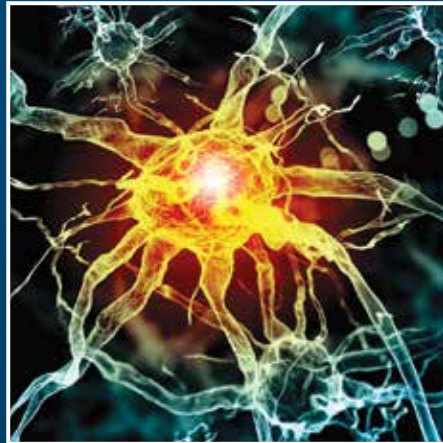
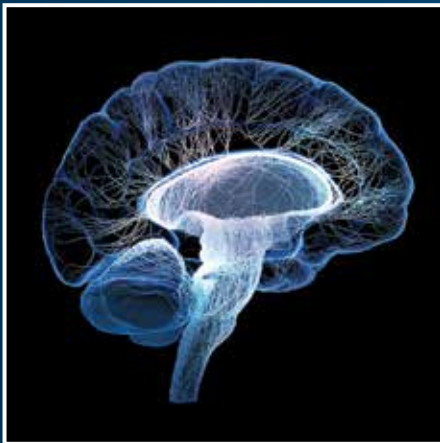


UNIFORMED SERVICES UNIVERSITY  
CENTER FOR THE STUDY OF TRAUMATIC STRESS

# 10th Annual Amygdala, Stress and PTSD Conference: Of Mice and Man

**APRIL 21, 2015**

**Sanford Auditorium & Lobby, Building B  
Uniformed Services University  
Bethesda, MD**



[www.AmygdalaPTSDconference.org](http://www.AmygdalaPTSDconference.org)

**SPONSORED BY:**

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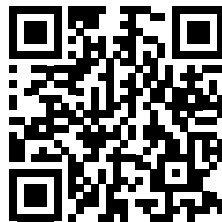
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Department of Psychiatry (WRNMMC)**



## Background

The Amygdala Conference series is sponsored by the Center for the Study of Traumatic Stress under the direction of Robert J. Ursano, MD, the USU Graduate Neuroscience Program under the direction of Sharon L. Juliano, PhD, and also by the Department of Family Medicine under the direction of Mark Stephens, MD.

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# Small Table Discussion Groups

Small Dining Room 0800–0900

## USU Cafeteria

Please join our small group discussions from 0800–0850 in the Small Dining Room of the USU cafeteria, Building B. Each of the conference speakers will be available for more personalized and direct interaction with conference attendees. *Separate registration for the discussion sessions is not necessary.* Everyone registered for the conference is welcome and encouraged to attend.

## Speakers

**Table 1: Dwight Bergles, PhD**

*Dynamic Behavior of Oligodendrocytes and their Progenitors in the Adult Brain*

**Table 2: Harvey Pollard, MD, PhD**

*Big Data Meets the Brain*

**Table 3: Abigail Marsh, PhD**

*Empathy on a Sliding Scale: Is Altruism the Inverse of Psychopathy?*

**Table 4: Jacek Debiec, MD, PhD**

*The Neurobiology of the Intergenerational Social Transmission of Emotional Trauma*

**Table 5: Daniel Stein, MD, PhD**

*Trauma and PTSD in South Africa*

## AGENDA

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0800-0900	Registration, Small Group Discussions and Poster Review
0900-0905	Conference Announcements <b>Gary H. Wynn, MD</b>
0905-0915	Welcome and Introduction <b>Robert J. Ursano, MD</b>
0915-1000	<b>Dwight E. Bergles, PhD</b> — <i>Dynamic Behavior of Oligodendrocytes and their Progenitors in the Adult Brain</i>
1000-1045	<b>Harvey B. Pollard, MD, PhD</b> — <i>Big Data Meets the Brain</i>
1045-1115	Coffee Break and Poster Review in Lobby
1115-1145	Discussion Panel 1 — Moderator, <b>Christopher G. Ivany, MD</b>
1145-1245	Lunch
1245-1330	<b>Abigail Marsh, PhD</b> — <i>Empathy on a Sliding Scale Is Altruism the Inverse of Psychopathy?</i>
1330-1415	<b>Jacek Debiec, MD, PhD</b> — <i>The Neurobiology of the Intergenerational Social Transmission of Emotional Trauma</i>
1415-1445	Coffee Break and Poster Review in Lobby
1445-1530	<b>Daniel Stein, MD, PhD</b> — <i>Trauma and PTSD In South Africa</i>
1530-1600	Discussion Panel 2 — Moderator, <b>Geoffrey G. Grammer, MD</b>
1600-1615	<b>Robert J. Ursano, MD</b> — <i>Closing Remarks and Presentation of Travel Awards</i>

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## Conference Speakers

### Dwight E. Bergles, PhD



Dr. Bergles is Professor in the Solomon H. Snyder Department of Neuroscience at Johns Hopkins University in Baltimore, Maryland, where he also holds a joint appointment in the Department of Otolaryngology-Head and Neck Surgery. He serves as Director for the Multiphoton Imaging Core facility at JHU, Co-Director of the Neuroscience Graduate Program and has been a faculty member in the Neurobiology Course at the MBL.

Dr. Bergles received his bachelor's degree in Biology from Boston University and PhD in Molecular and Cellular Physiology from Stanford University. He completed a postdoctoral fellowship at the Vollum Institute in Portland, Oregon before joining the faculty at Johns Hopkins University in 2000 as Assistant Professor. He was promoted to Professor in 2011. The goals of Dr. Bergles's laboratory are to understand how neurons and glial cells interact at synapses, and how glial cells contribute to CSN repair and disease progression. His studies have included analysis of glutamate transporter function in astrocytes, ATP release from glial cells in the developing cochlea, and the development and dysfunction of oligodendroglia.

