals began each recording anesthetized with isoflurane, then allowed to awaken, and then administered saline, 7.5 mg/kg ketamine, or 15 mg/kg ketamine while exploring a novel arena. Compared to the pre-ketamine, wakeful state, the anesthetized mPFC showed significantly reduced functional activity ($p < .01$),and connectivity ($p < .01$) with the basal ganglia. In addition, compared to the pre-ketamine, wakeful state, the post-15 mg/kg recordings showed significantly decreased functional activity ($p< .05$) and connectivity ($p < .05$) in the mPFC. No significant changes were detected with 7.5mg/kg. These blood volume change-based FUSI findings support the electrophysiological findings, that subanesthetic ketamine decreases the functional activity and connectivity of the mPFC, which may contribute to its therapeutic action. Furthermore, such electrophysiological and blood volume measurements could act as biomarkers of treatment efficacy, enabling personalized, targeted, predictive, and measurable treatment strategies.

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Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.036/Web Only

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: National Science and Technology Council (TW) (109-2314-B-002-120-MY3)
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National Taiwan University (NTU-107L880305)
National Taiwan University (NTU-AS-112L104306)
National Taiwan University Hospital (111-UN0007)
Academia Sinica (AS-IA-112-M03)
Mission MSA (MSAC-2023-12-002)

Title: Cholesterol homeostasis and oxidative stress-related novel plasma biomarkers for MSA patients

Authors: *H.-H. LIN-WANG[1,3], J.-W. HUANG[4], M.-C. KUO[5], Y.-T. TSAI[6], C.-C. LU[1], P.-J. KUNG[2], C.-K. LAI[7], K. UEDA[8], R.-M. WU[9], S.-P. LIN[2,3];
[1]Natl. Taiwan Univ., Taipei City, Taiwan; [2]Natl. Taiwan Univ., Taipei, Taiwan; [3]Inst. of biotechnology, Taipei, Taiwan; [4]Inst. of Statistical Science, Academia Sinica, Taipei, Taiwan, Taipei, Taiwan; [5]Med., Natl. Taiwan Univ. Cancer Ctr., Taipei, Taiwan; [6]Inst. of Biotechnology, Natl. Taiwan Univ., Taipei, Taiwan; [7]Inst. of Atomic and Mol. Sciences, Academia Sinica, Taiwan, Taipei, Taiwan; [8]Cancer Precision Med. Ctr., Japanese Fndn. for Cancer Res., Tokyo, Japan; [9]Natl. Taiwan Univ. Hosp., Taipei, Taiwan

Abstract: Multiple system atrophy (MSA) is a form of atypical parkinsonism that shares clinical features with Parkinson's disease (PD) but possesses unique pathological characteristics and shows limited responsiveness to (conventional) medication. The discovery of reliable biomarkers is critical for improving differential diagnosis and the development of targeted therapies. We profiled the proteomics of plasma-derived extracellular vesicles (EVs) from MSA patients, PD patients, and healthy controls (HCs) using liquid chromatography–mass spectrometry (LC–MS/MS). We developed Biomedical Oriented Logistic Dantzig (BOLD) Selector, a modified linear programming system particularly suitable for unsupervised biomarker identification from -omic profiling datasets where the number of the variables (1272 EV proteins in this case) are significantly larger than the numbers of patients from each category. The top EV protein candidates, integrated into our logistic regression model for distinguishing MSA patients from HCs, included LCAT, CRKL, Kallistatin, and CSE1L. For differentiating MSA patients from PD patients, the key proteins were APOE, ALDH4A1, ABCC4, and Kallistatin. Moreover, we have

developed clinically compatible sandwich ELISA platforms that can examine peripheral circulating Kallistatin and LCAT in total plasma without the need for prior EV isolation. Results show that total circulating Kallistatin in plasma can significantly distinguish MSA from HC. ($p < 0.0001$, MSA = 31, HC = 25). The total plasma LCAT also demonstrated a significant difference between MSA and HC ($p = 0.0217$, MSA = 10, HC = 10). Gene ontology analysis revealed that these EV proteins are predominantly involved in "cholesterol transport." Other significant biological processes associated with these proteins include oxidative stress modulation, inflammation, and demyelination. Targeting these candidates with novel therapeutic strategies to regulate cholesterol homeostasis, reduce oxidative stress, and mitigate glial inflammation may offer neuroprotective benefits against these neurodegenerative diseases.

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Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.037/LBA36

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Advancing migraine therapy with novel mucoadhesive eletriptan formulations

Authors: *O. SINGH;
Maharishi Markandeshwar Col. of Pharm., Mullana, Ambala, India

Abstract: Migraine, a debilitating neurovascular disorder, imposes a significant burden on affected individuals globally. Despite advancements in acute migraine management, challenges persist, particularly regarding the delayed onset of action and gastrointestinal issues associated with oral administration of eletriptan succinate. This study aimed to address these limitations by developing and evaluating novel mucoadhesive formulations of eletriptan succinate. Specifically, microparticulate systems combining eletriptan with mucoadhesive polymers (chitosan, glutamate, and carbopol) and thermoreversible gels based on pluronic and mucoadhesive polymers were investigated. The objectives included formulation optimization, characterization, in vitro permeation studies, histopathological evaluation, pharmacokinetic assessments, and efficacy and toxicity evaluations in animal models. Additionally, analytical methods for eletriptan estimation using UV-visible spectroscopy and HPLC with UV detection were developed and validated. Results demonstrated the potential of mucoadhesive formulations to enhance drug absorption and efficacy, offering a promising avenue for improving migraine therapy outcomes.

Disclosures: O. Singh: None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.038/LBA37

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Development of a novel microglial specific marker antibody: Anti-P2RY12 guinea pig polyclonal antibody

Authors: *D. HIRATSUKA[1], S. ONODERA[1], S. MIYATA[2], R. YOSHIMURA[2], M. KOJIMA[1];
[1]FUJIFILM Wako Pure Chem. Corp., Osaka, Japan; [2]Dept. of Applied Biol., Kyoto Inst. of Technol., Kyoto, Japan

Abstract: Microglia are the primary resident immune cells of the brain parenchyma and perform a variety of functions, such as releasing cytokines and phagocytosis of foreign and dead cells. The heterogeneity of microglial populations and the concept of disease-associated microglia have been proposed, and their relationship to neurological diseases has been actively investigated. On the other hand, macrophages have recently been reported to be resident in specific areas of the central nervous system (CNS). These macrophages, called CNS-associated macrophages (CAMs), are found in the meninges and perivascular spaces, and their properties are very similar to those of microglia. To understand the true microglial dynamics and their causal relationship to CNS disease, it is critical to accurately distinguish microglia from macrophages.Purinergic receptor P2Y, G-protein coupled 12 (P2RY12) and Transmembrane Protein 119 (TMEM119) are currently used as markers to discriminate between microglia and macrophage. It has been reported that the expression of these markers is altered by microglial activation, and their expression is often compared with that of Ionized calcium-binding adapter molecule 1 (Iba1), a common microglial marker. Currently, however, commercially available microglial specific marker antibodies are limited to a limited number of animal species and lack versatility in multiplex staining. In this study, we set out to develop a guinea pig derived anti-P2RY12 antibody with high versatility for different immunohistochemical staining methods. First, we determined the target sequence from protein conformation prediction and designed antigen peptides. The designed antigen peptide was immunized to guinea pigs, and antiserum was collected and purified. Purified antibodies were co-stained with anti-Iba1 antibodies to examine staining performance. Results showed that P2RY12 signal was detected in the cerebral cortex, hippocampus and arch nucleus, all of which were localized in Iba1-positive microglia. The P2RY12 signal was also observed at the projection ends of microglia and detected fine projection structures compared to the Iba1 signal. In conclusion, we expect that guinea pig derived anti-P2RY12 antibody will be a useful tool for future research breakthroughs toward a more accurate understanding of microglial function and characteristics.

Disclosures: D. Hiratsuka: None. **S. Onodera:** None. **S. Miyata:** None. **R. Yoshimura:** None. **M. Kojima:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.039/LBA38

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Advancements in multiplexed spatial phenotyping of CNS tissue using Primary Antibody Conjugates

Authors: *D. BEACHAM[1], L. MONTOYA[2], A. CARTIER[3], **B. S. MANDAVILLI**[4]; [1]Thermo Fisher Scientific, Eugene, OR; [2]Thermo Fisher Scientific, EUGENE, OR; [3]Neurosci., Thermo Fisher Scientific, San Diego, CA; [4]Cell. Imaging and Analysis, Thermo Fisher Scientific, Eugene, OR

Abstract: Spatial omics is an expanding research area focused on integrating spatial knowledge of tissue with transcriptomics (RNA) and proteomics (protein). The intrinsic tissue complexity of biological structure is an important aspect of brain and cancer immunotherapy research, requiring accurate target classification. Simultaneous translational profiling of 4+ targets on a single sample presents challenges that include panel design, staining protocols, and data analysis. Furthermore, designing a reliable multi-target biomarker panel in the brain introduces complexities such as protein abundance and localization, fluorophore compatibility, diverse cell types, and data characterization. While recent advances in cyclic staining and target detection with automated fluidics enable a growing plexity of diverse target types, these approaches suffer from low simultaneous target throughput. Here, we test and compare a streamlined process for CNS and other tissue types that enables detection of high multiplexed panels, completed within a couple of hours. With this new methodology, we explore detection of a range of protein markers across CNS and other tissue types used in biological research applications with our uniform technique of labelling.

Disclosures: D. Beacham: A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **L. Montoya:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **A. Cartier:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **B.S. Mandavilli:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.040/LBA39

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: UW-Madison
Promega Corp
Idor

Title: Non-destructive luminescence imaging to monitor microenvironments in microphysiological systems: a brain metastasis model using dissociated cerebral organoids

Authors: C. REED-MCBAIN[1], R. TURAGA[1], S. ZIMA[1], A. CUNHA[2], *S. REHEN[3,4], **H. BORGES**[2,4], J. AYUSO[1];
[1]Univ. of Wisconsin, Madison, WI; [2]Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [3]D'Or Inst. For Res. and Educ., Rio de Janeiro, Brazil; [4]Promega Corp., Fitchburg, WI

Abstract: During brain metastasis, tumor cells interact with the surrounding stroma, including neurons and astrocytes, to create a tumor-promoting microenvironment. However, the molecular and cellular factors driving tumor-neural stroma interactions remain unclear. Here, we developed a co-culture model of metastatic melanoma by combining metastatic melanoma cells with dissociated human iPSC-derived cerebral organoids, consisting of neurons and astrocytes, in a microfluidic device. We cultured these astrocytes and neurons in a 3D hydrogel that contained a domain with metastatic melanoma cells. This approach generated a spatially organized co-culture system with no physical boundary between the tumor and stromal compartments. Then, we leveraged several imaging modalities to study tumor-stroma interactions and changes in the microenvironment. Using non-destructive, luminescence-based methods, we spatially resolved changes in cell viability, metabolite concentration, and other biochemical parameters. This model provides a robust platform for investigating the crosstalk between tumor cells and neural scaffolds, offering valuable insights into the molecular and cellular factors driving tumor-neural interactions.

Disclosures: C. Reed-McBain: None. **R. Turaga:** None. **S. Zima:** None. **A. Cunha:** None. **S. Rehen:** A. Employment/Salary (full or part-time):; Promega Corp. **H. Borges:** A. Employment/Salary (full or part-time):; Promega Corp.. **J. Ayuso:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.041/LBA40

Topic: I.06. Computation, Modeling, and Simulation

Support: Blue Brain Project

Title: Predicting inter-region connectome by detailed axonal morphology generation

Authors: *R. PETKANTCHIN, A. BERCHET, H. MARKRAM, L. KANARI;
EPFL-Blue Brain Project, Lausanne, Switzerland

Abstract: Recent experimental advancements, including electron microscopy (EM) reconstructions, have produced detailed connectivity data for local brain regions. On the other hand, large-scale imaging techniques such as MRI provide insights into inter-regional connectivity. However, the link between local and large scale connectivity is missing. Understanding the links between local and long-range connectivity is essential to study the healthy and pathological conditions of brain activity. We present a novel technique to predict whole-brain connectivity at single cell level by generating detailed whole-brain axonal morphologies from sparse experimental data. The computationally generated axons accurately reproduce the morphological properties of experimental reconstructions. Furthermore, these models establish inter-regional connectivity, enabling the in-silico experimentation of large brain regions.

