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Military Service Members Face Unique and Sustained Threats to Optimal Brain Health

Research offers promise of improved treatments for traumatic brain injury and chemical exposure

WASHINGTON, DC — Military service exposes soldiers to a unique set of physical challenges, including toxic chemicals and traumatic brain injury, which can have profound effects on their health and well-being. New research examines the effects of military-related brain disorders and possible paths toward treatment, as well as a potential way to harness our brain's learning capabilities to better train pilots. The studies were presented today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

More than 21 million Americans are military veterans, and a growing number of them are grappling with the lifelong physical and cognitive effects of brain injuries. Neuroscientists are continuing to improve our understanding of these stressors on soldiers' health, with the goal of improving life for veterans to the greatest extent possible.

Today's new findings show that:

- Novice military aviators can improve their visual responses to challenging environments by observing how expert pilots move their eyes (Stephen Macknik, abstract 493.01, see attached summary).
- Blast-induced traumatic brain injury enlarges the amygdala, damages the frontal lobe, and accelerates patterns of brain aging in rats (Alaa Kamnaksh, abstract 107.03, see attached summary).
- Transplanted neural stem cells can help replace and protect brain tissue damaged by severe traumatic brain injury in rats (Shyam Gajavelli, abstract 336.11, see attached summary).
- Widespread disruptions in communication among brain networks may underlie commonly reported symptoms of Gulf War Illness, including changes in visual processing, language function, pain perception, and mood regulation (Kaundinya Gopinath, abstract 456.09, see attached summary).

Other recently published research shows that:

- A molecule that stabilizes a critical structural component of neurons reverses some of the cellular effects seen in cultured neurons exposed to a chemical related to sarin (Ankita Patil, abstract 71.06, see attached summary).

"Our soldiers have already given so much only to then face especially challenging lives after leaving the battlefield," said Colonel Deborah Whitmer, DVM, PhD, of the Walter Reed Army Institute of Research. "These studies improve our understanding of risks to brain function because of unique combat hazards as well as offer hope for potential treatments and enhancement of adaptation and learning."

This research was supported by national funding agencies such as the National Institutes of Health, as well as other public, private, and philanthropic orgnaizations worldwide. Find out more about brain issues affecting military service members on *BrainFacts.org*.

Related Neuroscience 2017 Presentation
Minisymposium: *In Vivo* Imaging of CNS Injury and Disease
Monday, Nov. 13, 1:30–4 p.m., WCC Ballroom C

Abstract 493.01 Summary

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Novice Pilots Improve Visual Responses to Emergency Simulation by Watching Experts' Eye Movements

Eye movements reliably distinguish between novice and expert military pilots

Novice military pilots can improve their visual responses to a simulated emergency procedure by observing the eye movements of expert pilots, according to new research presented at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's leading source of emerging news about brain science and health.

High-quality visual input is restricted just to the very centers of our retinas. Our eyes thus make several movements every second to combine these snippets of information into a visual representation of our immediate environment. Previous research has shown that eye movements in response to visual stimuli can serve as a biomarker for brain states such as fatigue or high mental concentration.

To explore how eye movements might relate to expertise in a challenging task, researchers evaluated eye tracking as an objective means of classifying novice versus expert military helicopter pilots. The study found that eye movement differences are so pronounced and predictable between novices and experts that computers can use an eye tracking algorithm to accurately classify them more than 80 percent of the time.

The researchers also explored whether the differences in eye movements between expert and novice pilots could be developed into a training regimen. One group of novices watched a video in which an expert pilot solved a complex emergency procedure in a military flight simulator. Another group watched the same video, but with a representation of the expert pilot's eye movements superimposed onto the video (a dot moved around the screen in real time, indicating eye position). When retested, only the latter group had acquired expert eye movement techniques. This occurred without explicit instructions about what the dot was or how to use it. The results suggest that modeling expert eye movements may benefit pilot training.