As a postdoctoral fellow, Dr. Bergles discovered that a distinct class of glial progenitor cells in the CNS known as "oligodendrocyte precursor cells" or "NG2+ cells" form direct synapses with neurons. This remains the only known example of glial cell innervation. As a faculty member at JHU, he has continued to study the behavior of NG2+ cells, using a variety of electrophysiological, imaging and genetic approaches. To gain insight into the biology of these enigmatic glial cells, his group developed new lines of transgenic mice that enable visualization and manipulation of NG2+ cells and their oligodendrocyte progeny in vivo, as well as mice in which NG2+ cells can be selectively deleted from the adult brain. These tools are providing new insight into the behavior and function of these ubiquitous progenitors in both health and disease.

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### Jacek Debiec, MD, PhD



Dr. Debiec is an Assistant Professor in the Department of Psychiatry and an Assistant Research Professor in the Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor. He received his MD from Jagiellonian University in Krakow, Poland where he also completed a psychiatric

residency and doctoral studies in transcultural psychiatry during which he investigated the phenomenon of possession trance. He also holds a DPhil. in philosophy of science from John Paul II Pontifical University. As a Fulbright Fellow he trained in neuroscience with Joseph E. LeDoux at New York University where he completed his second residency in psychiatry and a fellowship in child and adolescent psychiatry. He studies the neurobiological mechanisms of emotional learning. He was the first to demonstrate that noradrenergic blockade by propranolol disrupts the reconsolidation of fear memories in the amygdala.

In his current projects he studies molecular and neural mechanisms of fear learning in infancy. His lab investigates how trauma affects attachment and how healthy attachment and bonding protect from the effects of trauma. His group works on identifying neural circuits and molecular mechanisms underlying infant's vulnerability and resilience to psychological trauma with the ultimate goal of developing interventions reversing negative effects of these early childhood adversities. His recent work on intergenerational transmission of trauma (Debiec & Sullivan, PNAS 2014) was featured by numerous national and international media including: *Newsweek*, *Los Angeles Times*, *Chicago Tribune*, *The Verge*, *Daily Telegraph*, *Daily Mail*, *CTV News*, *Shanghai News*, *The Times of India*, *YTN*, *Al-Jazeera*, *Fars News*, *Die Welt*, *Deutschlandfunk*, *La Stampa* and others. He recently published "The Emotional Brain Revisited" (Copernicus Center Press, 2014).



## Abigail Marsh, PhD



Dr. Marsh is an Associate Professor of Psychology at Georgetown University where she teaches and conducts research on social and affective neuroscience. She received her PhD in Social Psychology from Harvard University in 2004, and conducted post-doctoral research in the Unit on Affective Cognitive Neuroscience at the

National Institute of Mental Health (NIMH) from 2004-2008. At Georgetown, her research program focuses on characterizing the neural substrates of empathy and behaviors like altruism and aggression that empathy can promote or inhibit. This research is primarily aimed at addressing questions like: How do people understand what others think and feel? What drives us to help other people? What prevents us from harming them? She addresses these questions using multiple methods that include functional and structural brain imaging in adolescents and adults from both healthy and clinical populations, as well as behavioral, cognitive, genetic, and pharmacological techniques.

Her work with James Blair at the NIMH includes the first ever neuroimaging studies to identify the pathophysiology of psychopathy in adolescents. This research implicated disruptions in the functioning of the amygdala and associated structures in the striatum and prefrontal cortex in the development of psychopathy. Her subsequent research has directly linked the amygdala pathophysiology identified in youths with psychopathic traits to their aggressive behavior. Recent research aims to explore empathy by assessing neural and cognitive function in extraordinary altruists.

She recently completed the first ever series of structural and functional neuroimaging studies comparing altruistic living kidney donors to controls. This research found that highly altruistic individuals exhibit patterns of amygdala structure and functioning that are opposite to those of psychopaths, suggesting that empathic responsiveness may exist on a spectrum, and that common mechanisms can be used to understand both very prosocial and very antisocial behavior.

## Harvey B. Pollard, MD, PhD



Dr. Pollard is Director of the USU Center for Medical Proteomics, sponsored originally by the National Heart, Lung and Blood Institute (NHLBI). He is also Director of the Collaborative Health Initiative Research Program (CHIRP), a whole genome sequencing (WGS) program of investigation, jointly

sponsored by NHLBI and the Department of Defense. The goal is to develop “precision medicine” as an aid to diagnosis and treatment of disorders of common interest in both civilian and military disease cohorts.

Dr. Pollard received his undergraduate degree from Rice University, and his MD and PhD from the University of Chicago. Following postdoctoral training with Dr. Christian B. Anfinsen at the NIH, and with Professors David Phillips and Louise Johnson at Oxford University, Dr. Pollard returned to the NIH in the United States Public Health Service (USPHS), eventually becoming intramural Chief of the Laboratory of Pathology, and the Laboratory of Cell Biology and Genetics, NIDDK. Dr. Pollard subsequently became Chair of the Department of Anatomy, Physiology and Genetics, at the Uniformed Services University School of Medicine, Bethesda, MD. His principal hypothesis-driven research focus has been on the genetics of calcium signaling in the brain, traumatic brain injury, Posttraumatic Stress Disorder, and the role of downstream pro-inflammatory signaling as a mediator of tissue injury, both centrally and peripherally. Dr. Pollard has received the NIH Inventor’s Award and has authored over 300 peer reviewed papers and numerous invited chapters.

## Daniel Stein, MD, PhD



Dr. Stein is Professor and Chair of the Department of Psychiatry and Mental Health at the University of Cape Town, Director of the Medical Research Council (MRC) Unit on Anxiety & Stress Disorders, and Visiting Professor of Psychiatry at Mt. Sinai Medical School in New York. He is interested in the psychobiology and management

of the anxiety, obsessive-compulsive and related, and traumatic and stress disorders. He has also mentored work in other areas that are of particular relevance to South Africa and Africa, including neuroHIV/AIDS and substance use disorders.