Disclosures: R. Petkantchin: None. **A. Berchet:** None. **H. Markram:** None. **L. Kanari:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.042/LBA41

Topic: I.06. Computation, Modeling, and Simulation

Support: NRF-2021R1A2C1095564

Title: A 3D spheroid co-culture system of neurons and astrocytes derived from Alzheimer's disease patients for drug efficacy testing

Authors: *H. PARK;
Hanyang Univ., Ansan-si, Korea, Republic of

Abstract: Cell culture systems derived from the progenitor cells of human patients have many advantages over animal models for therapeutic drug testing and studies of disease pathogenesis. Here we describe a three-dimensional (3D) spheroid co-culture system of neurons and astrocytes derived from induced pluripotent stem cells-neural precursor cells (iPSCs-NPCs) of Alzheimer's disease (AD) patients or healthy individuals that can provide information on drug efficacy unobtainable by 2D co-culture or monoculture approaches. iPSCs-NPCs of healthy controls or AD patients were seeded onto 96-well U-bottom plates and incubated with neuronal

differentiation medium for one week and with astrocytic medium for two weeks to replicate the temporal order of cell maturation during brain development. These 3D spheroid models expressed marker proteins for mature neurons and astrocytes. In particular, patient-derived spheroids showed beta-amyloid (Aβ) accumulation as revealed by thioflavin T (ThT) staining and ELISA. Aggregation of Aβ induced caspase activation and cell death, while the neuroprotectants nordihydroguaiaretic acid (NDGA) and curcumin (CU) reduced the levels of both ThT and caspase staining. Taken together, these results demonstrate the feasibility of our 3D spheroids combined with ThT and caspase staining as a patient-based anti-AD drug screening platform.

Disclosures: H. Park: None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.043/LBA42

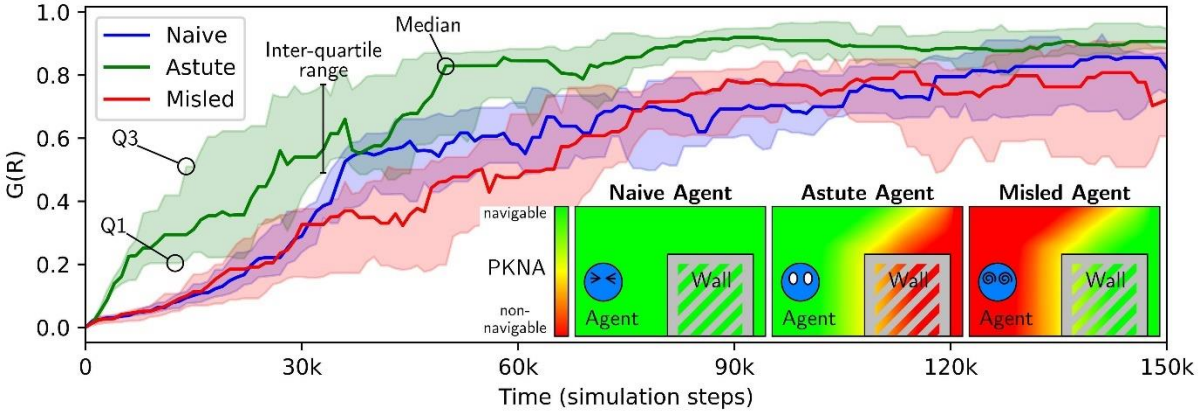
Topic: I.06. Computation, Modeling, and Simulation

Title: Generating adaptive behavior via a self-mutating neural search process to solve complex spatiotemporally continuous problems

Authors: *A. BARANSKI;
OIST, Onna-son, Japan

Abstract: Animal behavior is highly adaptable, allowing for the navigation and exploitation of complex, continuous state-spaces, recovery from mistakes, and execution of temporally extended actions. We explore the possibility that this adaptability can be understood by viewing behavior as the physical manifestation of a self-modifying search protocol. Inspired by the hippocampus, we introduce a mutable neural graph with place-cell-like vertices whose field responses (induced by grid cells) partition state-space. Physically executing complex actions (trajectories sampled from paths over the graph) yields graph-modifying experiences (edge-traversal failure/success), influencing future actions through edge-(dis)inhibition and vertex-addition. Dynamic global edge-(dis)inhibition is crucial for controlling the range of accessible paths and is regulated by edge-traversal and pathfinding failures. This on-the-fly learning doesn't require extensive training, and creates a link between the search for paths and the search through graph-space, leading to a tight model/behavior feedback loop. Our system can use perceptual knowledge of navigability affordances (PKNA) to build the graph more efficiently, using deep networks trained from the graph itself. We tested the system by allowing it to explore random mazes, measuring the distance-weighted target-reaching success rate, called graph reliability R(G) (reported as [Q1, median, Q3]). R(G) ranges from 0 to 1 (no to perfect reliability). We ran 16 trials each for a naive agent (no PKNA), astute agent (good PKNA), and a misled agent (bad

PKNA). After 150000 simulation steps, the naive agent's R(G) was [.74, .82, .87], the astute agent's was [.88, .91, .95], and the misled agent's was [.61, .72, .89]. These results demonstrate that generating behavior via search is adaptable and robust to variations in prior knowledge. The requirement for fast non-local (context-sensitive) edge-(dis)inhibition could be fulfilled by astrocytes, suggesting they may have an active (rather than passive) computational role in behavioral adaptation.



Disclosures: A. Baranski: None.
Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.044/LBA43

Topic: I.06. Computation, Modeling, and Simulation

Title: Feedback modulation of Hebbian plasticity enhances learning robustness in Hopfield neural networks

Authors: *L. GONG[1,2], S. CHING[1];
[1]Washington Univ. in St. Louis, Saint Louis, MO; [2]Yale Univ., New Haven, CT

Abstract: The modification of synaptic plasticity by neuromodulators is a generic feature of brain networks. To the extent that plasticity implements a process of learning and optimization, such modulation must ostensibly be associated with higher-level functional endpoints. In this work, we examine this issue through the lens of Hopfield neural networks (HNNs) with synaptic plasticity, a classical mathematical model of neuronal interactions and the basis of influential theories of associative memory function. A central aspect of this model is the implementation of plasticity mechanisms that lead to the adaptation of synaptic weights as a function of time and network activity. Over time, this adaptation causes the formation of stable equilibria in the network dynamics, corresponding to minima of the Hopfield network energy function, thus

enacting the encoding of memories. Classical implementations of HNNs rely on a static, Hebbian plasticity mechanism, i.e., one where the learning rate and functional form do not adapt over time. These static implementations have limited capacity to reshape the network attractor landscape, which can lead to inefficient and sub-optimal solutions for learning and optimization. In the current work, we formulated and studied a dynamic, modulated Hebbian plasticity within HNNs. Specifically, our model introduces a variable learning rate conditioned on a feedback signal obtained from the network energy function. This modulating signal enacts, in essence, a low-rank meta-plasticity by modifying learning in response to the global network state, at a slower time-scale than the plasticity itself. This dynamic learning rate can be interpreted as a mechanism of context-dependent meta-plasticity. Analysis and simulation of the modulated plasticity mechanism demonstrate that it can achieve more consistent optimization and learning, with the network converging to the desired global energy minimum. This contrasts with the case of fixed Hebbian plasticity, which does not reliably achieve such convergence. Our results provide a theoretical schema for how feedback neuromodulation of plasticity can stabilize learning toward high-quality solutions, enhancing robustness and adaptability across tasks.

Disclosures: L. Gong: None. **S. Ching:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.045/LBA44

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R90DA060341
NIH Grant R01NS104818

Title: Randomness in connections enhances history-dependent information processing in inhibition-stabilized networks with multiple low firing-rate attractor states

Authors: *C. HILTY[1], P. MILLER[2];
[2]Biol., [1]Brandeis Univ., Waltham, MA

Abstract: For effective information processing, the response to a stimulus should depend on the history of prior stimuli. Neuronal networks built around recurrent excitation display such behavior but are only stable at unrealistically high firing rates. We demonstrate how a randomly connected inhibition-stabilized attractor network can preserve the computational abilities of recurrent excitatory networks, while stabilizing at arbitrarily low firing rates. Such networks may underlie many cognitive tasks, suggesting a functional role for inhibition-stabilized dynamics in cortical computation. The network is a simple threshold-linear firing-rate model, consisting of "units" representing the average activity of populations of inhibitory and excitatory neurons.

Strong connections *within* pairs of inhibitory and excitatory units render each pair bi-stable and produce inhibition-stabilized dynamics. Weak cross-connectivity *between* pairs generates a multiplicity of attractor states. These dynamics result in "paradoxical" responses to stimuli, where excitatory input to inhibitory populations reduces both inhibitory and excitatory activity, a phenomenon observed *in vivo* in a variety of brain areas. Phase diagram analysis reveals multi-stability across large regions of parameter space. In the inhibition-stabilized regime, negative feedback from inhibitory populations prevents runaway excitatory activity, permitting stability at arbitrarily low firing rates. Around its attractor states, the network can exhibit transient oscillatory dynamics that are sufficient for itinerancy — the ability to transition between states in response to stimulation. At stimulus onset, both the prior network state and the properties of the stimulus determine the next network state, encoding incoming information in the context of the preceding pattern of stimuli. These history-dependent network responses are sensitive to the dynamic properties of stimuli and are robust across a wide parameter space. We find a statistically significant (n=10) nonmonotonic relationship between heterogeneity in the weak cross-connectivity and the robustness of network itinerancy. Insufficient heterogeneity limits the number of possible state transitions, while excessive heterogeneity reduces the number of attractor states. Between these extremes, the network can behave like a finite-state machine, capable of discriminating between sequences of stimuli in an evidence-accumulation task. The ability to perform this cognitive task at low firing rates makes the multi-attractor inhibition-stabilized network a realistic model for cortical computation.

Disclosures: C. Hilty: None. **P. Miller:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.046/LBA45

Topic: I.06. Computation, Modeling, and Simulation

Support: University of Michigan BioInterfaces Institute

Title: A comprehensive, realistic model to simulate the full repertoire of human seizure dynamics using bifurcation theory

Authors: *C. SHECKLER;
Univ. of Michigan, Arlington, VA

Abstract: Epileptic seizures involve the brain transitioning from a resting state to an abnormal state of synchronized bursting, akin to a bifurcation in dynamical systems where a parameter shift triggers a sudden change in behavior. Several past works have focused on specific bifurcations to simulate a select group of human seizures. More recently, a comprehensive model

proposed using a range of equations to simulate fast-slow bursting in a single point source, capable of simulating 16 “dynamotypes” of seizures that span the full range of theoretical dynamics. This model delineates between fast oscillations within a seizure (dictated by fast variables) and the transition between seizure and rest (dictated by slow variables), showcasing a bifurcation-induced dynamic. In the current work, we developed a dynamical atlas of all 16 possible onset-offset combinations, each characterized by distinct features in the simulated EEG-like recordings. We developed a primer and GUI allowing a user-friendly guide for generating diverse datasets of simulated seizure recordings and enhancing their resemblance to human EEG data through the addition of pink noise in post-processing and an electrode drift correction filter. This toolbox can thus produce large numbers of diverse seizure patterns that have similar noise and filtering characteristics as human EEG, which can aid in training seizure detection algorithms, understanding brain dynamical behavior for clinicians, and exploring the impact of noise on EEG recordings.

Disclosures: C. Sheckler: None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.047/LBA46

Topic: I.06. Computation, Modeling, and Simulation

Support: CNS2022-135870 funded by MCIN/AEI/ 10.13039/501100011033 and by “European Union NextGenerationEU/PRTR”

Title: Artificial bee colony algorithm for the search of retinal electrostimulation patterns in visual prosthesis.

Authors: J. JARA BALSERA[1,2], H. GUZMÁN-MIRANDA[1], ***A. BARRIGA-RIVERA**[2,3]; [1]Electronic Engin., [2]Applied Physics III, Univ. de Sevilla, Sevilla, Spain; [3]Sch. of Biomed. Engin., Univ. of Sydney, Sydney, Australia

Abstract: Retinal degeneration conditions can be treated by retinal implants. However, the inability of retinal implants to convey the patterned neural information of physiological vision seems to be a major limitation. Researchers are investigating different stimulation strategies to provide spatial, time, and cell-specific selectivity to deliver more meaningful neural patterns to higher visual centers. The amalgam of possible stimulation waveforms is vast and the search time consuming. Under the hypothesis that there exist stimulation waveforms able to elicit mimicked physiological patterns, we have built a computational model based on the artificial bee colony (ABC) algorithm to provide an estimate of the time required to find these waveforms in electrophysiological experiments. Briefly, a set of 50 target waveforms (each consisting of 400

samples with a bandwidth of 10 kHz) was defined as the optimal waveforms to be found. A hive with 20 employed and 20 onlooker bees was implemented in Matlab following the description by Karaboga 2010. The most relevant adaptation made to this model was pairing each bee position to a random waveform, which is modified by the algorithm as the bee 'moves' to a different location. As a fitness measure, we used the Pearson's correlation coefficient, as this allows to calculate the similarity between the waveform estimated by the algorithm and the predefined optimal waveforms. Therefore, our adaptation of the ABC algorithm receives as feedback a fitness vector with 50 values, corresponding to the correlation with each target waveform. A successful identification was considered when any of the employed bees achieve 95% correlation value. The whole search was repeated 30 times, obtaining different solutions each time. Then, the average ensemble of the waveforms found was computed, in order to reduce estimation-related distortion. The average number of trials, understood as waveforms tested (i.e., correlations calculated) was 3345.2 ± 185.1 (error given by the standard deviation). If a similar experiment was conducted *in vivo* or *in vitro*, allowing an average of 1 s between stimulation trials, each iteration would last about 40 seconds (20 trials for employed bees, 20 for onlooker bees, and scout bees being used when needed, but not every iteration). Therefore, the total duration of the experiment could be estimated to below 40 hours, that is, less than one hour per optimal waveform. This study suggests swarm intelligence algorithms can assist with improving the neural information elicited by, not only visual prosthetics, but also other forms of electrical neurostimulation.