"We discovered that when novice pilots learn how to move their eyes by watching the eye movements of expert pilots via eye tracking technology, they rapidly improve their visual scanning strategies in the cockpit, even without explicit instructions," said senior author Stephen Macknik, PhD, of the State University of New York Downstate Medical Center. "This breakthrough could pave the way for a new type of eye movement–based training of aviators."

Research was supported with funds from the United States Army.

Scientific Presentation: Tuesday, Nov. 14, 8–9 a.m., WCC Halls A–C

17448. An objective classifier of expertise in United States Marine Corps combat aviators
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TECHNICAL ABSTRACT: We and others have previously shown that oculomotor dynamics serve as a valid biomarker for fatigue and high mental workload, and other brain states—measured in applied environments. We obtained eye movements from both instructor and trainee United States Marine Corps (USMC) combat aviators to determine the differences in dynamics as a function of expertise. The pilots flew different simulated mission types and we determined their ocular kinematics—as a function of mission type and cohort—across many dimensions. We observed that there are differences in specific eye movement signals between novice and expert helicopter pilots. From this data we created a classifier of expertise, which performed with an accuracy of >70%. We then studied whether novice pilots benefit more from viewing movies of experts performing emergency procedures or the same movies with the expert's eye position scanpaths overlaid. As an innovation, we did not measure the benefit to novices as a function of performance, but instead measured their oculomotor dynamics as a function of the expert scanpaths—assessed by our objective expertise discriminator. We tasked novice pilots with repeatedly resolving an Emergency Procedure (dual engine failure cascade), followed by watching a video with the expert eye position indicated, and the other half watched the video without the eye movements superimposed. Pilots who were given access to the expert's scanpaths significantly changed, in comparison to pilots who saw the same movies without scanpaths. These results suggest that physiological biomarkers such as oculomotor dynamics may provide a rich source of data—in a short amount of time and within challenging operational environments. This also suggests that our oculomotor systems learn to use eye tracking information—even without being instructed to—very quickly. Future research will determine if the fast oculomotor learning we observed translates to true improvements of performance.

Abstract 107.03 Summary

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Lasting Neurobehavioral Problems After Repeated Brain Injury May Stem From Changes in Brain Networks

Rats exposed to a series of mild blasts show altered pattern of brain aging, increase in fear center

The long-term cognitive and behavioral effects associated with repeated mild traumatic brain injury may result from changes in how brain networks recover and age after injury, according to new animal research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Mild traumatic brain injury (mTBI), resulting from exposure to explosive blasts, is often considered the "signature wound" of soldiers who experienced combat in Iraq or Afghanistan. For some individuals, the symptoms of blast-induced mTBI are mild and transitory, but for others the effects are more prolonged. Over time, repeated blast-induced mTBI can lead to increased anxiety, depression, and aggression as well as memory loss.

To better understand the consequences of repeated blast-induced mTBI, a research team led by Denes Agoston of the Uniformed Services University exposed rats to repeated mild blasts that simulated the blasts a soldier might encounter in combat. In collaboration with Walter Reed Army Institute of Research and Duke University, the team examined micro-scale changes in brain structure one week and three months after the blasts using a magnetic resonance imaging (MRI)–based brain-scanning method known as diffusion tensor imaging (DTI). Rats that experienced repeated blasts showed alterations in brain structure over time, compared to uninjured rats; while some of these changes appeared early on, largely subsiding by three months, others persisted and worsened with time. In addition, rats that experienced the blasts had accelerated growth in the amygdala, a brain region involved in emotional processing. Increased activity of the amygdala has been correlated with an exaggerated response to perceived threats in military veterans. The DTI scans also revealed structural damage to the frontal lobe and hindbrain of rats that had experienced repeated blasts.

"Since the regions affected by blast perform some of the most complex executive and cognitive functions in the brain, TBI-induced damage may permanently impair numerous aspects of brain function and everyday behavior in soldiers," said lead author Alaa Kamnaksh. The team is now working to identify the molecular foundation of the observed changes as the next step toward better diagnosis and treatment of repeated mild blast-induced TBI.