Dr. Stein did his undergraduate and medical degrees at the University of Cape Town, and his doctorate (in the area of clinical neuroscience) at the University of Stellenbosch. He trained in psychiatry, and completed a post-doctoral fellowship (in the area of psychopharmacology) at Columbia University in New York. His training also includes a doctorate in philosophy. He is inspired by the way in which psychiatry integrates

science and humanism, and contributes to addressing some of the big questions posed by life.

Dr. Stein's work ranges from basic neuroscience, through clinical investigations and trials, and on to epidemiological and cross-cultural studies. He is enthusiastic about the possibility of clinical practice and scientific research that integrates theoretical concepts and empirical data across these different levels. Having worked for many years in South Africa, he is also enthusiastic about establishing integrative approaches to services, training, and research in the context of a low and-middle-income country.

Dr. Stein has authored or edited over 30 volumes, including "Cognitive-Affective Neuroscience of Mood and Anxiety Disorders", and "The Philosophy of Psychopharmacology: Smart Pills, Happy Pills, Pep Pills." His work has been continuously funded by extramural grants for more than 20 years. He is a recipient of the Max Hamilton Memorial Award from the Collegium Internationale Neuropsychopharmacologicum (CINP) for his contribution to psychopharmacology, and of CINP's Ethics and Psychopharmacology Award for his contribution to the philosophy of psychopharmacology.

## Moderators

### Lieutenant Colonel Christopher G. Ivany, MD



Dr. Christopher Ivany is Chief of the Behavioral Health Division at the Office of the Army Surgeon General and Army Director of Psychological Health. Dr. Ivany was born in Madison, WI. He attended Providence College where he majored in Biology and earned his Army

commission through ROTC in 1997. Dr. Ivany attended medical school at the University of Texas, Health Science Center in San Antonio, TX and graduated in 2001. He completed his internship and residency in Psychiatry at Walter Reed Army Medical Center, where he served as Chief Resident from 2004–2005. In 2007, he completed a fellowship in Child and Adolescent Psychiatry at Tripler Army Medical Center in Honolulu, HI. Dr. Ivany was assigned to Ft. Hood, TX where he served as the 4th Infantry Division Psychiatrist. He deployed with 4ID to Baghdad for OIF 07-09. In 2009, Dr. Ivany and his family moved to Ft. Carson, CO. From 2010 to 2012, Dr. Ivany served as the Chief of the Department of Behavioral Health at Evans Army Community Hospital. Dr. Ivany has several publications in national peer-reviewed journals. He also has several professional recognitions and military awards, including the Bronze Star.

### Colonel Geoffrey G. Grammer, MD



COL Grammer is Chief of Research, National Intrepid Center of Excellence (NICoE), Walter Reed National Military Medical Center. COL Grammer currently holds board certification in Psychiatry, Geriatric Psychiatry, and Behavioral Neurology and Neuropsychiatry. He is also

an Assistant Professor of Psychiatry at the Uniformed Services University (USU), Bethesda, MD. Prior to his present position, COL Grammer served as Chief of Inpatient Psychiatry Services for eight years at Walter Reed National Military Medical Center which covers the 28 bed General Psychiatry and 6 bed Neuropsychiatry wards.

COL Grammer completed his Bachelor of Science in Biology at the Virginia Polytechnic Institute before beginning his training at USU where he graduated in 1996. Subsequently, he completed a residency in Internal Medicine and General Psychiatry at Walter Reed Army Medical Center, followed by a fellowship in Geriatric Psychiatry.

COL Grammer has completed two deployments to Iraq. During his first deployment he served as the Medical Director for the 785th Combat Stress Control Company and he was a psychiatrist at the Combat Support Hospital at COB Speicher during his second deployment.

COL Grammer's military awards include the Bronze Star Medal, Meritorious Service Medal, Army Commendation Medal (3rd Award), Army Achievement Medal (3rd Award), Iraq Campaign Medal (3stars), Afghanistan Campaign Medal, Global War on Terrorism Service Medal, NATO ISAF Medal, National Defense Service Medal (2nd Award), Army Service Ribbon, Army Superior Unit Award and Overseas Service Ribbon (3rd Award).

## Conference Leadership

### Lieutenant Colonel Gary H. Wynn, MD



Dr. Wynn is Assistant Chair and Associate Professor, Department of Psychiatry, Uniformed Services University and Scientist, Center for the Study of Traumatic Stress. After graduating from West Point in 1996, Dr. Wynn received his medical degree from the Uniformed Services University (USU) in Bethesda,

MD. Dr. Wynn completed a residency in Psychiatry and Internal Medicine at Walter Reed Army Medical Center. After completing his residency, he spent a year as the Division Psychiatrist for the 2nd Infantry Division at Camp Casey, Korea. Dr. Wynn spent the next three years as the Assistant Chief of Inpatient Psychiatry at Walter Reed Army Medical Center where he worked with service members returning from the conflicts in Iraq and Afghanistan. From 2009 through 2013, Dr. Wynn worked as a research psychiatrist in the Military Psychiatry Branch of the Center for Military Psychiatry and Neuroscience at the Walter Reed Army Institute of Research in Silver Spring, MD. In July, 2013, Dr. Wynn joined the USU Department of Psychiatry. He has published textbooks on the topics of drug interaction principles for medical practice and the clinical management of post traumatic stress disorder (PTSD) as well as fourteen book chapters and seventeen journal articles. His presentations at national and local conferences have covered topics ranging from drug interactions to PTSD and mild traumatic brain injury.