Disclosures: J. Jara Balsera: None. **H. Guzmán-Miranda:** None. **A. Barriga-Rivera:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.048/LBA47

Topic: I.06. Computation, Modeling, and Simulation

Support: R01NS125298 (NINDS)
Kavli Institute for Brain and Mind

Title: Neurons with nonlinear parallel synapses achieve a large classification capacity

Authors: Y. SONG, ***M. K. BENNA**;
UC San Diego, La Jolla, CA

Abstract: Many neurons establish multiple synaptic contacts with the same postsynaptic cell. To avoid functional redundancy of these parallel synapses, it is crucial that each synapse exhibits distinct computational properties. We systematically investigate models of a neuron in which the current to the soma contributed by each synapse is described by a sigmoidal transmission

function of its presynaptic input, whose shape can be learned. We evaluate the classification capacity of a neuron equipped with such nonlinear parallel synapses, and show that with a small number of parallel synapses per axon, it substantially exceeds that of the perceptron. Furthermore, the number of correctly classified data points can increase faster than linearly with the number of presynaptic axons.
In order to evaluate these parallel synapses on a problem that requires generalization to held-out data, we use them in a feedforward neural network trained to classify handwritten digits, and demonstrate that they can increase the test accuracy.
For synapses with simple step-like transmission functions, we can train models with an a priori unlimited number of parallel connections. Such a model neuron can effectively implement an arbitrary aggregate transmission function for each axon, constrained only by monotonicity. Nevertheless, the successfully optimized model typically employs only a small number of parallel synapses, consistent with observations in the brain. In addition, the learning of the nonlinear synaptic transmission functions can also be implemented in a more biologically plausible online fashion. Therefore, our study shows that the presence of multiple synapses per input axon can be understood as enhancing a neuron's computational power.

Disclosures: Y. Song: None. **M.K. Benna:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.049/LBA48

Topic: I.06. Computation, Modeling, and Simulation

Support: JHU Discovery Award co-funded with the One Neuro Initiative (SPM)
Startup funds from Johns Hopkins University (SPM)

Title: Characterizing information stored in synaptic connections rather than firing activities: An analytical information-theoretic framework

Authors: *X. FAN[1], S. P. MYSORE[2];
[2]Psychological and Brain Sci., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: The study of how information is stored in the brain has a long and rich history. It is well-accepted that information is stored in synaptic interconnections, with robust experiments linking learning to predictable weight changes. However, theoretical and computational studies on information storage have traditionally focused on the relationships between input data and neuronal firing activities. Directly characterizing the information stored by connection weights within neural networks, relative to input data, remains significantly underexplored. One challenge in this endeavor is the complex and opaque relationship between input data and weight

values in artificial neural networks, compared to the clear mapping between input data and firing activity. Here, we address this issue by introducing a basic information-theoretic model as an initial step toward a deeper understanding of information storage in connection weights. We employ the continuous Hopfield model to represent an associative neural network and, without loss of generality, hypothesize that data patterns follow a log-normal distribution. Through this model, we derive analytical solutions for the Shannon mutual information between individual synaptic connections and the data, based on the mean and covariance of the data distribution. Extending this approach, we derive analytical expressions for the information encoded jointly across pairs, triplets, quadruplets, and up to n-tuples of synaptic connections. By providing explicit expressions for mutual information, our work offers a clear and interpretable framework for exploring how information is distributed and encoded across synaptic connections. Overall, this research presents a novel theoretical perspective for characterizing information storage in the brain, emphasizing the dual importance of synaptic connectivity and neural population activities underlying cognitive processes.

Disclosures: X. Fan: None. **S.P. Mysore:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.050/LBA49

Topic: I.06. Computation, Modeling, and Simulation

Support: Blue Brain Project /Ecole Polytechnique Fédérale de Lausanne (EPFL)
King Abdullah University of Science and Technology (KAUST) Office of Sponsored Research (OSR) - OSR-2017-CRG6-3438

Title: Effective skeletonization of neuronal mesh models segmented from electron microscopy reconstructions

Authors: *M. ABDELLAH;
Blue Brain Project, EPFL, Geneva, Switzerland

Abstract: Accurate three-dimensional models of neuronal morphologies are fundamental in neuron modeling to understand cellular functions. Recent advances in volume electron microscopy and AI-powered segmentation techniques have enabled the reconstruction of massive amounts of high-resolution ultrastructures from neural circuits. Neurons are automatically segmented using flood-filling networks algorithms and represented by triangular surface meshes. However, resulting meshes are typically composed of fragmented partitions and have severe geometric artifacts, such as overlapping facets and floating vertices. Even with the manual proofreading efforts to correct some of these critical structural artifacts, automated

reconstruction of high-fidelity - and *complete* - morphological models from segmented meshes remains highly challenging. We introduce an effective and unconditionally robust algorithm that can reconstruct precise and detailed morphological (or skeletal) models of neurons from their respective surface mesh representations. This algorithm can handle large meshes that are composed of thousands of fragmented partitions and millions of unstructured triangle soups. It maps an input fragmented mesh of a neuron to a single connected graph. This graph is then used to (i) identify, localize, and segment the soma and dendritic spines, (ii) reconstruct a high-fidelity morphological skeleton of the different arbors of the neuron, and (iii) classify the arbors. Resulting morphologies are finally exported to standard SWC files. Our implementation has been applied to thousands of neuronal meshes that have a wide variety of morphological types for mouse (datasets are available from the IARPA MICrONS program) and human (H01 datasets) neurons resulting in a large database of detailed neuronal morphologies and their individual spine geometries.

Disclosures: M. Abdellah: None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.051/LBA50

Topic: I.06. Computation, Modeling, and Simulation

Support: North Rhine-Westphalia Ministry of Culture and Science, KI-Starter 2210kis004
BMBF program for Female Junior Researchers in Artificial Intelligence 01IS20054
Hosted at the Center for Molecular Medicine Cologne

Title: Deep Learning imputation of missing data empowers behavior analysis across species

Authors: *F. ROSE[1], M. MICHALUK[2], T. BLINDAUER[1], B. M. IGNATOWSKA-JANKOWSKA[3], L. O'SHAUGHNESSY[5], G. J. STEPHENS[6], T. D. PEREIRA[7], M. Y. UUSISAARI[4], K. BOZEK[1];
[1]Inst. for Med. Informatics, Univ. of Cologne, Cologne, Germany; [2]Fac. of Mathematics, Informatics and Mechanics, Univ. of Warsaw, Warsaw, Poland; [3]Neuronal Rhythms in Movement Unit, Okinawa Inst. of Sci. and Technol., Onna-Son, Japan; [4]Okinawa Inst. of Sci. and Technol., Onna-son, Japan; [5]Dept. of Physics and Astronomy, VU Univ., Amsterdam, Netherlands; [6]Vrije Univ., Amsterdam, Netherlands; [7]TPEREI, Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Video pose estimation and motion capture now allow tracking of fine animal movements over extended periods. However, these methods suffer from low precision detection

and missing data. Few works have effectively addressed these issues, with most relying on linear interpolation and smoothing (e.g. Kalman filter) only suitable for short gaps, or lacking large-scale testing.
We hypothesize that recent advances in deep learning architectures and self-supervised learning can recover missing data by learning dynamics within and between keypoints.
By estimating the frequency of missing keypoints and gap lengths, we incorporated realistic gaps to samples drawn from intact data portions. We trained unsupervised an artificial neural network (ANN) to reconstruct the incorporated gap coordinates. We tested several ANNs, including a custom transformer named DISK (Deep Imputation of Skeleton data).
DISK outperforms other methods on seven datasets, which cover 2D and 3D data, five species, and 1-to-2 animal setups (42% +/- 3.3% to 89% +/- 0.3% root mean square error improvement compared to linear interpolation, calculated between true coordinates and imputed ones on a held-out test set - one value per dataset). For users, DISK provides an estimated error, allowing to filter out less reliable predictions and control the amount of noise in the imputed dataset (Pearson correlation between the real error and the estimated error: 0.746 to 0.890 - one value per dataset). We demonstrated the usefulness of imputing data with DISK in two examples: 1) in a two fish fighting dataset, DISK accurately imputes data if the fish are closely interacting even when all keypoints of one fish are missing. This can be particularly useful in social settings when pose estimation often fails or swaps keypoints between animals that are close to each other. 2) in a mouse dataset, imputing data with DISK led to a better detection of steps measured on the mouse rear limbs (57% more steps on average per 1-minute recording after imputation; compared with manual counts, 40% missed steps after imputation versus 53% on average with up to 79% missed before, paired t-test, $p=7.7e{-}5$, $n=22$ recordings).
We made our imputation solution DISK, available as an open-source package (github.com/bozeklab/DISK). DISK can enhance results from any tracking algorithm, facilitating downstream analysis. DISK's learning capacities can reduce the need for additional experimental data or manual annotations, and enable finer behavior analysis.

Disclosures: F. Rose: None. **M. Michaluk:** None. **T. Blindauer:** None. **B.M. Ignatowska-Jankowska:** None. **L. O'Shaughnessy:** None. **G.J. Stephens:** None. **T.D. Pereira:** None. **M.Y. Uusisaari:** None. **K. Bozek:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.052/LBA51

Topic: I.06. Computation, Modeling, and Simulation

Support: NRF Grant RS-2024-00415347

Title: The necessity of detailed state separation of L-DOPA response in hemi-parkinsonian 6-OHDA rats

Authors: *J. KIM[1], S. KANG[3], K. LEE[2], E. KIM[1], H. JANG[1], J.-W. CHOI[1];
[1]Electrical Engin. and Computer Sci., [2]The Interdisciplinary Studies of Artificial Intelligence, DGIST, Daegu, Korea, Republic of; [3]Neurol., UCSF, San Francisco, CA

Abstract: Investigating the L-DOPA response in 6-OHDA rats significantly contributes to the understanding of Parkinson's Disease (PD). Typically, the L-DOPA response is analyzed by comparing pre- and post-medication states (OFF/ON). This classification allows for an intuitive analysis of the differences between the two states. However, such traditional classification limits the exploration of potential states that may occur between these states. For example, some research has suggested that the L-DOPA response can be categorized into four states (OFF, Diphasic dyskinesia, ON, Peak-dose dyskinesia) from a behavioral perspective in Parkinson's disease patients. Diphasic dyskinesia is a state occurring before the ON state and is a type of dyskinesia caused by rapid changes in plasma L-DOPA levels. As a result, diphasic dyskinesia can often be misinterpreted as dyskinesia occurring after reaching the ON state, leading to the erroneous conclusion that the therapeutic drug has achieved the ON state. Unfortunately, to our knowledge, there are no instances of dividing and analyzing the response to L-DOPA injection in 6-OHDA rodents into these four states. Therefore, we applied a well-known change point detection method to the quantified metrics of rotational behavior to numerically segment the states of the L-DOPA response. We then examined firing activity recorded from extracellular recordings and tonic dopamine levels derived from fast-scan cyclic voltammetry (FSCV) across these four segmented states, using stochastic analysis and machine learning techniques. The classification into these four states demonstrated significant changes in firing rates, dopamine levels, and rotational behavior for each state. The conventional two-state classification method did not allow for the observation of detailed changes as seen with the four-state classification. Furthermore, our results suggest that estimating the onset of contralateral rotation as the ON state may lead to the misclassification of diphasic dyskinesia as peak-dose dyskinesia. We confirmed that using the tonic DA level derived from processed FSCV signals allows us to predict the four states with near-perfect accuracy. Additionally, even using only the firing rates of single units, we could effectively predict the four states. Consequently, we propose the necessity and methodology for classifying the L-DOPA response into four distinct states within the 6-OHDA rodent model. This approach suggests the possibility of establishing a foundation for more refined and customized treatment strategies in the management of Parkinson's Disease.