Research was supported with funds from U.S. Army Medical Research Acquisition Activity and the National Institute of Biomedical Imaging and Bioengineering.

Scientific Presentation: Sunday, Nov. 12, 8:30–8:45 a.m., WCC 156

17450. The dynamics of structural changes after repeated mild TBI
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TECHNICAL ABSTRACT: A history of mild traumatic brain injury (mTBI), particularly repeated mTBI (rmTBI), has been identified as a risk factor for late-onset neurodegenerative conditions. Although civilian and military populations are equally affected, blast-induced rmTBI (rmbTBI) in young service members can have significant implications for force readiness and the military health care system. While the transient and mild nature of early neurobehavioral and cognitive symptoms impede the timely diagnosis in young soldiers exposed to blast, age-associated neurocognitive changes can confound the diagnosis of injury-induced neurodegeneration and its symptomatology in veterans. Therefore, we used DTI to quantify the extent and nature of rmbTBI-related pathology at 7 and 90 days post-injury, and its evolution between the two time points in young male rats. Animals were exposed to repeated mild blast overpressure (3 total; peak total pressure = 15.5-19.4 psi) or anesthetized as shams, and perfused and their brains imaged and analyzed. We found that total brain volumes were similar in injured and sham rats at 7 and 90 days. However, we detected local volume reductions 7 days post-injury, and more extensive changes at 90 days, in white matter tracts including the internal capsule (medial longitudinal fasciculus) as well as in gray matter volumes of the olfactory, striatal, septal, thalamic and cerebellar areas. Among areas showing increased volume, the amygdala, an important substrate for anxiogenic behavior, was significantly enlarged at 90 days. DTI also detected changes in white matter microstructure, most notably a widespread increase in radial diffusivity 7 days post-injury, which largely subsided by 90 days. Conversely, differences in white matter integrity detected at 7 days persisted in injured rats as decreased fractional anisotropy at 90 days. Importantly, we found significant age by injury interactions on regional volumes and diffusion tensor parameters, indicating an altered ageing/developmental trajectory as result of injury. Our findings suggest that in addition to its direct short- and long-term effects on the brain, rmbTBI can adversely alter the course of late stage neurodevelopment at microstructural levels. If proven clinically, these findings can have short-term implications for force readiness and have long-term effects for the military health care system.

Abstract 336.11 Summary

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Neural Stem Cell Transplantation Improves Outcomes After Traumatic Brain Injury in Rats

Transplanted stem cells integrate into host brain and mitigate tissue loss

Neural stem cell transplantation could help replace and protect brain tissue damaged by severe traumatic brain injury (TBI), according to new animal research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The study reveals how neural stem cells integrate into an injured brain, demonstrating the potential for future TBI treatments that would improve the long-term well-being of soldiers.

Severe penetrating TBI, such as soldiers might receive from a bullet or shrapnel, is associated with poor outcomes among survivors, characterized by lifelong physical and cognitive disabilities, increased risk of seizures and neurodegenerative disorders, and reduced life expectancy. This is due in part to an active process of cell death that continues for years, magnifying the effects of the primary injury. Human neural stem cells (NSCs) are one potential remedy for treating brain damage associated with TBI because of their unique ability to integrate into an injured brain.

To investigate the efficacy of neural stem cells for treating TBI, the researchers transplanted human NSCs into brains of rats with penetrating TBI, either directly into the injured area or adjacent to the site of injury. NSCs transplanted near, but not directly within, an injured area significantly reduced the spread of the damage and preserved greater amounts of host tissue that was otherwise destined for destruction by the immune system. The transplanted cells also appeared to improve clearance of debris from damaged tissue.

"The transplanted cells appeared to act as a robust barrier to effectively reduce the spread of the injury and thus improve functional outcome," said lead author Shyam Gajavelli, PhD, of the University of Miami. "The current results are very promising, particularly given that human neural stem cells have already been demonstrated to be safe for use in humans with other central nervous systems disorders."