### Robert J. Ursano, MD



Dr. Ursano is Professor of Psychiatry and Neuroscience and Chairman of the Department of Psychiatry at the Uniformed Services University, Bethesda, Maryland. He is founding Director of the Center for the Study of Traumatic Stress. In addition, Dr. Ursano is Editor of *Psychiatry*, the distinguished

journal of interpersonal and biological processes, founded by Harry Stack Sullivan. Dr. Ursano completed twenty years service in USAF medical corps and retired as Colonel in 1991. He was educated at the University of Notre Dame and Yale University School of Medicine and did his psychiatric training at Wilford Hall USAF Medical Center and Yale University.

Dr. Ursano served as the Department of Defense representative to the National Advisory Mental Health Council of the National Institute of Mental Health and is a past member of the Veterans Affairs Mental Health Study Section and the National Institute of Mental Health Rapid Trauma and Disaster Grant Review Section. He is a Distinguished Life Fellow in the American Psychiatric Association and a Fellow of the American College of Psychiatrists. Dr. Ursano was the first Chairman of the American Psychiatric Association's Committee on Psychiatric Dimensions of Disaster. This work greatly aided the integration of psychiatry and public health in times of disaster and terrorism. Dr. Ursano was an invited participant to the White House Mental Health Conference in 1999. He has received the Department of Defense Humanitarian Service Award and the highest award of the International Traumatic Stress Society, The Lifetime Achievement Award, for "outstanding and fundamental contributions to understanding traumatic stress." He is the recipient of the William C. Porter Award from the Association of Military Surgeons of the United States, the William Menninger Award

*Continued*

*Robert J. Ursano, MD, Continued*

of the American College of Physicians and the James Leonard Award of the Uniformed Services University. He is a frequent advisor on issues surrounding psychological response to trauma to the highest levels of the US Government and specifically to the Department of Defense leadership.

Dr. Ursano has served as a frequent member of the National Academies of Science, Institute of Medicine Committees and working groups including the Committee on Psychological Responses to Terrorism, Committee on PTSD, the Committee on Compensation for PTSD in Veterans and the Committee on Nuclear Preparedness; and the National Institute of Mental Health Task Force on Mental Health Surveillance After Terrorist Attack. In addition, he has served as a member of scientific advisory boards to the Secretary of Health and Human Services for disaster mental health and

the Centers for Disease Control for preparedness and terrorism. Dr. Ursano is co-principal investigator of the largest NIMH grant ever given for the study of suicide in the U.S. Army. In collaboration with his co-principal investigators at Harvard University, the University of Michigan and University of California, San Diego, the Army STARRS grant will be the Framingham Study of suicidal behavior, and address a national as well as DoD mental health need. In 2014, Dr. Ursano and Dr. Matthew Friedman of the VA National Center for PTSD co-founded the Friedman-Leahy Brain Bank supported through Senator Patrick Leahy (D-VT). It is the first human brain bank dedicated to PTSD. This joint effort of many people was a 12 year project developing concepts, pilot data and support. Dr. Ursano has over 300 publications. He is co-author or editor of eight books.

## Conference Committee

**Robert J. Ursano, MD**

Professor and Chair  
Department of Psychiatry  
Director  
Center for the Study of Traumatic Stress  
Uniformed Services University

**Gary H. Wynn, MD, 2015 Chairman**

LTC, MC, USA  
Assistant Chair, Associate Professor  
Department of Psychiatry  
Scientist  
Center for the Study of Traumatic Stress  
Uniformed Services University

**David Mears, PhD**

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**Ronald J. Whalen, PhD**

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**Syrus Henderson, MSgt, USAF**

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Program Support Specialist  
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*We extend special thanks to:*

**Gina Carlton, CMP, CGMP**

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Henry M. Jackson Foundation for the  
Advancement of Military Medicine



# Conference Posters

## Presented in Lobby

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## TRAVEL AWARD WINNER

# Modeling HIV-1-Induced Platelet-Mediated Dysfunction of the Blood-Brain Barrier

### Authors

Letitia Jones, MS<sup>1</sup>, Vir Singh, PhD<sup>1</sup>, Donna Davidson, PhD<sup>2</sup>, Sanjay Maggirwar, PhD<sup>1</sup>

### Affiliations

1. Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY
2. National Institute for Occupational Safety and Health, Pathology and Physiology Research Branch, Morgantown, WV

### ABSTRACT

**Background:** Normally, the blood-brain barrier (BBB) serves to regulate transport into and out of the CNS, thus serving as a protective barrier; however, in HIV-1-infected individuals, the integrity of the BBB is compromised due to an increase in the expression of proinflammatory mediators as well as viral proteins. sCD40L is released upon platelet activation and is an important mediator of the pathogenesis of HAND. However, the molecular mechanisms underlying this phenomenon are not fully understood. In order to recapitulate the factors observed in HIV-1 positive individuals, an animal model is needed.

**Method:** Wild-type C57BL/6 mice are administered either saline or the ecotropic virus, EcoHIV, via intraperitoneal injection. Mice are sacrificed at 1, 2, 4 and 8 weeks post-infection. All harvested tissues and plasma is stored at -80°C. Plasma is analyzed for platelet activation and brain tissues are analyzed for a change in blood-brain barrier (BBB) permeability. All data is analyzed for statistical significance by t-test, one-way or two-way ANOVA using GraphPad Prism software.

**Results:** In this study, upon infection with Eco-HIV, platelets are activated as demonstrated by the increase in platelet factor 4 (PF4), sCD40L and the decreased bleeding time in infected mice. In addition, the BBB's permeability is increased as early as two-weeks post-infections, as indicated in the decreased expression of tight junction proteins and the increase of cellular factors that would be impermeable in an uncompromised BBB.

**Conclusion:** These results are evidence that platelet activation and sCD40L are still mediators of BBB disruption in a model of chronic inflammation. Therefore, this animal model will serve as a stepping-stone toward expanding research into the molecular mechanisms underlying HAND, and underscores the utility of this model to study further therapeutic treatments.