Disclosures: **J. Kim:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); RS-2024-00415347. **S. Kang:** None. **K. Lee:** None. **E. Kim:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); RS-2024-00415347. **H. Jang:** None. **J. Choi:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); RS-2024-00415347.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.053/LBA52

Topic: I.06. Computation, Modeling, and Simulation

Support: NINDS F32NS129585

Title: Parameter inference for CNS diffusion models

Authors: K. KUMAR[1], A. SRIVASTAVA[2], D. TARTAKOVSKY[2], *J. KRUEGER[2];
[1]Monta Vista High Sch., Cupertino, CA; [2]Stanford Univ., Stanford, CA

Abstract: Maintaining central nervous system (CNS) function requires careful and directed metabolic homeostasis. Metabolites, such as oxygen and glucose, are essential components of biochemical processes that supply energy to all facets of CNS activity including, but not limited to, small-scale local computations and large-scale network signaling. These metabolites reach their intended target sites via diffusion, a process that is difficult to study *in vivo* but can be modeled utilizing computational methods. Experimental methods provide sparse observations of oxygen concentration, from which it is difficult to directly estimate the diffusion field. To address this, we employ a reaction-diffusion model for oxygen concentration in the brain that allows us to infer the diffusion field from sparse observations. To understand oxygen diffusion within specific brain regions, we select a finite-element discretization (as opposed to finite difference or finite volume-based methods) that allows us to adaptively discretize the field. We use the Ensemble Kalman filter to test the identifiability of the diffusion field parameters from noisy synthetic observations. The filtering enables us to match the temporal evolution of the predicted concentration with observed data, while accounting for the missing physiological processes, such as chained consumption reactions. This filtering protocol allows us both to obtain the diffusion field estimates and to quantify the uncertainty associated with these estimates. Our findings here provide quantitative descriptors that identify the diffusion field and show that prediction uncertainty depends on the number of observations and the signal-to-noise ratio in a systematic manner: increases in observations or in signal-to-noise ratio decrease uncertainty. Spatial and temporal dynamics match those few data reported in the literature. Follow up work will include updating the estimated synthetic diffusion fields with more experimental observations. That resulting calibrated diffusion field would then allow us to predict the local spatiotemporal evolution of the oxygen concentration, which could then be related back to neural activity. This is a crucial first step in characterizing the dynamic interplay of energy needs and metabolite availability and its impact on neural circuit function in the healthy brain and in disease.

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Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.054/LBA53

Topic: I.06. Computation, Modeling, and Simulation

Support: NEI Grant R01 EY032125

Title: qPRF recovers center-surround properties of population receptive fields

Authors: *S. WAZ[1], Y. WANG[2], Z.-L. LU[3];
[1]New York University, Ctr. For Neural Sci., New York, NY; [2]Arizona State Univ., Tempe, AZ; [3]New York Univ. Ctr. For Neural Sci., New York, NY

Abstract: The population receptive field (PRF) model of Dumoulin & Wandell (2008) has become the standard model in retinotopic mapping for decoding BOLD signals. We have recently developed a technology to rapidly accelerate the estimation of PRF model parameters, called qPRF. The introduction of qPRF created an opportunity to fit an elaborated version of the PRF model. Here, we considered a Difference-of-Gaussians (DoG) PRF model, wherein an excitatory PRF model was initially fit to the BOLD signal, and an inhibitory PRF model was optimized at the same receptive field location. Namely, the size and compressive exponent of this inhibitory model were optimized. As anticipated, the estimates of receptive field size were generally larger for the inhibitory PRF than the excitatory PRF (97.3% of vertices tested), consistent with the known center-surround properties of receptive fields. On average, the addition of an inhibitory component improved the R^2 of the model by 0.2% (absolute difference, R^2 ranging from 0% to 100%). The DoG PRF model significantly improved the fit for the majority of vertices ($p < 0.05$). This work serves as a proof-of-concept that qPRF can facilitate the recovery of receptive field properties, established in physiology, which have been otherwise difficult to recover non-invasively in humans.

Disclosures: S. Waz: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional patent filed. **Y. Wang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional patent filed. **Z. Lu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional patent filed.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.055/LBA54

Topic: I.07. Data Analysis and Statistics

Support: NIH EB029343
NIMH R01 MH104324
NIMH U01 MH110274
Cognitive Computational and Systems Neeuroscience Pathway Fellowship

Title: Early Life Neuroimaging: The Generalizability of Cortical Area Parcellations Across Development

Authors: *J. TU[1], J. LI[6], X. WANG[2], D. DIERKER[3], C. M. SOBOLEWSKI[7], T. K. DAY[8], A. SNYDER[4], J. KENLEY[4], S. KAPLAN[9], E. FECZKO[10], O. KARDAN[9], O. MIRANDA-DOMINGUEZ[11], L. A. MOORE[12], C. M. SYLVESTER[13], D. A. FAIR[12], J. ELISON[11], C. SMYSER[15], E. GORDON[14], A. T. EGGEBRECHT[5], M. WHEELOCK[4];
[1]Washington Univ. in St. Louis, St Louis, MO; [2]Dept. of Radiology, [3]Radiology, [4]Washington Univ. in St. Louis, St. Louis, MO; [5]Radiology, Washington Univ. in St. Louis, Saint Louis, MO; [6]Dept. of Statistics, Univ. of Chicago, Chicago, IL; [7]Virginia Commonwealth Univ., Richmond, VA; [8]Ctr. for Brain Plasticity and Recovery, Georgetown Univ., Minneapolis, MN; [9]Univ. of Michigan, Ann Arbor, MI; [10]Univ. of Minnesota, Twin Cities, Minneapolis, MN; [12]Masonic Inst. for the Developing Brain, [11]Univ. of Minnesota, Minneapolis, MN; [13]Psychiatry, Washington Univ. Sch. of Med., St Louis, MO; [14]Radiology, Washington Univ. Sch. of Med., St. Louis, MO; [15]Neurol., Washington Univ., Saint Louis, MO

Abstract: The cerebral cortex consists of discrete cortical areas that form during development. The differentiation of cortical features that shape the formation of those areas depends on extrinsic input from thalamocortical axons, with postnatal exposure to sensory input likely playing a substantial role. Accurate area parcellation facilitates comparison of results across studies. Given the substantial changes in volume, microstructure, and functional connectivity observed in the first years of life, we hypothesize that the areas in 1-to-3-year-olds would exhibit major differences from those in neonates and increasingly resemble adults as development progresses.Here, we delineated maps of cortical areas using local functional connectivity gradients in 92 toddlers at 2 years. We demonstrated high reproducibility of cortical areas across 1-to-3-year-olds across two independent datasets. We further demonstrated that infant/toddler area boundaries are more similar to adults than to neonates. While age-specific group parcellation fits better to the underlying functional connectivity in individuals in the first 3 years, some area parcellations from adults performed only marginally worse and still captured the functional connectivity organization better than chance in infants and toddlers (Figure 1). Further, adult parcells performed better than infant/toddler parcellations in children at 6-15 years, suggesting best fit and utility for lifespan studies. Finally, we provided the connectivity-based community assignments of infant parcels which aligned with the canonical adult systems. These findings lend support to the stability of areas across the lifespan and guide the use of area parcellations in lifespan studies.

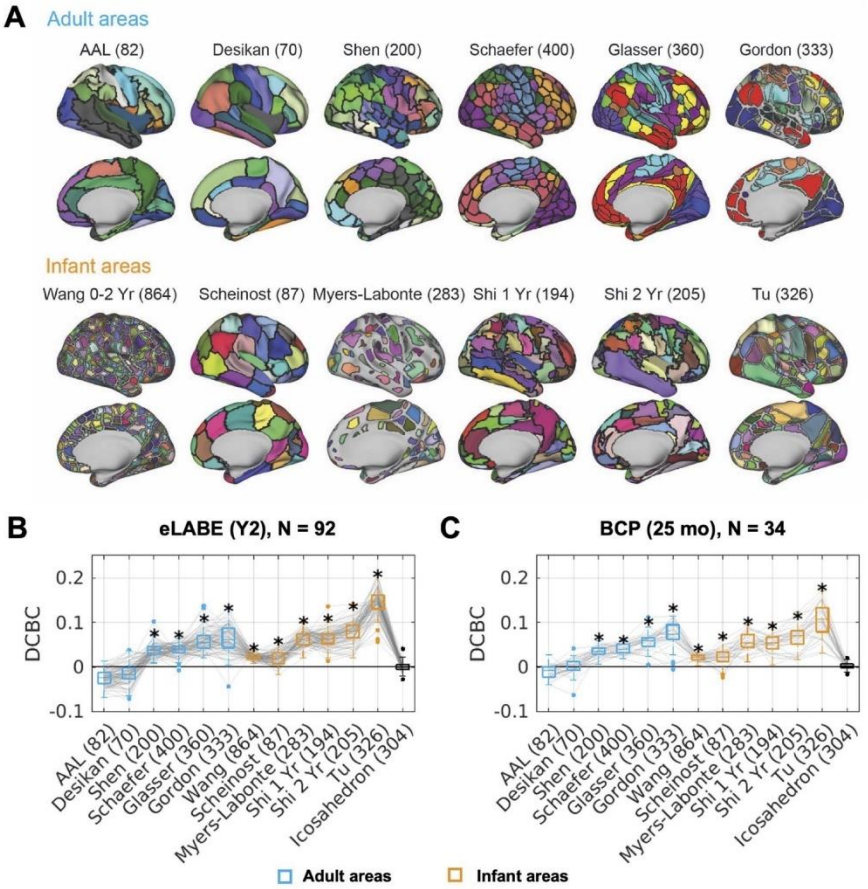

Figure 1. *Cluster validity for different area parcellations evaluated with a distance-controlled boundary coefficient (DCBC) measure.* (A) Adult area parcellations and neonatal/infant area parcellations. (B) DCBC quantified in individuals in the same eLABE (N=92, 2 yr) dataset used to derive the Tu (326) parcels. (C) DCBC quantified in individuals in an independent dataset (BCP). * p<0.05 after FDR correction for one-sample t-test against 0.

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Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.056/LBA55

Topic: I.07. Data Analysis and Statistics

Support: T32 Grant #: T32DA050560

Title: Connectome-based prediction of craving intensity in Methamphetamine Users

Authors: *H. MAHDAVI-DOOST[1], G. SOLEIMANI[2], K. O. LIM[2], M. LUCIANA[1], H. EKHTIARI[2];
[1]Psychology, [2]Psychiatry and Behavioral Sci., Univ. of Minnesota, Minneapolis, MN

Abstract: Aims: Craving plays a pivotal role in substance use disorder (SUD) and is typically evaluated using subjective self-report measures, which can be introspective and influenced by context. To create a robust model predicting craving intensity based on brain connectivity, we employed connectome-based predictive modeling (CPM), a machine learning algorithm that identifies neural networks associated with specific behaviors.**Methods:** We collected block-designed fMRI data from 68 methamphetamine users. The design alternated between neutral and methamphetamine-related images, with cue-induced cravings assessed using Likert scales at each block's end. A Leave-one-out (LOO) cross-validation approach with a 20% holdout set was used to predict craving levels from the fMRI data. CPM was applied to each block across subjects, averaging results. Statistical significance was confirmed via permutation tests.**Results:** We used the CPM algorithm and optimized it by trying different correlation thresholds between connectivity matrices and behavioral measures, achieving an optimal threshold of 0.1. This resulted in RMSE of 0.97 ± 0.03 and a correlation coefficient of 0.74 ± 0.02 for each subject. This result confirms what we have obtained previously from analyzing the functional activity data. When plotting predicted versus true craving, the average slope connecting minimum to maximum craving was 0.71 ± 0.05, confirming a positive trend. Out-of-sample performance showed an average RMSE of 1.15 and an average correlation coefficient of 0.74 with an average slope of 0.90 for each subject. Permutation tests on RMSE yielded p-values < 0.001, indicating significant results. Through the training, the connections that were frequently utilized and significantly contributed to the correlation were identified as the key networks. They included the DMN, ventral and dorsal attention networks (VAN and DAN), and sensory-motor processing networks, highlighting interactions among self-referential thinking, attention, cognitive control, and motor functions in processing craving. Conclusion: We developed a pipeline to predict craving intensity in methamphetamine users using CPM. Our algorithm highlights brain networks contributing to craving, aiding in the development of neuromarkers for addiction and informing future personalized treatments and interventions.