Research was supported with funds from the Department of Defense.

Scientific Presentation: Monday, Nov. 13, 8 a.m.–noon, WCC Halls A–C

17451. Distribution and morphology of transplanted human neural stem cells in rats with penetrating ballistic-like brain injury

***S. GAJAVELLI**[1], S. W. LEE[1], M. S. SPURLOCK[1], Z. HU[1], K. N. RIVERA[1], L. QUESADA[1], *G. R. GAJAVELLI[1], *C. J. ALVAREZ[1], A. MAHAVADI[2], D. A. SHEAR[3], T. G. HAZEL[4], R. M. BULLOCK[1]; [1]Miami Proj Cure Paral, Univ. Miami, Miami, FL; [2]Neurosurg., Univ. of Miami, Miami, FL; [3]Walter Reed Army Inst. of Res., Silver Spring, MD; [4]Neuralstem, Inc, Germantown, MD

TECHNICAL ABSTRACT: Severe penetrating traumatic brain injury (PTBI) is associated with the worst outcomes in terms of high mortality and severe disability among survivors. Loss of cells combined with incomplete endogenous repair mechanisms may be an underlying cause of disability. Currently no treatment strategies are available. Using a fetal human neural stem cell line (hNSC; Neuralstem Inc.) that has been approved by FDA for use in clinical trials we have previously shown durable engraftment in a rat model of penetrating ballistic-like brain injury (PBBI). However, the best transplant location to rebuild lost circuitry is unknown. Here we describe follow-on studies wherein cells were transplanted either in the lesion core or in the penumbra in PBBI animals. 12 weeks post-transplantation we assessed graft survival and lesion volume by histology. PBBI was induced in anesthetized rats. At one-week post-PBBI, immuno-suppressed rats received stereotactic injections of green fluorescent protein (GFP) expressing hNSCs (1 million/rat) into the lesion core (Intralesional; n=10) or lesion penumbra (Perilesional; n=10). An additional group of uninjured rats received hNSC transplant as controls (n=10). 12 weeks post-transplant brain sections were stained to assess (1) axonal damage, (2) lesion volume, and (3) distribution of transplant-derived projections. Results of lesion volume measurements at 12-weeks post-transplantation revealed significant reductions in lesion volume following both perilesional and intralesional engraftment of hNSCs ($p < .05$ vs. PBBI+Vehicle). PBBI-injured animals that received perilesional hNSC engraftments showed a significant reduction in lesion volume compared to animals that received intralesional hNSC transplants. Silver staining revealed significant damage to the intratelenchephalic and corticostriatal white matter. GFP+ hNSC survival was significantly greater in PBBI animals compared to Sham animals. However, no differences in hNSC transplant survival were detected between groups. The transplant derived projections traversed corticofugal subcerebellar pathways akin to layer 5 cortical neurons. These results suggest the PBBI milieu at one-week post injury supports hNSC engraftment independent of transplant location. Integration of transplanted hNSCs into the host may provide therapeutic benefit by salvaging endogenous tissue destined for secondary damage. The distribution of the transplant derived projections in the corticofugal subcerebellar motor pathway suggests a potential role for graft-derived cells in amelioration of motor deficits.

Abstract 456.09 Summary

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Disrupted Brain Communication Patterns May Lie at the Root of Gulf War Illness

Brain network functions affected in veterans with GWI include vision, pain perception, and mood regulation

The brains of veterans with Gulf War Illness (GWI) show widespread communication abnormalities in networks that support a multitude of brain functions, according to new research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The observed patterns of impairment provide objective neurophysiological evidence to support the self-reported symptoms of numerous veterans with GWI.