## Psychophysiological Investigation of Combat Veterans with Subthreshold PTSD Symptoms

### Authors

Michelle E. Costanzo, PhD<sup>1,2</sup>, Tanja Jovanovic, PhD<sup>3</sup>, Seth D. Norrholm, PhD<sup>4</sup>, Rochelle Ndiongue, RN<sup>5</sup>, Brian Reinhardt, MS, MLS<sup>6</sup>, Michael Roy, MD<sup>1,2</sup>

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1. Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA
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6. Department of Research Programs, Walter Reed National Military Medical Center, Bethesda, MD, USA

### ABSTRACT

**Objective:** Military service members (SMs) with subthreshold combat-related PTSD symptoms often have clinically significant functional impairment, even though they do not meet full PTSD criteria.

We therefore assessed the psychophysical responses of SMs, upon their return from Afghanistan or Iraq, to a fear conditioning paradigm in order to better understand the biological underpinnings of symptom severity.

**Methods:** Heart rate, skin conductance, electromyography startle, and respiratory rate were monitored throughout three distinct phases of the paradigm—fear acquisition, fear inhibition, and fear extinction—while plasma catecholamines (epinephrine, norepinephrine and dopamine) were measured at the end of fear acquisition.

**Results:** Those with higher PTSD symptom severity demonstrated elevations in startle response to danger cues, heart rate response to both danger and safety cues, impaired inhibition of fear, self-reported anxiety, and a trending respiratory rate response during fear extinction. Moreover, an inverse relationship was seen between plasma dopamine and heart rate during fear inhibition for those with high symptoms.

**Conclusion:** Overall, the physiological responses we observed in our subthreshold PTSD population parallel what has been previously observed in full PTSD, making a case for addressing subthreshold PTSD symptoms in combat veterans.

## Improved Sleep in Military Personnel is Associated with Changes in the Expression of Inflammatory Genes and Improvement in PTSD and Depression Symptoms

### Authors

Whitney S. Livingston, BA<sup>1</sup>, Heather L. Rusch, MS<sup>1</sup>, Paula V. Nersesian, MPH<sup>1,2</sup>, Tristin Baxter AAS<sup>3</sup>, Vincent Mysliwiec, MD<sup>3</sup>, Jessica M. Gill, PhD<sup>1</sup>

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2. Johns Hopkins University School of Nursing
3. Madigan Army Medical Center

### Abstract

**Background/Objectives:** Sleep disturbances are common in military personnel following deployment and are associated with an increased risk for psychiatric morbidity, including posttraumatic stress disorder and depression, as well as inflammation. Improved sleep quality is linked to reductions in inflammatory proteins; however, the underlying mechanisms remain elusive.

**Methods:** In this study we examine whole genome expression changes related to improved sleep in 68 military personnel diagnosed with insomnia. Subjects were classified into the following groups and then compared: improved sleep (n=46), or non-improved sleep (n=22) following three months of standard of care treatment for insomnia. Within subject differential expression was determined from microarray data using the Partek Genomics Suite analysis program and the interactive pathway

analysis was used to determine key regulators of observed expression changes. Changes in symptoms of depression and posttraumatic stress disorder were also compared in both groups.

**Results:** At baseline both groups were similar in demographics, clinical characteristics, and gene-expression profiles. The microarray data revealed that 217 coding genes were differentially expressed at the follow-up period compared to baseline in the participants with improved sleep. Expression of inflammatory cytokine genes were reduced, including: IL-1 $\beta$ , IL-6, IL-8 and IL-13, with fold changes ranging from -3.19 to -2.1. There were increases in the expression of inflammatory regulatory genes including toll-like receptors 1, 4, 7, and 8 in the improved sleep group compared to the non-improved group. Interactive pathway analysis revealed 6 gene networks, including ubiquitin, which related to observed gene-expression changes. The improved sleep group also had a significant reduction in the severity of depressive as well as diminished PTSD symptoms.

**Conclusions:** Interventions that restore sleep likely reduce the expression of inflammatory genes, which relate to ubiquitin genes and reductions in depressive and PTSD symptoms following deployment. This study suggests that sleep restoration may be a previously observed in full PTSD, making a case for addressing subthreshold PTSD symptoms in combat veterans.

## Individual Differences in Opioid Analgesia, Opioid Self-Administration and Gene Expression in White Blood Cells of Rats

### Authors

Kevin Nishida<sup>1,2</sup>, Michael Nieves<sup>3</sup>, Youngmi Ji<sup>4</sup>, Lei Zhang<sup>1,2,3</sup>, He Li<sup>1,2,3</sup>, Robert J. Ursano<sup>1,2,3</sup> and Kwang Choi<sup>1,2,3</sup>

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3. Program in Neuroscience, USUHS, Bethesda, MD 20814
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### Abstract

**Background:** As many as one hundred million people may suffer from chronic pain and over 2 million Americans may be addicted to opioid pain medications. Although opioids are widely prescribed, their analgesic efficacy fades gradually with repeated use. Therefore, progressively higher doses of opioids are required to achieve comparable analgesic effects, and this may increase the likelihood of opioid addiction.

**Method:** We investigated individual differences in morphine-induced antinociception and gene expression in white blood cells (WBCs) of rats. Male Sprague Dawley rats self-administered intravenous morphine (0.5 mg/kg/infusion, 4 hrs/day) or saline for 3 weeks. Antinociception was measured at

a baseline, day 1, 3, and 5 of self-administration.

Blood samples were collected at multiple time points including a baseline, during and after self-administration in order to measure mRNA levels of glucocorticoid and cannabinoid receptors in WBCs with real-time quantitative PCR.