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Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.057/LBA56

Topic: I.07. Data Analysis and Statistics

Title: An excessive-demand measure outperforms other demand proxies in explaining lab asset-market price changes: Toward a neuroeconomic biomarker of excessive demand

Authors: *J. L. HARACZ;
Dept. of Psychological and Brain Sci., Indiana Univ., Bloomington, IN

Abstract: Objective: Dynamic stochastic general equilibrium models have been criticized for failing to forecast the Global Financial Crisis (Yellen, 2010; Vines & Wills, 2020). This and other flaws of neoclassical economics were proposed to arise partly from the failure of equilibrium-based models to capture *excessive demand* (Haracz, 2021, 2022, 2023), which exceeds the balanced "excess demand" in general equilibrium theory (Arrow, 1974, p. 266; Debreu, 1984, p. 270). Excessive demand is defined as demand that promotes disequilibria in asset or goods markets and drives prices above fundamental values (e.g., an asset-price bubble). Neuroimaging studies are elucidating the neuroeconomics of asset-price bubbles (Smith, A. et al., 2014). However, these studies have been limited in characterizing individual-level brain-behavior relationships due to the lack of a subject-level measure of excessive demand. The present study makes such a measure available to neuroimaging researchers.Methods: In a standard lab asset-market design (Smith, V.L. et al., 1988), 9 experiments each included 9 undergraduate-student subjects. The subject groups included males and females, but sex-related results were not assessed. Each experiment consisted of 15 2.5-minute periods of trading cash and an asset with a commonly known fundamental value that declined across periods. To capture excessive demand, the end of each Period 1-14 was followed by a survey that elicited each subject's number of asset shares that they want to hold at the end of the next period. This measure was designed to tap into anticipatory euphoria that may drive price bubbles. Two other predictive measures included excess bids (Smith et al., 1988) and momentum, which was measured as the most recent inter-period price change.Results: The excessive-demand measure (EDM), which explained 34% of the variance in asset-price changes, significantly outperformed the excess-bids and momentum measures, which each explained less than 10% of this variance.Conclusions: The outperformance of the EDM in predicting price changes aligns with numerous other findings that underscore the predictive power of measures related to anticipatory affect. For example, fMRI-measured activity in nucleus accumbens, an area implicated in anticipatory affect, performed better than choice behavior in forecasting crowdfunding outcomes (Genevsky et al., 2017). Similarly, the survey-elicited EDM, which may reflect anticipatory affect, was a better price-change predictor than the behavioral excess-bids measure. Therefore, the presently introduced EDM may facilitate finding an excessive-demand biomarker with market-level predictive power.

Disclosures: J.L. Haracz: None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.058/LBA57

Topic: I.07. Data Analysis and Statistics

Title: Stress kills, but does immune function? the comparison of statistical techniques on the stress function, immune, and biological factors in the metastasis progression of cancer patients

Authors: *S. N. WATTS[1], M. BARDI[1,2];
[1]Psychology and Behavioral Neurosci., Randolph-Macon Col., Ashland, VA; [2]Univ. of Pisa, Pisa, Italy

Abstract: Evaluating heterogeneous data from various perspectives can provide a more accurate approach to cancer treatment. The issue is that complex data requires sophisticated analytical tools as well. In this study, we aimed to identify which statistical methodology (classical, multivariate, or Bayesian) provided a more accurate interpretation of the data in a model of immune and biological function in addition to resilience against stress in the progression of metastases within prostate cancer (PC) patients. Data was collected from clinical patients (n=27) at the University of Pisa, Italy which includes age, psychological-assessment results, immune cell activity, presence of metastases, presence of mutated breast cancer (BRCA) 1 and 2 genes, hypothalamic-pituitary-adrenal (HPA) activation, and dehydroepiandrosterone (DHEA)/ cortisol (CORT) levels. The Statistical Package for the Social Sciences (SPSS) and the Jeffreys's Amazing Statistics Program (JASP) performed classical statistics, multivariate statistical modeling, and Bayesian statistics tests. Three models examined this study's questions: 1) metastasis progression versus biological, immune, and oncological factors, 2) metastasis progression versus psychological-assessment results, and 3) overall model of metastasis progression versus biological, immune, and oncological factors as well as psychological-assessment results. Preliminary results demonstrated that DHEA-sulfate, CORT, DHEA, CD68, and CD163, Interleukin 2 receptor, CD21, and CD11 were related to the probability of finding metastases in PC patients and predicting future outcomes of metastasis presence. A small sample size proved difficult to interpret the use of multivariate statistical modeling techniques in comparison to classical and Bayesian statistics in order to understand the intervening and independent relationships of our models. However, classical statistics and Bayesian statistics only provided information of specific variables to metastasis presence in PC patients, rather than a holistic view of how the variables interacted with each other. This research reinforced the idea of a need to account for what types of statistical tools are being used to interpret the results based on the sample size and complexity of the models.

Disclosures: S.N. Watts: None. **M. Bardi:** None.

Late-Breaking Poster

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Program #/Poster #: LBA009.059/LBA58

Topic: I.07. Data Analysis and Statistics

Support: This study was supported by funding to the Blue Brain Project, a research center of the École polytechnique fédérale de Lausanne (EPFL), from the Swiss government's ETH Board of the Swiss Federal Institutes of Technology.

Title: Automated construction of single-cell electrical models: BluePyEModel, an integrated Python library

Authors: *I. F. KILIÇ, T. DAMART, A. T. JAQUIER, D. MANDGE, A. TUNCEL, A. ARNAUDON, S. VAN DORP, G. FICARELLI, L. KANARI, H. MARKRAM, W. VAN GEIT; Blue Brain Project, EPFL, Geneva, Switzerland

Abstract: Creating biophysically detailed neuron models is crucial for understanding the complex functions and behaviours of individual neurons. Building such models involves a multifaceted workflow including data extraction, parameter optimisation, model validation, and subsequent analysis. To simplify this process, we introduce BluePyEModel, an integrated Python library designed to automate and streamline the construction of single-cell electrical models (e-models) based on the NEURON simulator. BluePyEModel manages the entire e-model building process by leveraging Blue Brain's software for the different stages: (i) electrical features (e-features) extraction from intracellular/extracellular electrophysiology data using eFEL and BluePyEfe, (ii) multi-objective optimisation, and (iii) validation of e-model parameters using BluePyOpt. The entire workflow employs the Luigi pipeline management tool and supports both local data storage and integration with Knowledge Graphs via the Blue Brain Nexus ecosystem, facilitating efficient data organisation and management of e-models. BluePyEModel makes building accurate and reliable neuronal models more accessible to researchers, enhancing the reproducibility and efficiency of neuron modelling.

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Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

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Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.060/LBA59

Topic: I.07. Data Analysis and Statistics

Support: NSF Grant 58503110

Title: Just because you've saved it doesn't mean it's there: the effects of video compression on data quality

Authors: *I. SAFFARIAN-DEEMYAD[1], M. HOGAN[2], M. VERSHININ[2];
[1]Physics, Stanford Univ., Stanford, CA; [2]Physics, Univ. of Utah, Salt Lake City, UT

Abstract: Single-molecule imaging, both at and below the diffraction limit, is relevant for the investigation of synaptic vesicle release and cellular cargo transport in neural cells. Advances in nanoscale imaging technology have enabled the capture of multicolor super-resolution videos that can exceed 1 Tb per video. Because most research institutions and funding agencies have stringent rules about data storage and retention, many researchers use commercial video compression algorithms to store imaging data. However, little research has been done to investigate the effects of the latest lossy algorithms such as Advanced Video Coding (H.264), High Efficiency Video Coding (H.265), and AOMedia Video 1 (AV1) on data quality. Using simulated imaging data mimicking typical datasets, we investigated methods of preserving data quality while maximizing storage efficiency.
A point source imaged at the diffraction limit is well-approximated by a 2D gaussian peak. We confirm prior sporadic reports that most video compression algorithms allow for accurate tracking of the 2D Gaussian peak location. However, older codecs such as H.264 decrease the performance of motion-tracking algorithms more than newer codecs for a given compression ratio. Interestingly, we also found that under certain conditions, compression with newer codecs such as AV1 actually improves the performance of common motion-tracking approaches relative to uncompressed data.
The background noise contained in a dataset often contains valuable statistical information for meta-analyses. We found that newer, more efficient compression algorithms such as AV1 disproportionately target (i.e. remove or blur) background noise in order to achieve higher compression ratios. We also found that above a certain threshold all three codecs (H.264, H.265, and AV1) distort the data so much that metadata recovery (signal-to-noise and gain back-calculation) becomes questionable or impossible . We further demonstrate that Airy or Gaussian spatial data subjected to high compression ratios can no longer be accurately modeled as Gaussian.

Disclosures: I. Saffarian-Deemyad: None. **M. Hogan:** None. **M. Vershinin:** None.

Late-Breaking Poster

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Program #/Poster #: LBA009.061/LBA60

Topic: I.07. Data Analysis and Statistics

Support: RS-2024-00415347

Title: Temporal decomposition and domain adapation for fast-scan cyclic voltammetry

Authors: *E. KIM[1], Y. JEONG[1], S. KANG[2], J.-W. CHOI[1];
[1]Electrical Engin. and Computer Sci., DGIST, Daegu, Korea, Republic of; [2]Univ. of California, San Francisco, San Francisco, CA

Abstract: Fast Scan Cyclic Voltammetry (FSCV) faces significant hurdles, including problems with long-term measurements due to background drift and distributions shift caused by environment changes from in-vitro training set to in-vivo real-world data. We suggest a new machine-learning method to solve these issues. Our approach decomposes the background signal from FSCV data and reduces the effects of distribution shifts caused by environmental changes called domain shift. Our process has two main parts: (1) getting an environment-invariant feature from the voltammogram and (2) learning a temporal structure to remove background drift from voltammetry. The encoder maps the voltammogram from the observation space to a hidden space with domain-invariant loss, which captures the domain-invariant feature. Permutation contrastive learning (PCL) learns the temporal structure to decompose the hidden variable into independent components like concentration changes and background drift. It makes the model work properly in various environments, staying robust even when environmental changes. We tested our method using in-silico simulation, in-vitro probe-variance control, and in-vivo long-term experiments. In in silico simulations, we modeled environments with varying background ion distributions and tested the generalization performance accordingly. Proposed model shown the best and robust performance across the environment changes. It handled the distribution changes and make accurate concentration estimation in various scenario. Also, in in-vitro settings, our method effectively controlled for inter-probe variance, showing superior performance in both intra-domain and inter-domain scenarios. Finally, in-vivo experiment, our model caught long-term neurotransmitter changes, showing it can make challenging long-term measurements of multiple neurotransmitters in natural environments. This new approach makes to more accurate and reliable FSCV measurements. We believe that our method contributes to understands and treat brain conditions better by monitoring neurotransmitters more.

Disclosures: E. Kim: None. **Y. Jeong:** None. **S. Kang:** None. **J. Choi:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.062/LBA61

Topic: I.07. Data Analysis and Statistics

Support: KBRI grant 24-BR-02-01

NRF Korea RS-2024-00398223

Title: Quantification of stretch-attend posture based on morphometric and kinematic analysis of behavioral syllables in mice

Authors: *S. LEE[1], J. KIM[2], H. KIM[2];
[1]Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; [2]Korea Brain Res. Inst., Daegu, Korea, Republic of

Abstract: In certain behavioral tests, deciphering fear responses in mice is a complex challenge that requires precision and objectivity. When a rodent detects a potential threat, it shows a stretch-attend posture (SAP) characterized by a distinct stretching movement followed by an attentive pause. Traditional SAP measurement methods rely on subjective observer judgment,leading to inconsistencies and potential observer-expectancy bias, thus compromising the reliability of research findings. Additionally, the transient nature of behavioral changeschallenges the accuracy of direct observation. To overcome these limitations, we developed a program called SAP-Detector to measure SAP objectively and accurately in mice basedon measurement and segmentation of distance ratio. By employing this SAP-Detector, we propose a more precise analysis of behavioral responses, which can reveal differences ininteraction time with targets that may not be apparent through traditional metrics alone.

Disclosures: S. Lee: None. **J. Kim:** None. **H. Kim:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.063/LBA62

Topic: I.07. Data Analysis and Statistics

Support: T32AA026577
R01DA025634
T32DK128782

Title: Photometry Toolbox: an open-source MATLAB toolbox for the processing and analysis of fiber photometry data

Authors: *R. DONKA[1], M. K. LOH[2], V. R. KONANUR[1], M. F. ROITMAN[3], J. D. ROITMAN[3];
[2]Dept. of Cell. and Mol. Pharmacol., [3]Psychology, [1]Univ. of Illinois Chicago, Chicago, IL

Abstract: Fiber photometry is a rapidly growing technique to record real-time neural signaling in awake, behaving subjects. However, the processing and analysis of photometry data streams can be highly complicated, and there is wide divergence in methods across the field. While

several open-source signal processing tools exist, platforms can be inflexible in accommodating experimental designs, lack consistency in signal peak detection, and be difficult to use for naive users. To remedy these challenges, we developed an open-source MATLAB based toolbox for the processing and analysis of fiber photometry data. To validate our pipeline, we conducted recordings using three sensors capturing mesolimbic dopamine dynamics: GRABDA2H, dLight1.3b, and GCaMP6f. We injected Long Evans rats with viral vectors and targeted fiber optic implants to the NAc (WT; GRABDA2H: n = 10; dLight1.3b: n = 10) or VTA (TH Cre+; GCaMP6f: n = 10). Recording sessions were conducted 4 weeks post-surgery in operant chambers and we compared signal processing methods across sensors. First, to correct photobleaching and motion artifacts in the signal streams, we use Fast Fourier Transform (FFT) to convert both signal and control streams and perform subtraction in the frequency domain. FFT subtraction outperforms regression in removing photo bleaching and motion artifacts with all three sensors. This advantage was most apparent with GRABDA2H, for which 405nm wavelength is a suboptimal isosbestic control. After applying a bandpass filter, the signal is normalized as df/f or z-scores. Multiple options for normalization (full session, session baseline, trial, etc.) are available in the toolbox, allowing for customization. Following normalization, we conduct peak analysis to detect individual transient events. Other tools implement a sliding window and absolute amplitude threshold approach. Our peak detection determines pre-peak baselines and thresholds transients based on the increase from baseline, allowing for more reliable detection of events and characterization of transient kinetics (event amplitude, rise time, fall time, and width). This approach provides a more robust picture of neural dynamics. Additional functions to detect signal magnitude and individual events by trial, across long time windows, with drug injections, and numerous other paradigms are included in the toolbox to allow users maximum flexibility. While operating through MATLAB, the code is annotated to be readable, accessible, and adaptable for new users. Ultimately, our photometry toolbox introduces customizable, user friendly platform to process fiber photometry signals and detect events.