As many as 250,000 veterans who served in Iraq, Kuwait, and Saudi Arabia during the 1991 Gulf War may currently experience GWI. Symptoms include difficulty remembering things, trouble finding words while speaking, motor coordination, mood swings, fatigue, and chronic pain. GWI is thought to be caused by exposure to a mix of chemical and biological warfare agents and hazardous chemicals.

To better understand brain changes in GWI, researchers compared the brains of 22 veterans with GWI to the brains of 30 healthy veterans of similar age. Using a technique called resting state functional magnetic resonance imaging (fMRI), researchers analyzed patterns of communication among regions of the brain known to control different functions and behavior. They identified changes in functional networks related to many commonly reported GWI symptoms: Individuals with GWI showed clear deficits in neural communication in the sectors of the brain responsible for visual processing, mood regulation, motor coordination, sensory processing, and language command, but increased communication in networks related to pain perception during rest.

"The results from this study provide strong evidence of neuropathology in GWI patients from exposures to neurotoxic agents," said lead author Dr. Kaundinya Gopinath, PhD, of Emory University. Next, "the aim is to establish brain mechanisms underlying GWI, which in turn can lead to development of treatments."

Research was supported with funds from the Department of Defense.

Scientific Presentation: Tuesday, Nov. 14, 10–10:15 a.m., WCC 152B

17453. Brain functional network impairments and abnormal processing at rest in Gulf War Illness: A resting state fMRI study
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TECHNICAL ABSTRACT: Up to 250,000 veterans of the 1991 Gulf War suffer from illness (GWI) characterized by multiple deficits in cognitive, emotion, vision, somatosensory and pain domains as assessed by analysis of self-reported symptoms. In this study we employed resting state fMRI (rsfMRI) to map impairments in brain function in GWI with advanced network analysis. 22 veterans with GWI (mean age 49.4 yrs.) and 30 normal controls (NC) (mean age 49.8 yrs.), were scanned in a Siemens 3T MRI scanner using a 12-channel Rx head coil. Written informed consent was obtained from all participants in the protocol approved by the local Institutional Review Board. rsfMRI data were acquired with a 10-min whole-brain gradient echo EPI (TR/TE/FA = 2000/24ms/90°, resolution = 3mm x 3mm x 3.5mm). The preprocessed rsfMRI data for all subjects were temporally concatenated and a group spatial independent component analysis (ICA) was performed which yielded 27 group ICs. Voxel-wise GWI vs NC t-tests were conducted on the back-reconstructed and scaled subject-level components for each IC in order to examine between-group differences in functional connectivity (FC) within the resting state brain function networks represented by that IC. The GWI group exhibited significantly (multiple-comparison corrected $p < 0.05$) increased resting state functional connectivity (rsFC) in the visual attention network compared to NC but decreased FC in visual processing networks like the ventral visual stream and visual memory. This is consistent with symptoms of deficits in visual processing reported by GWI patients. GWI group also exhibited higher rsFC in perceptuomotor network compared to NC as well as increased rsFC between perceptuomotor and default mode networks (DMN) consistent with symptoms of heightened state of vigilance during rest reported by GWI patients. Further GWI group exhibited increased rsFC in somatosensory pain perception areas including the recruitment of dorsolateral prefrontal cortex into the pain neuromatrix. This is consistent with symptoms of chronic pain observed in GWI patients. GWI group also exhibited increased rsFC within affective processing networks and increased FC of limbic areas to DMN during rest consistent with symptoms of persistent mood disturbances reported by GWI veterans. Apart from this GWI group also exhibited decreased rsFC in executive function and language processing networks consistent with symptoms of deficits observed in these domains. Thus ICA of rsfMRI data is able to reveal impairments and abnormal processing in brain function networks consistent with symptoms of GWI, thereby providing a key to understanding the mechanisms underlying this illness.