**Results:** Animals showed a wide range of antinociception following 4 hours of intravenous morphine self-administration. The animals were grouped into good responders (GRs) and poor responders (PRs) based on a median split of anti-nociception. PRs exhibited addiction-like behavior such as increased drug intake, behavioral sensitization and weight change when compared with GRs. Gene expression assay of glucocorticoid and cannabinoid receptors in WBCs of these animals is in progress.

**Conclusion:** Individuals who do not respond well to opioid pain medications may also be predisposed to opioid addiction, when given repeated access to drugs. This finding is clinically important because poor responders to opioid medications require higher doses of opioids and/or other pain medications, which may facilitate the addiction process in those individuals. Early identification and intervention of vulnerable individuals may improve the treatment strategy for pain management and opioid abuse.

## Emotional Contrast Avoidance versus Emotional Avoidance in Mediating the Relationship Between Worry and PTSD Symptom Severity

### Authors

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### Abstract

**Background:** Individuals with PTSD experience difficulties regulating their emotions signified by increased emotion reactivity, fear of emotions, and reduced connectivity to prefrontal areas of the brain that could regulate or reduce the emotion (Sripada et al., 2012). One of the ways individuals with PTSD may be attempting to regulate their emotions is through worry. The majority of literature on emotion regulation difficulties linking worry and PTSD has specifically focused on emotional avoidance. However, this is in contrast to all the evidence that PTSD is associated with emotional hyperreactivity, sustained hyperarousal, and chronic negative emotion. This evidence points more toward the theory of emotional contrast avoidance, understood as maintaining a constant state of negative arousal through worry as an attempt to avoid emotional contrasts or strong shifts in one's emotional states (Newman & Llera, 2011).

**Method:** The present study analyzed the differential effects of emotional contrast avoidance and emotional avoidance in mediating worry on PTSD symptom severity. Undergraduate students from a diverse university completed multiple questionnaires, in a lab setting, assessing PTSD symptom severity, worry, emotional avoidance, and emotional contrast avoidance. Multiple mediation models and bootstrapping confidence intervals were analyzed to determine which variables resulted in the best fitting model for mediating this relationship.

**Results:** The results demonstrated that *emotional contrast avoidance* was the only significant mediator between worry and PTSD symptom severity.

**Conclusion:** Furthermore, because worry has been shown to increase negative affect and prevent further increases in response to negative stimuli (Llera & Newman; 2010, 2014), our data show that those with PTSD may be using worry to create a continuous negative emotional state and thereby avoid experiencing negative emotional contrasts.

## High Frequency Amygdalar Stimulation Upregulates the Neuro-Peptide Y System and Decreases Anxiety in Post-Traumatic Stress Disorder

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### Abstract

**Background:** PTSD continues to be a disabling condition affecting many Soldiers returning from Iraq and Afghanistan. Increased Amygdala activity is in PTSD, led our group to hypothesize that amygdalar stimulation may attenuate PTSD-related symptoms. Additionally, human and animal studies indicate an anxiolytic function for the neurotransmitter Neuropeptide Y (NPY) in PTSD patients and models of PTSD. We hypothesized that amygdalar stimulation would attenuate behavioral effects in the predator scent model of PTSD, and that effects would be mediated by NPY.

**Methods:** Lewis rats (n=4/group, aged 10-12 weeks) were exposed to feline urine soaked cat litter or fresh cat litter for 15 minutes. Control groups consisted of no urine exposure and urine exposure without stimulation. One-week later, rats underwent anxiety test-

ing with the elevated plus maze, confirming anxiety symptoms existed. Next, stimulating electrodes were implanted in the basolateral nucleus of the amygdala bilaterally. Rats underwent stimulation one week later (4 hours/day for 7 days; current 300mA, pulse width of 120 $\mu$ s, 160Hz). All animals were connected to the electrodes but current was only delivered to the stimulation groups. After stimulation, all animals were tested on the elevated plus maze. After sacrifice, rats were processed for immunohistochemistry of NPY, C-fos, and DAPI in the amygdala.

**Results:** Bilateral stimulation resulted in increased mean time in the open arm of the elevated plus maze (87 $\pm$ 16.8 vs 32 $\pm$ 9.7 sec, p<0.05, n=4), indicating decreased anxiety, while rats undergoing sham stimulation showed no change. Immunohistochemistry showed a twelve-fold increase in NPY peptide levels in the amygdalae of stimulated rats.

**Conclusions:** Bilateral amygdalae stimulation attenuated anxiety-like behavior in the predator scent model of PTSD, and treatment was correlated with increased amygdalar NPY. Amygdalar stimulation may alleviate PTSD symptoms, and these data provide the first evidence of a possible underlying molecular mechanism.

# Differential Diagnosis of Post-Traumatic Stress Disorder and Traumatic Brain Injury using Serum MicroRNA Signatures: A Comparative Study of Closed Head Injury and Traumatic Stress Rodent Models

## Authors

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## Abstract

**Background:** Post-traumatic stress disorder (PTSD) is often associated with mild traumatic brain injury (mTBI) and their overlapping symptoms makes distinction between these two disorders very difficult. MicroRNAs (miRNAs) are small, endogenous, noncoding RNA and the key regulators of gene expression. Recently, circulating miRNAs in blood have been reported to be sensitive and specific biomarkers of various diseases including brain injury. The main objective of this study was to identify serum miRNA signatures as differential biomarkers between PTSD and mTBI.

**Methods:** In this study, we used a mouse model of weight drop injury to recreate closed head traumatic brain injury (CH-TBI) and a learned helplessness rat model of PTSD. Serum was collected at 3 h post in-

jury for four different CH-TBI groups and at 3 h and day 14 post stress for PTSD. Serum global miRNA expression profiles were generated using TaqMan MicroRNA Array cards.