Disclosures: R. Donka: None. **M.K. Loh:** None. **V.R. Konanur:** None. **M.F. Roitman:** None. **J.D. Roitman:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.064/LBA63

Topic: I.08. Methods to Modulate Neural Activity

Support: Fonds de recherche du Québec Health: Doctoral Training for Applicants with a Professional Degree (Qc, Canada)
Higher Degree Research Development and Research Training Grant (University of New South Wales, Sydney, Australia)

University International Postgraduate Award (University of New South Wales, Sydney, Australia)

Title: Optimal Transcutaneous Spinal Stimulation: The Comparative Effectiveness of Stimulation Waveforms

Authors: *J. PROVENCHER[1,2], H. T. FINN[4,3], S. GANDEVIA[4,2], J. E. BUTLER[4,3], M. E. HEROUX[4,3];
[1]Neurosci. Res. Australia, Randwick, NSW 2031, Australia, Sydney, Australia; [2]Sch. of Clin. Med., [3]Sch. of Biomed. Sci., Univ. of New South Wales, Sydney - Kensington, Australia; [4]Neurosci. Res. Australia, Sydney - Randwick, Australia

Abstract: Transcutaneous spinal stimulation (TSS) is a promising non-invasive intervention to improve sensorimotor function in people with a spinal cord injury. However, little is known about the optimal electrical waveform. Hence, there is variability among studies that select conventional pulses or bursts of short pulses in monophasic or biphasic waveforms, with no clear justification. Here, we evaluate the ability of various TSS waveforms to elicit spinally evoked motor responses (sEMR). Based on axonal properties, we expect longer continuous phase durations to recruit sEMRs more effectively. In participants with intact neurological function (n=12), ten TSS waveforms were tested: monophasic and biphasic, with high-frequency burst (HF) waveforms (2kHz, 5kHz, and 10kHz; 1ms duration) and without (conventional pulses; 400µs and 1000µs phase duration). The HF waveforms were matched in total phase duration to the 400µs conventional pulses. The base of the cathode was over L1 (5x10cm), and the anode was below the umbilicus (10x5cm); sEMRs were recorded from soleus with surface electrodes. Waveform effectiveness was measured with a) the minimal current intensity required to elicit an sEMR (threshold) and b) the peak slope of the recruitment curve (peak-to-peak sEMR amplitude vs TSS intensity) fitted with a log-logistic function. Waveform outcomes were compared using mean [95%CI] differences. The threshold and peak slope were similar between the biphasic and monophasic variants of each waveform (i.e. 400µs, 1000µs, 2kHz, 5kHz, 10kHz). Given the difference in phase duration, the conventional 400µs biphasic waveform had a higher threshold (67.1mA [53.07, 81.10]) and a lower peak slope (0.12mV/mA [0.08, 0.17]) than the 1000µs biphasic waveform (threshold mean difference: -19mA [-23.6, -14.4]; peak slope mean difference: 0.09mV/mA [0.01, 0.16]). Compared to the 400µs biphasic waveform with equivalent total phase duration, the sEMR thresholds were higher with the 2kHz (20.6 mA [15.6, 25.6]); 5kHz (83.6mA [61.6, 105.5]) and 10kHz (168.5mA [135.0, 202.0]) HF waveforms. Similarly, the peak slopes were generally lower for the 2kHz (-0.02mV/mA [-0.04, 0]), 5kHz (-0.07mV/mA [-0.09, -0.05) and 10kHz (-0.10 [-0.14, -0.06] HF waveforms. The differences in threshold and peak slope between waveforms were also present with the monophasic variant. Clinically available stimulation devices use biphasic waveforms without HF burst modulation. Our results indicate that these TSS waveforms are more effective (i.e. lower threshold, greater peak slope) at eliciting soleus muscle sEMR in people without neurological impairment compared to waveforms with HF.

Disclosures: J. Provencher: None. **H.T. Finn:** None. **S. Gandevia:** None. **J.E. Butler:** None. **M.E. Heroux:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.065/LBA64

Topic: I.08. Methods to Modulate Neural Activity

Support: Institute of Information & communications Technology Planning & Evaluation (IITP) grant RS-2023-00221742
National Research Foundation of Korea(NRF) grant RS-2024-00333219

Title: Analyze the effects of long-term trigeminal nerve stimulation on sleep and bio-signal parameters - preliminary study

Authors: *D. KANG, J. LEE, I. KIM;
Hanyang university, Seoul, Korea, Republic of

Abstract: Sleep is defined based on various physiological changes that distinguish it from the state of arousal. Abnormal sleep-arousal state regulation can cause sleep disorders, and many researchers have conducted studies to control sleep-arousal state and treat sleep disorders using non-invasive electrical stimulation. Trigeminal nerve stimulation (TNS) is a non-invasive electrical stimulation method approved by the Food and Drug Administration (FDA) for ADHD, and several studies have reported that drowsiness was induced during and after TNS. TNS regulates the central nervous system and autonomic nervous system involved in the regulation of sleep-arousal state through nucleus tractus solitarius (NTS). However, few previous studies have reported the effects of long-term TNS on sleep, and the effect of TNS on sleep varies from study to study. In this preliminary study, we conducted to analyze the effect of long-term TNS (4-week) on sleep and bio-signal parameters. Long-term TNS was applied to two adult males who had never been diagnosed with sleep disorders. We collected sleep questionnaires (insomnia severity index, ISI; Pittsburgh sleep quality index, PSQI), actigraph (sleep efficiency, SE; wake after sleep onset, WASO), and bio-signal parameters (heart rate variability, HRV; power of electroencephalography, power of EEG) at 2-week intervals. We analyzed the trends of parameter changes according to the stimulation period (0-week, 2-week, 4-week, respectively). As a result, subjective sleep parameters (sleep questionnaire) and objective sleep parameters (actigraph) improved in two subjects (ISI: 11.5, 5.5, 4; PSQI: 8.5, 3, 3; SE: 79.98, 83.45, 85.92; WASO: 83.67, 71.5, 57.33). The resting state RMSSD (root mean square of the successive differences), one of the HRV parameters indicating parasympathetic nervous system (PNS), showed a tendency to increase over time (47.4, 40.24, 28.54). However, the difference before and after TNS showed an increasing trend (-13.66, 3.95, 24.27). That is, as the TNS progressed (from 0-week to 4-week), the PNS was suppressed, but responsiveness to TNS was enhanced. Additionally, one subject had a decrease in resting state normalized beta power of EEG, which indicates hyperarousal of the cerebral cortex (0.1106, 0.0867, 0.0634). Through a preliminary

study, we analyzed the effects of long-term TNS on sleep and bio-signal parameters, and confirmed the possibility that the application of long-term TNS can help improve sleep quality. We plan to systematically analyze the effects of long-term TNS on sleep by targeting more subjects in the future to see if the same tendency is observed.

Disclosures: D. Kang: None. **J. Lee:** None. **I. Kim:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.066/LBA65

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01-MH127006

Title: Phenomenal mapping: stimulation-evoked sensations with intracranial stimulation

Authors: *Y. Y. REED[1], Z. JOURAHMAD[1], L. MATTAR[1], I. A. DANSTROM[1], J. ADKINSON[1], D. OSWALT[2], E. BARTOLI[1], A. WATROUS[1], K. BIJANKI[1];
[1]Baylor Col. of Med., Houston, TX; [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Electrical stimulation mapping is widely used for clinical characterization of epileptic and functional circuitry in patients undergoing stereoelectroencephalography (sEEG) for medication-resistant epilepsy. While stimulation is an essential tool for mapping functions of neural tissue, approaches vary widely by institution, and mapping of stimulation-evoked phenomena remains inconsistent. The current study aims to expand available data on the sensory responses to neurostimulation in areas under-studied in stereo-EEG evaluation - the insula, and centromedial thalamus - and to compare responses of these structures to those more commonly studied - superior frontal gyrus (SFG), anterior cingulate, orbitofrontal cortex (OFC), superior temporal gyrus (STG), and amygdala. Out of 32 patients taking part in an electrical stimulation experiment (varying parameters, including amplitude, frequency and duration), 10 patients reported stimulation-evoked phenomena, spanning sensory (15), affective (9), visual (4), motor (4), and interoceptive (2) sensations. Regions most regularly evoking responses are insula, centromedial thalamus, and pulvinar. Sensory responses were also reported, although more rarely, in response to stimulation to the superior frontal gyrus, the rostral anterior cingulate, the medial orbitofrontal cortex, the superior temporal gyrus and amygdala. Sensory phenomena were reported following stimulation to the insula in 4 cases, stimulation to the centromedial thalamus in 3 cases, as well as following stimulation to the SFG in one case. Affective phenomena were evoked by stimulation to the rostral anterior cingulate (1), the medial OFC (1), the insula (1), and the STG (1). Motor phenomena were evoked by stimulation to the pulvinar (1) and the SFG (1). Visual phenomena were evoked following stimulation to the medial amygdala in two cases.

Overall, the highest reported responses are somatosensory, highest reported regions are the insula and centromedial thalamus, with the majority responses in white matter contacts. The current findings suggest reduced stimulation amplitude and charge density when mapping insular and thalamic-adjacent contacts, even when in white matter. Understanding the differential sensitivity of neural structures to stimulation will enable optimized clinical evaluation of eloquent cortical anatomy in epilepsy. In addition, such knowledge may aid in training machine learning algorithms to predict sensory functions based on stimulation parameters, anatomical locations, and patient characteristics.

Disclosures: Y.Y. Reed: None. **Z. Jourahmad:** None. **L. Mattar:** None. **I.A. Danstrom:** None. **J. Adkinson:** None. **D. Oswalt:** None. **E. Bartoli:** None. **A. Watrous:** None. **K. Bijanki:** 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.; reports intellectual property (US Patent:11,241,575) related to electrical stimulation of the cingulum bundle for the treatment of depression, anxiety, and pain..

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.067/LBA66

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01 NS092882
Birdel Fund Mayo Clinic Philanthropy
Modulight.Bio

Title: Optogenetic Papez Circuit Modulation in Göttingen Micropig

Authors: *F. MIVALT[1], K. L. BAR-OR[2], D. MALTAIS[1], Y. KFIR[2], J. KIM[1], I. KIM[1], M. HERSHKO[2], O. LEVI[2], O. YIZHAR[3], Y. ELDAR[2], S.-Y. CHANG[1], G. A. WORRELL[1]; [1]Mayo Clin., Rochester, MN; [2]Modulight.Bio, Boston, MA; [3]Weizmann Inst., Rehovot, Israel

Abstract: Rationale: Mesial temporal lobe epilepsy (mTLE) is often drug-resistant and associated with significant comorbidity, including sleep disturbance, mood changes, and various memory problems. People with drug-resistant mTLE are candidates for neuromodulation therapies. Electrical brain stimulation has proven efficacy, but achieving long-term seizure freedom is difficult. Recent progress in cell type-specific neuromodulation using optogenetics shows promise and may prove more effective in controlling complex epilepsy networks. Various opsins have been developed and tested in animal models of epilepsy. We evaluated a technology platform for optogenetic modulation of Papez's circuit using eOPN3, a red-shifted, inhibitory

type-2 opsin (GPCR opsin), in a porcine seizure model to advance translational applications of integrated electrical and optogenetics therapy. **Methods:** We expressed eOPN3 in the anterior nucleus of the thalamus (ANT) and hippocampus (HPC) of 3 Göttingen micropigs to suppress synaptic transmission through the Gi/o signaling pathway. On Day 1, an MRI-guided stereotactic surgery was performed to deliver 15 - 60 µL of an optogenetic construct (AAV5/9-CaMKII-eOPN3-mScarlet + Gadolinium (Gad); AAV titer: 2 X 10^{12} particles /ml) into ANT and HPC. Post-procedure MRI Gad distribution confirmed targeting accuracy. Two to three months later, acute electro-optical experiments followed by euthanasia and histopathology were performed to demonstrate: 1) Opsin expression, 2) optical modulation of Papez circuit, 3) optical modulation of HPC kainic acid (KA) induced electrographic seizure activity 4) histological investigations to characterize the distribution of eOPN3 and electrode targeting. **Results:** The developed platform enables stereotactic delivery of KA, optogenetic constructs and integrated opto-electrodes for local field potential sensing and stimulation. The eOPN3 expression was demonstrated in HPC and ANT using fiber photometry. Optogenetic modulation of the Papez circuit was demonstrated by modulating electrical stimulation-evoked potentials and KA-induced electrographic seizures under ketamine/xylazine and isoflurane with 50/50 N_2O_2. **Conclusion:** The technology platform enables real-time electrophysiology and optical data visualization, and analysis to evaluate electrical and optogenetic stimulation therapy paradigms. We demonstrated accurate stereotactic delivery, cellular uptake, and neuromodulation of Papez circuit using the eOPN3 construct in a large mammal. These results will enable future translational research with the ultimate goal of human epilepsy applications.