Abstract 71.06 Summary

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Molecule Shows Promise in Reversing Effects of Sarin on Rat Neurons

Modest exposure to sarin and stress hormone negatively affect neuronal structure and function in rats

Molecules that stabilize neuronal structure hold promise for remediating damage due to exposure to sarin gas, a likely contributor to Gulf War Illness, according to recently published animal research presented today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Gulf War Illness (GWI) is a multisymptom disease that affects nearly 32 percent of veterans of the 1990–1991 Gulf War. Symptoms include increased muscular fatigue and gastrointestinal disorders as well as a host of neurological impairments in attention, memory, mood, and more. Sarin gas was used during the Gulf War as a nerve agent and is thought to be a contributor to GWI in veterans. Sarin is highly toxic in large doses, but the effects of prolonged low-level exposure are less well understood.

To test the effects of exposure to low levels of sarin, researchers treated rat neurons with an analogue of sarin called diisopropylfluorophosphate (DFP). Researchers also pre-treated the neurons with the stress hormone corticosterone to mimic the physical stress and toxic environment encountered by soldiers. The combination had several damaging effects on rat neurons, including destabilization of microtubules, an important structural component and transport system in neurons. It also reduced release of the signaling molecule dopamine, which is implicated in many neurodegenerative diseases.

Treating the affected rat neurons with a molecule called tubacin reversed the effects of sarin exposure. Tubacin works to correct the alterations in microtubule structure, suggesting that this approach might lead to an effective therapy for GWI.

The researchers are now starting to work with neurons derived from induced pluripotent stem cells from Gulf War veterans. This approach "will more closely mimic the disease state and provide a more detailed understanding of the effects of stress in Gulf War Illness, and thereby help us to test medicines that may improve the health of veterans," said lead author Ankita Patil, of the Drexel University College of Medicine.

Research was supported with funds from the Department of Defense Congressionally Directed Research Programs, the National Institute on Drug Abuse, and the National Institute of Neurological Disorders and Stroke.

Scientific Presentation: Saturday, Nov. 11, 2–3 p.m., WCC Halls A–C

17452. Sub-threshold exposure to sarin negatively affects neuronal microtubules in a manner exacerbated by stress: Implications for Gulf War Illness
***A. PATIL**[1], A. N. RAO[1], Z. D. BRODNIK[1], L. QIANG[1], R. A. ESPAÑA[1], K. A. SULLIVAN[2], M. M. BLACK[3], P. W. BAAS[1];
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TECHNICAL ABSTRACT: Recent work has identified the use of organophosphates (OP) such as Sarin and N,N-Diethyl-meta-toluamide (DEET) in the 1990-91 Persian Gulf War as being causally related to the development of Gulf War Illness (GWI), a multi-symptom illness experienced by deployed veterans. Prior culture work has shown deficits in axonal transport after OP exposure, however, these studies did not account for the elevated levels of stress hormones experienced by Gulf War veterans. In our studies, we treated rat cortical and fetal ventral mesencephalic neurons with diisopropylfluorophosphate (DFP), a Sarin gas analog, in conjunction with corticosterone (CORT) pretreatment. CORT pretreatment was administered to mimic the elevated level of stress hormones that would present in soldiers in war zones. Using this paradigm, we assessed changes in microtubule stability, mitochondrial dynamics, and neurotransmitter release. Western blot analysis showed that microtubule stability was affected, as evidenced by a decrease in the acetylated (stable) tubulin fraction after treatment. Additionally, microtubule polymerization, observed by ectopic expression of the plus-end binding protein EB3 conjugated to GFP, was diminished after DFP exposure. Using the mitochondrial-dye Mitotracker, we imaged the microtubule-based transport of mitochondria in living neurons. After DFP exposure, mitochondrial transport was significantly reduced. After DFP treatment, deficits were also observed in the levels of dopamine released from neurons isolated from the ventral mesencephalon (dopaminergic precursors). Interestingly, the effects of DFP were exacerbated in all parameters after CORT pretreatment. We sought to rescue cells from the effects of OP exposure by treating them with tubacin, an HDAC6 inhibitor, and saw notable improvement in MT stability, mitochondrial transport, and neurotransmitter release.