**Results:** MiRNA profiling in serum showed thirteen common miRNAs among four CH-TBI groups and nine common miRNAs between PTSD serum and amygdala respectively. However, the comparison of altered serum miRNAs of CH-TBI and PTSD showed no correlation. Pathway analysis of thirteen miRNAs and their validated targets showed few of them to have a direct correlation with axon guidance, depression and sensorimotor impairment associated pathways. In PTSD, five out of nine miRNAs - miR-142-5p, miR-19b, miR-1928, miR-223 and miR-421-3p showed that they may play a role in the regulation of genes associated with delayed and exaggerated fear.

**Conclusion:** The differences in the serum miRNA expression signatures of both the models could be an outcome of the different functional pathways activated post TBI or stress exposure in the brain which in turn gets reflected in the alteration of the global serum miRNA profile. These results indicate that miRNA signatures can be used for the differential diagnosis of PTSD and TBI.

## Acknowledgements

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## Overview of the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS)

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### Abstract

**Background/Objectives:** The Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) is a multi-component epidemiological and neurobiological study of suicide and mental health among soldiers. It was funded under a five-year cooperative agreement between the U.S. Army, National Institute of Mental Health, and an internationally recognized team of researchers from USUHS, the

University of California San Diego, Harvard Medical School, and the University of Michigan.

**Method:** The six Army STARRS components include: the Historical Administrative Data Study (HADS), an analysis of 38 integrated Army/DoD administrative data systems containing records for all active duty soldiers during 2004–2009; the New Soldier Study (NSS), a survey of soldiers just prior to the start of Basic Combat Training (BCT) that included self-administered questionnaires (SAQs), neurocognitive tests, and blood collection; the All Army Study (AAS), a representative cross-sectional survey (SAQs) of active duty soldiers, exclusive of those in BCT; the Pre-Post Deployment Study (PPDS), a multi-wave panel (SAQs, blood collection) of soldiers in three brigade combat teams surveyed before and after deployment to Afghanistan; and the Soldier Health Outcomes Studies, two retrospective case-control studies of soldiers who were hospitalized for attempting suicide (SHOS-A) or who died by suicide (SHOS-B).

**Results:** The HADS includes more than 1.1 billion administrative records for over 1.6 million soldiers. Approximately 110,000 soldiers attended Army STARRS survey sessions at 76 study sites around the world. The participation rate across the NSS, AAS, PPDS, SHOS-A, and SHOS-B, was generally 80–95%, with approximately 43,000 soldiers volunteering to give blood.

**Conclusion:** Army STARRS is the largest study of mental health risk and resilience ever conducted among U.S. Military personnel. It is designed to guide the development of data-driven methods to reduce suicidal behaviors and improve soldiers' overall health and functioning, while rapidly delivering actionable findings to U.S. Army leadership.

## Precision Medicine for PTSD and Elevated Risk for Cardiovascular Disease

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### Abstract

**Background/Objectives:** Post-traumatic Stress Disorder (PTSD) is a frequent consequence of exposure to intense emotional and/or physical trauma. In addition, the subsequently associated features of autonomic nervous system dysfunction, hypothalamic-pituitary-adrenal (HPA) axis dysregulation and tissue damage are linked to a *ca* 50% increased risk for cardiovascular disease (CVD). The **problem** is understanding how the biological links for PTSD enhance the risk for CVD, and if genetic and biological risk factors drive both conditions concurrently. Recent studies using conventional genetic analysis have identified genetic mutations that significantly elevate the risk of PTSD in individual subsets of PTSD patients, including identical twins. With the advent of rapid, cost effective Whole Genome Sequencing (WGS) technology, we are adopting a *precision medicine* approach to help unravel the link between stress and CVD. Our aim is to comprehen-

sively identify the contributing genetic risk factors for both conditions.

**Method:** We have performed a comprehensive meta-analysis of all published studies testing for the linkage between candidate genes and likelihood of risk for PTSD. We also tested whether any of the PTSD risk genes were also independent predictors of cardiovascular disease.

**Results:** Preliminary genetic studies have identified variants in 55 candidate genes which may be responsible for PTSD. Importantly, 23 (*viz. ca.* 42%) of these candidate PTSD genes are also reported to be independent risk factors for cardiovascular disease, atherosclerosis or hypertension. Preliminary bioinformatics analysis suggests that these PTSD/CVD risk genes are mostly correlated with inflammation through the NFκB signaling pathway.

**Conclusions:** However, to test the generality of this meta-analysis, WGS profiling through *precision medicine* studies are warranted. Analysis of single nucleotide variants and structural variation for a large population of individuals with well-defined clinical and phenotypic data are central approaches in precision medicine initiatives. Profiling repository samples with linked clinical data from the Army STARRS study may generate a robust genomic sequence dataset for identifying novel genetic risk factors and biological mechanisms in relation to PTSD etiology.



## Mediation of Deployment Preparedness on the Association between Augmentee Status and PTSD Symptoms in Reserve and National Guard Members

### Authors

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### Abstract

**Background:** The Reserve Component (RC) of the United States Armed Forces are at higher risk of post-deployment mental health concerns, particularly posttraumatic stress disorder (PTSD), relative to their Active Component (AC). We examined the mediating role of deployment preparedness on the association between individual augmentee status (deploying without one's regular unit) and posttraumatic stress disorder (PTSD) symptoms among RC enlisted Army and Marine male personnel.

**Methods:** A nationally representative sample of 2,003 RC personnel was selected in 2010, of which 705 were Army and Marine enlisted males with deployment experiences. Factor analysis was first used to examine the factor structure of deployment preparedness measure, adapted from the Deployment

Risk and Resilience Inventory (DRRI), and post-deployment PTSD symptoms, i.e., the PTSD Checklist-Civilian (PCL-C). Structural equation modeling (SEM) was then used to test whether deployment preparedness mediates the association between individual augmentee status and PTSD symptoms.