Disclosures: **F. Mivalt:** A. Employment/Salary (full or part-time):; F. Mivalt: Received salary support from Cadence Neuroscience Inc.. **K.L. Bar-Or:** None. **D. Maltais:** None. **Y. Kfir:** None. **J. Kim:** None. **I. Kim:** None. **M. Hershko:** None. **O. Levi:** None. **O. Yizhar:** None. **Y. Eldar:** None. **S. Chang:** None. **G.A. Worrell:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.068/LBA67

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH grant NS12368101
Stanford BIO-X

Title: A fast and responsive voltage indicator with enhanced sensitivity for unitary synaptic events

Authors: ***A. Y. HAO**[1], S. LEE[2], R. H. ROTH[3], S. NATALE[4], J. B. DING[5], T. C. SUDHOF[6], T. CLANDININ[2], M. Z. LIN[7];

[1]Stanford Univ., STANFORD, CA; [2]Neurobio., [3]Stanford Univ., Stanford, CA; [4]Stanford Univ., Palo Alto, CA; [5]Neurosurg., [6]Dept. of Mol. & Cell. Physiol., Stanford Univ., Stanford, CA; [7]Neurobio., Stanford, Stanford, CA

Abstract: A remaining challenge for genetically encoded voltage indicators (GEVIs) is the reliable detection of excitatory post-synaptic potentials (EPSPs). Here, we developed ASAP5 as a GEVI with enhanced activation kinetics and responsivity near resting membrane potentials for improved detection of both spiking and subthreshold activity. ASAP5 reported action potentials (APs) *in vivo* with higher signal-to-noise ratios than previous GEVIs, and successfully detected graded and subthreshold responses to sensory stimuli in single 2-photon trials. In cultured rat or human neurons, somatic ASAP5 reported synaptic events propagating centripetally, and could detect ~1-mV EPSPs. By imaging spontaneous EPSPs throughout dendrites, we find that EPSP amplitudes decay exponentially during propagation, and that amplitude at the initiation site generally increases with distance from the soma. These results extend the applications of voltage imaging to the quantal response domain including in human neurons, opening up the possibility of high-throughput high-content characterization of neuronal dysfunction in disease

Disclosures: A.Y. Hao: None. **S. Lee:** None. **R.H. Roth:** None. **S. Natale:** None. **J.B. Ding:** None. **T.C. Sudhof:** None. **T. Clandinin:** None. **M.Z. Lin:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.069/LBA68

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH Grant MH133020
BBRF Grant 31298

Title: Reduction of water exchange rate in the dorsal striatum following focused ultrasound-induced blood-brain barrier opening: a diffusion-prepared pCASL study

Authors: *D. LIU[1], F. A. MUNOZ[1], X. SHAO[4], S. SANATKHANI[1], E. KONOFAGOU[2], D. J. WANG[4], V. P. FERRERA[3];
[1]Zuckerman Inst., [2]Biomed. Engin., [3]Neurosci., Columbia Univ., New York, NY; [4]Stevens Neuroimaging and Informatics Inst., USC, Los Angeles, CA

Abstract: Objective: Transcranial focused ultrasound (FUS) is a non-invasive technique used to reversibly disrupt the blood-brain barrier (BBB), facilitating drug delivery or directly modulating brain activity. This study aims to investigate the impact of FUS-mediated BBB opening (FUS-BBBo) on water transport dynamics, utilizing diffusion-prepared pseudo-continuous arterial spin labelling (DP-pCASL) to measure cerebral blood flow (CBF) and water exchange metrics in

dorsal striatum of non-human primates (NHPs).
Methods: The FUS experiments were conducted on three healthy NHPs, using 2-minute FUS exposures (500 kHz, peak negative pressure (PNP) of 550 kPa with 65% skull attenuation, pulse repetition frequency (PRF) of 2 Hz, pulse length (PL) of 10 ms, and 2% duty cycle) combined with intravenous microbubbles (4-5 μm diameter, $2.5*10^8$microbubbles/kg) to open the BBB in the right caudate. A DP-pCASL MRI (three post-labelling delays ranging from 600 to 1700 ms, diffusion coefficients ranging from 0 to 25 s/mm^2, 2.2 × 2.2 × 5 mm^3 resolution, axial acquisition, 12 mins total time) was performed in a 3T MRI scanner to assess perfusion and BBB function changes without (6 sessions, 3 NHPs) and with FUS exposure combined with microbubbles (5 sessions, 3 NHPs) in the right caudate. Gadolinium-enhanced MRI scans were performed to confirm the success of FUS-BBBo of NHPs. Cerebral blood flow (CBF), arterial transit time (ATT), and water exchange rates (kw) in the chosen region of interest (ROI), as confirmed by contrast-enhanced MRI, were derived using a two-compartment single-pass approximation (SPA). Permutation tests with 400 random combinations were performed using perfusion MRI datasets without and with BBB opening.
Results: The group average CBF, ATT, and kw of the whole brain were 27.7/33.9 ml/100g/min, 1096/1137 ms, and 50.1/58.3 min^{-1} for non-BBBo/FUS-BBBo conditions, respectively. With ROI located in the caudate, no significant difference in CBF and ATT was found between non-BBBo and FUS-BBBo conditions ($p>0.05$, permutation test). However, a significant reduction in the BBB kw in the caudate following FUS-BBBo was observed compared to non-BBBo conditions ($p<0.01$, permutation test), with a group average kw of 37.8 min^{-1} with FUS-BBBo versus 54.7 min^{-1} for non-BBBo conditions.
Conclusion: This study demonstrates that FUS exposure with microbubbles can reduce the water exchange rate in the striatum, as measured by DP-pCASL. This finding supports the potential for using non-contrast perfusion MRI to detect and confirm FUS-induced BBB opening, facilitating efficient and safe clinical translation of FUS technology.

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Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.070/LBA69

Topic: I.08. Methods to Modulate Neural Activity

Support: 1RF1NS128569

Title: Noninvasive targeted modulation of pain circuits with focused ultrasonic waves

Authors: *J. KUBANEK[1], T. RIIS[2], D. FELDMAN[2];
[1]Univ. of Utah, 36 S Wasatch Dr, UT; [2]Biomed. Engin., Univ. of Utah, Salt Lake City, UT

Abstract: Chronic pain is often resistant to existing treatments.The posterior part of the anterior cingulate cortex (pACC) has been traditionally involved in the unpleasantness of pain.This deep brain regions has been difficult to modulate with existing approaches.We have applied low-intensity transcranial focused ultrasound to suppress the activity in this target directly, selectively, and non-invasively, predicting a decrease in pain symptoms.
We have developed an approach that delivers focused ultrasound into confined deep brain targets while compensating for the severe and unpredictable attenuation of ultrasound by the human head and hair.The method delivers into specified brain targets controlled ultrasound intensity.Twenty patients with chronic pain received two 40-minute active or sham pACC stimulation protocols over a two-week randomized sham-controlled cross-over trial (NCT05674903).
60% of subjects experienced clinically meaningful reduction of pain on day 1 and on day 7 following the active stimulation, while sham stimulation provided such benefits only to 15% and 20% of subjects, respectively.On average, active stimulation reduced pain by 60.0% immediately following the intervention and by 43.0% and 33.0% on days 1 and 7 following the intervention.The corresponding sham levels were 14.4%, 12.3%, and 6.6%.The stimulation was well tolerated, and no adverse events were detected. Side effects were generally mild and resolved within 24 hours.
Together, the direct, ultrasonic stimulation of the pACC offers rapid, clinically meaningful, and durable improvements in the severity of chronic pain.

Disclosures: J. Kubanek: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SPIRE Therapeutic. **T. Riis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SPIRE Therapeutic. **D. Feldman:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.071/LBA70

Topic: I.08. Methods to Modulate Neural Activity

Support: Natural Science Foundation of China 62088102
Natural Science Foundation of China 62222508
Natural Science Foundation of China 62071272
China Postdoctoral Science Foundation 2023M731983

Title: S-slim: a novel multi-color volumetric fluorescence imaging system for neuroscience

Authors: Z. LU, F. SUN, ***Q. ZHANG**, J. WU, Q. DAI;
Dept. of Automation, Tsinghua Univ., Beijing, China

Abstract: Capturing three-dimensional images with multiple fluorescent colors simultaneously at high speeds is a significant hurdle. We address this challenge by developing S-SLiM, an advanced computational intravital microscopy, which revolutionizes high-speed, volumetric multi-color fluorescent imaging by seamlessly integrating meticulously optimized hardware with deep learning algorithms. This innovative technique effectively disentangles complex fluorescent spectral volumes containing multiple channels from several color-modulated multi-view images, enabling diffraction-limited resolution, millisecond acquisition speeds, exceptional noise resilience, and enhanced fidelity across multiple dimensions. Furthermore, with high-throughput imaging capability, S-SLiM empowers the acquisition of massive datasets, paving the way for comprehensive biological analyses and potentially groundbreaking discoveries. This powerful method holds immense promise for unraveling the intricate neural underpinnings of decision-making behaviors in NeuroPAL worms at improved speed of 12 volumes per second, shedding light on the mechanisms underlying highly dynamic cognitive processes. Notably, S-SLIM extends beyond *C. elegans*, offering a valuable tool for investigating diverse neural systems in *zebrafish*, *Drosophila* and mice, ranging from subcellular dynamics to organismal interactions.

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LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.072/LBA71

Topic: I.08. Methods to Modulate Neural Activity

Title: Transcranial focused ultrasound stimulation on amygdala during a facial expression recognition task

Authors: *Y. WEI[1], K. ENOMOTO[2], M. HARUNO[3];
[1]Grad. Sch. of Frontier Biosci. Osaka Univ., Osaka Univ., Osaka, Japan; [2]Neural Information Engin. Lab., [3]Natl. Inst. of Information and Communication Technol., Osaka, Japan

Abstract: Transcranial focused ultrasound stimulation (tFUS) is a novel, non-invasive neuromodulation technique that uses ultrasound waves to stimulate brain structures. Compared to other non-invasive stimulation methods, tFUS offers higher spatial resolution and the ability to stimulate deeper brain regions.The amygdala, a part of the limbic system located deep in the brain, is a central hub for emotion processing. Although existing studies have reported modulatory effects of tFUS on cortical areas and the striatum, it remains largely unknown

whether and how tFUS can modulate activity in the amygdala and alter behavior.In this study, we conducted a tFUS/fMRI experiment targeting the amygdala in healthy human participants performing a facial expression recognition task. Participants were required to classify presented facial expressions into three categories: fear, neutral, and happy. On the first day of the experiment, participants performed the task in an MRI scanner. Based on GLM analysis using SPM12, we determined the location of peak activity in the right amygdala central nucleus (or basolateral amygdala if the central nucleus activity was not identifiable). On the second day, participants (n=24) received 40 seconds of low-intensity (30 W/cm²) tFUS stimulation targeting the identified location, followed by a second run of the task in the MRI scanner. The control group (n=28) performed the same task, with the exception that the tFUS target location was white matter between the amygdala/hippocampus and the cortex. We observed a significant decline in the accuracy of fearful face recognition immediately following stimulation, exclusively in the tFUS group ($p<0.05$). To confirm that this behavioral decline differed between the two groups, we conducted a generalized least squares (GLS) model analysis of the behavioral data, using "group" (tFUS:1 and control:0) and other explanatory variables. After stimulation, we observed significant negative effects on accuracy for the interaction term fear*group ($p < 0.05$). In the fMRI analysis, we observed an increase in amygdala activity immediately after tFUS stimulation in the tFUS group in the central amygdala and superficial amygdala. We also found a positive correlation ($p < 0.05$) between the decrease in accuracy for fearful faces and the increase in amygdala activity.These results demonstrate that tFUS can disrupt amygdala function in discriminating emotional facial expressions while increasing its activity. Given that amygdala dysfunction is associated with many psychiatric disorders, our research may contribute to the development of tFUS-based therapies for psychiatric conditions.

Disclosures: Y. Wei: None. **K. Enomoto:** None. **M. Haruno:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.073/LBA72

Topic: I.08. Methods to Modulate Neural Activity

Support: R01NS120594
R01NS122904

Title: Ultra-short micro-magnetic stimulation pulses induce localized neuronal cortical activity measured by optical glutamate changes

Authors: L. GOMEZ CID[1], F. MARTURANO[1], Y. ZHANG[3], J. DENG[3], I. AY[1], X. YU[2], ***G. BONMASSAR**[4];

[2]Radiology, [1]Massachusetts Gen. Hosp., Charlestown, MA; [3]Harvard Univ., Cambridge, MA; [4]Harvard Med. Sch., Charlestown, MA

Abstract:

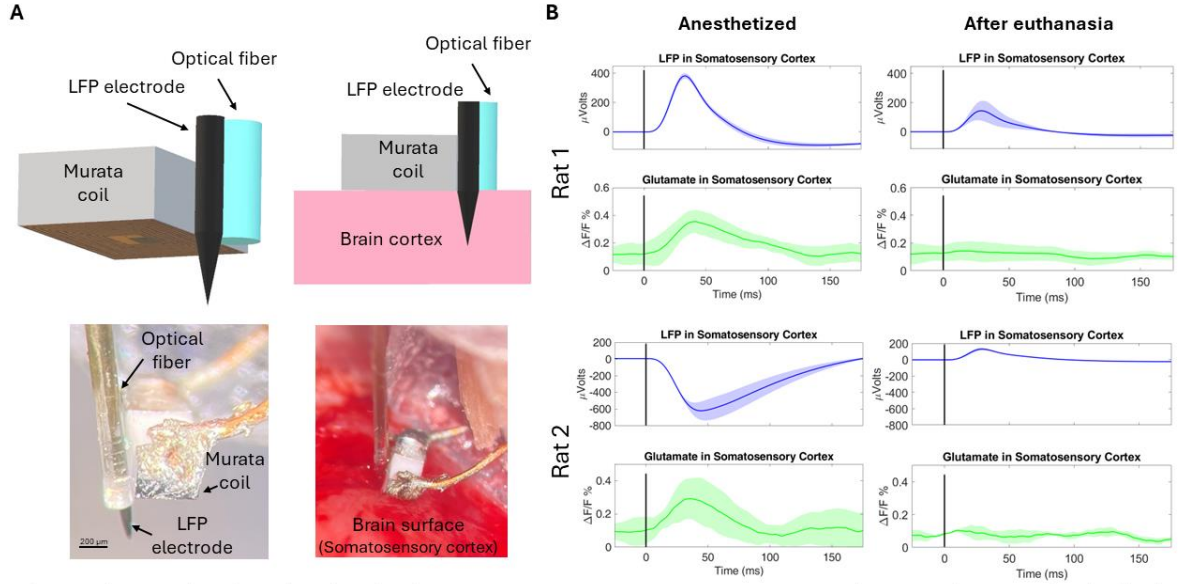

Figure 1. A) Murata micro-stimulation coil, optical fiber and LFP electrode setup and placement onto the brain surface. **B)** Electrophysiological (LFP) and optical (glutamate) recordings in response to micro-magnetic stimulation in two rats under anesthesia and after euthanasia (Mean ± SD). Black bar corresponds to the time of stimulation. Average of N= 1650 pulses (Rat 1) and N=450 pulses (Rat 2) per condition.

Micro-magnetic stimulation could serve as an implantable transformative tool for circuit manipulation of neurons. However, the design, the stimulation parameters, and the capability of micro-coils to induce localized cortical activation in vivo have yet to be determined. In this work, we tested the potential of a micro-magnetic stimulator to induce cortical activation in rodents. Long-Evans rats were injected with viral vector 98929-AAV9 from Addgene to optically sense glutamate in the surface of the somatosensory cortex (S1Tr, 3.0 ML -2.5 AP, -0.4 DV). After 3 weeks, the animals were anesthetized (2% isoflurane) and a craniotomy was performed at the target region. A skull screw with a wire served as a reference for the local field potential (LFP) electrophysiological recordings. A rectangular micro-coil (LQP15MN3N3B02D, Murata) was mounted with an optical fiber and an LFP electrode and placed onto the target brain surface (Fig. 1A). Magnetic stimulation was performed at 1 Hz with a 5s on/15s off stimulation paradigm using an audio power amplifier (Pyle), a generator (Tektronix) and a current sensor. We used a bipolar square pulse of 10 µs and an amplified 10A peak-to-peak current. A BIOPAC system recorded the stimulation times, LFP and glutamate changes with fiber-photometry. Control recordings were included after the rat was euthanized under the same settings. Preliminary results show that micro-magnetic stimulation induced local neuronal activation and subsequent increase in extracellular glutamate (as shown by increased optical signal, Fig. 1B). However, we observed interferences of the magnetic stimulation on the electrophysiological recording system (LFP recording changes still present after the animal was euthanized). On the contrary, optical recordings were clean from these interferences as the optical signals showed no alterations after euthanasia. In the future, we plan to explore different coil designs and field orientations to investigate the potential of micro-magnetic stimulation to focally activate cortical neurons at multiple spatial and temporal scales.

Disclosures: L. Gomez Cid: None. **F. Marturano:** None. **Y. Zhang:** None. **J. Deng:** None. **I. Ay:** None. **X. Yu:** None. **G. Bonmassar:** None.
Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.074/LBA73

Topic: I.08. Methods to Modulate Neural Activity

Support: ERC Synergy 810377

Title: Real-time brain state-coupled network-targeted dual-site TMS enhances working memory

Authors: *B. JOVELLAR[1], P. BELARDINELLI[2], U. ZIEMANN[3];
[1]Univ. of Tuebingen, Tuebingen, Germany; [2]Eberhard-Karls-University of Tuebingen, Tübingen, Germany; [3]Eberhard Karls Univ. of Tuebingen, Tübingen, Germany

Abstract: Working memory impairment is a common affliction in disorders such as Alzheimer's disease, attention-deficit hyperactivity disorder (ADHD), and major depression. Brain stimulation is a promising tool for modulating brain networks and improving cognitive performance. We applied non-invasive brain stimulation—using transcranial magnetic stimulation (TMS)—in a real-time brain state-dependent manner to dorsomedial regions of the fronto-parietal network, incorporating a spike-timing-dependent plasticity (STDP) induction protocol. Using theta oscillation phase as a brain state marker, we compared the effects of brain state-coupled vs. -uncoupled dual-site TMS on: 1) EEG dynamics time-locked to the TMS pulses; 2) working memory performance, and 3) oscillation power during the memory task. We found that: 1) the brain state-coupled protocol caused greater amplitudes of evoked activity within 90 ms post-TMS pulse; 2) the brain state-coupled condition enhanced working memory accuracy; and 3) correct vs. incorrect working memory trials had broadband differences in power across encoding, retention, and recall periods at baseline and these were differentially modulated after brain state-coupled vs. -uncoupled stimulation. Our work provides a crucial first step in personalized pathway-targeted brain stimulation in cognitive networks that may minimize potential adverse effects and maximize its cognitive enhancement potential in healthy individuals or in people with network disorders affecting memory such as Alzheimer's disease, major depression, or ADHD.

Disclosures: B. Jovellar: None. **P. Belardinelli:** None. **U. Ziemann:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.075/LBA74

Topic: I.08. Methods to Modulate Neural Activity

Title: Tracking Human Single- and Multi-units over Days during 24 h Recording

Authors: *Z. JOURAHMAD, J. ADKINSON, E. BARTOLI, S. A. SHETH, A. WATROUS; Baylor Col. of Med., Houston, TX

Abstract: Microelectrode recordings of single neurons have long been a cornerstone in animal studies. However, the application of this technique in humans is still evolving due to technical and practical challenges. For example, a significant challenge is the variability in electrode placement and patient movement, which can affect the stability of recorded neurons. The primary challenge in such recordings is maintaining accurate single-unit identification across multiple sessions, given the potential for electrode movement and evolving neural activity patterns. Here we addressed these challenges via long-term unit tracking in human subjects, focusing on the development and implementation of an “online” spike sorting system that operates on continuous 24-hour recordings over days. Initial implementation of this system in our hospital indicates successful tracking of neurons over time. By addressing these challenges, our method improves the reliability of single-unit tracking and enhances the accuracy of neural data analysis over extended periods in humans. This advancement holds promise for both basic research and clinical applications, where long-term monitoring is crucial for understanding complex neural dynamics and disorders.

Disclosures: Z. Jourahmad: None. **J. Adkinson:** None. **E. Bartoli:** None. **S.A. Sheth:** F. Consulting Fees (e.g., advisory boards); Consulting fees, advisory boards (Boston scientific). **A. Watrous:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.076/LBA75

Topic: I.06. Computation, Modeling, and Simulation

Title: Shifts in Brain Dynamics and Drivers of Consciousness State Transitions

Authors: *J. BODENHEIMER[1], P. BOGDAN[3], S. PEQUITO[4], A. ASHOURVAN[2]; [1]The Univ. of Kansas, LAWRENCE, KS; [2]The Univ. of Kansas, Lawrence, KS; [3]USC, Los Angeles, CA; [4]Univ. de Lisboa, Lisbon, Portugal

Abstract: Understanding the neural mechanisms underlying the transitions between different states of consciousness is a fundamental challenge in neuroscience. Thus, we investigate the underlying drivers of changes during the resting-state dynamics of the human brain, as captured by functional magnetic resonance imaging (fMRI) across varying levels of consciousness (awake, light sedation, deep sedation, and recovery). We deploy a model-based approach relying on linear time-invariant (LTI) dynamical systems under unknown inputs (UI). Our findings reveal distinct changes in the spectral profile of brain dynamics - particularly regarding the stability and frequency of the system's oscillatory modes during transitions between consciousness states. These models further enable us to identify external drivers influencing large-scale brain activity during naturalistic auditory stimulation. Our findings suggest that these identified inputs delineate how stimulus-induced co-activity propagation differs across consciousness states. Notably, our approach showcases the effectiveness of LTI models under UI in capturing large-scale brain dynamic changes and drivers in complex paradigms, such as naturalistic stimulation, which are not conducive to conventional general linear model analysis. Importantly, our findings shed light on how brain-wide dynamics and drivers evolve as the brain transitions towards conscious states, holding promise for developing more accurate biomarkers of consciousness recovery in disorders of consciousness.

Disclosures: J. Bodenheimer: None. **P. Bogdan:** None. **S. Pequito:** None. **A. Ashourvan:** None.

Late-Breaking Poster

LBA009: Theme I Late-Breaking Posters

Location: MCP Hall A

Time: Tuesday, October 8, 2024, 1:00 PM - 5:00 PM

Program #/Poster #: LBA009.077/LBA76

Topic: I.08. Methods to Modulate Neural Activity

Title: Recording Neural activity using Scanless 2-Photon Voltage Imaging: A Commercial Implementation

Authors: *O. ASSAYAG[1], R. SIMS[2], Y. ATLAS[1], I. BENDIFALLAH[3], S. DOMINGUEZ[2], K. KILBORN[4], V. EMILIANI[5];
[1]Intelligent Imaging Innovations SAS, Paris, France; [2]Inst. de la Vision, Paris, France; [3]Inst. de la Vision, Sorbonne Université, INSERM, CNRS, Paris, France; [4]3i, Denver, CO; [5]Photonics Dept., Vision Insitut, Paris, France

Abstract: In this work we present the first commercial demonstration scanless Multiphoton voltage Imaging using a 2-photon imaging microscope (VIVO Multiphoton RS+, Intelligent Imaging Innovations combined with a Holographic module with Temporal Focusing (Nouveau Phasor, Intelligent Imaging Innovations) and a high speed sCMOS camera (Kinetix K22, Photometrics). All the results discussed were obtained from neurons in hippocampal organotypic

slices expressing the recently developed, negative-going, 2P-optimized, soma-targeted voltage indicator JEDI-2P-Kv [1]. In a first step, we used patch-clamp electrophysiology recording to assess the correspondence between APs in the electrophysiological and the camera- based fluorescent traces. In a second step, we use a low repetition rate, high pulse energy femtosecond laser emitting at 1030nm (Satsuma, Amplitude) to generate computer generated holographic circular patterns to allow for simultaneous activation of all the GEVI presents in the cell soma. Using the multiplexing capability of computer-generated holography, we could also record the activity of multiple targets simultaneously. Several activation protocols were tested and optimized to obtain high SNR induced voltage response at an acquisition rate of 1kHz with ~10mW of average stimulation laser power per cell using ~15µm diameter circular holographic patterns[2]. We optimized the stimulation protocol to minimize any photoinduced physiological perturbations during 30s, high duty cycle recordings. Our protocol provided high spike detection reliability of 95%. References: 1. Liu, Z. et al. Sustained deep-tissue voltage recording using a fast indicator evolved for two-photon microscopy. Cell 185, 3408-3425.e29 (2022) 2. Sims, R.R., Bendifallah, I., Grimm, C. *et al.* Scanless two-photon voltage imaging. *Nat Commun* 15, 5095 (2024).).

Disclosures: O. Assayag: A. Employment/Salary (full or part-time):; Intelligent Imaging Innovations. **R. Sims:** None. **Y. Atlas:** A. Employment/Salary (full or part-time):; Intelligent Imaging Innovations. **I. Bendifallah:** None. **S. Dominguez:** None. **K. Kilborn:** A. Employment/Salary (full or part-time):; Intelligent Imaging Innovations. **V. Emiliani:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inserm.