**Results:** The SEM provided desirable indices of goodness-of-fit, CFI = 0.992, TLI = 0.991, and RMSEA = 0.032. The associations between individual augmentee status and deployment preparedness ( $b = -0.173, p = 0.011$ ), and between deployment preparedness and PTSD symptoms ( $B = -0.552, p < .001$ ) were both statistically significant, which indicates mediation by deployment preparedness. The results of direct, indirect and total effects further indicated that individual augmentee status had a significant indirect effect on PTSD symptoms ( $b = 0.096, p = 0.013$ ). The direct influence was not significant ( $b = 0.056, p = 0.530$ ). And the total influence was approaching significant ( $b = 0.152, p = 0.087$ ).

**Conclusion:** Individual augmentee status is associated with different levels of deployment preparedness. Deployment preparedness is relevant to PTSD symptoms. Providing more training among those who deploy without their regular unit could serve as a potential target for future prevention or intervention efforts.

## Serial FDG-PET Imaging Reveals Functional Changes in the Amygdala of a Controlled Cortical Impact Small Animal Model of Traumatic Brain Injury

### Authors

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### Abstract

**Background:** Previously, cross-sectional analysis of data from our study revealed a significant decrease in FDG uptake, corresponding with significant decreases in ADC and increases in T2 values, at sub-acute time points following moderate CCI injury. For the work presented herein, our goal was to characterize the temporal glucose uptake pattern following sham, mild, moderate, and severe controlled cortical impact (CCI) TBI using longitudinal monitoring by microPET/CT.

**Method:** Male Sprague Dawley rats (n=40, 250-300g) were categorized as injured (n=24), sham with craniotomy (n=8) or naïve (n=8). Injured animals were subjected to a mild (n=8), moderate (n=8) or severe (n=8) controlled cortical impact (CCI) injury. PET-FDG imaging was performed prior to injury and at 3-6 hours, 1, 3, 7, 10 and 20 days post-injury. Whole brain normalization and two-way ANOVA with repeated measures was used to evaluate group differences for 14 brain regions.

**Results:** Significant group differences were observed in the amygdala at several time points post injury. Decreased FDG uptake was again observed in the amygdala at day 3. At this time point, FDG-PET could detect differences between moderate and severe injuries when compared to controls. Differences between mild and control groups were observed at day 3, but did not reach statistical significance.

**Conclusion:** FDG-PET imaging provides a sensitive, non-invasive method for detecting functional changes in the amygdala after TBI. Future work includes the analysis of left and right hemisphere data and correlation with behavioral and pathological data.

## Analysis of Functional and Structural Changes after Explosive Blast Injury: A Rat Pilot Study

### Authors

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### Abstract

**Background:** Electroencephalogram (EEG) and visual evoked potential (VEP) registration are part of noninvasive neuro-monitoring methods. The origin of the cortical potentials are due to excitatory or inhibitory postsynaptic potentials developed by the cell body and large dendrites of pyramidal neurons. Alteration in dendritic spine densities have been identified in controlled cortical impact and fluid percussion injury models.

Explosive-blast traumatic brain injury has been associated with neuro-psychiatric, EEG and evoked potential alterations; Alterations in EEG phase synchronization as well as irregular slow wave activity have been identified.

Our previous studies have demonstrated damage to the rat visual pathway after explosive blast. In

this study we analyzed post-blast neuronal function and structure changes with electrophysiology and histology, respectively, in order to find correlative neurophysiologic alterations.

**Methods:** Sprague-Dawley rats were exposed to a single mild explosive-blast. The EEGs were analyzed with fast Fourier transformation, Hjorth methods and correlation. VEP was generated by signal averaging and analyzed by correlation and cross-correlation for signal symmetry and phase shift. Neuronal structural changes were characterized by cortical dendritic spine density. Results of pre-blast and post-blast, 1 day and 7 days, were compared. Statistical analysis of VEPs were performed using repeated measures ANOVA. Dendritic spine densities were compared using ANOVA.

**Results:** Preliminary results comparing left and right hemisphere VEPs for synchronicity while accounting for lag, show mean cross-correlation changes. Dendritic spine density decrease in cortical layer II/III. Pathology and EEG analysis are in progress.

**Conclusion:** Brain function generates electrical waveforms with various frequency and voltage. In this study we analyzed EEG background and VEP for functional changes and characterized dendritic spine density as well as gross pathology for structural changes post-blast exposure. Preliminary data indicate a decrease in cortical dendritic spines and increased VEP latencies at 1d post-blast exposure.

## Continuing Education Credit

### Physicians

This live activity, Amygdala, Stress and PTSD Conference on April 21, 2015 has been reviewed and is acceptable for up to 5.25 prescribed credits by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

### Psychologists

The Department of Psychology, Walter Reed National Military Medical Center, is approved by the American Psychological Association to sponsor continuing education for psychologists. The Department of Psychology, Walter Reed National Military Medical Center maintains responsibility for this program and its contents. **Five hours of CE credit** will be given for full attendance at the workshop. **Two hours of CE credit** will be given for the morning session and **3 hours of CE credit** will be given for the afternoon session. **No credit will be provided for partial session attendance.** On the day of the conference, participants must submit an evaluation sheet for each session to receive CE credit and document their attendance for each session via sign-in and out rosters.

### Social Workers

The Department of Social Work, Walter Reed National Military Medical Center, maintains responsibility for this program and has been granted automatic authorization from the Maryland Board of Social Work Examiners to offer **5 category I CEU credits** for this professional training activity. **Two hours of CEU credit** will be given for the morning session and **3 hours of CEU credit** will be given for the afternoon session. **No credit will be provided for partial session attendance.** On the day of the conference, participants must submit an evaluation sheet for each session to receive CE credit and document their attendance for each session via sign-in and out rosters.

### Nurses

We regret we are unable to offer CEUs for nurses in 2015.

**Psychologists and Social Workers attending the conference will be required to complete an evaluation form in order to receive continuing education credit.**

**Questions? Please visit the Continuing Education table located in the lobby.**









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