UNIFORMED SERVICES UNIVERSITY

CENTER FOR THE STUDY OF TRAUMATIC STRESS

9th Annual Amygdala, Stress and PTSD Conference: Bench to Bedside

APRIL 22, 2014

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

www.AmygdalaPTSDconference.org

SPONSORED BY:

The Center for the Study of Traumatic Stress (USU), Department of Psychiatry (USU), Neuroscience Program (USU), Department of Family Medicine (USU), and Department of Psychiatry (WRNMMC)

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Background and Conference Committee

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.

Conference Committee

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Director
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Department of Psychiatry
Scientist
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We extend special thanks to:
Gina Carlton, CMP, CGMP
Meetings Manager
Office of Education and Meetings
Henry M. Jackson Foundation for the Advancement of Military Medicine

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Small Table Discussion Groups

Small Dining Room 0800–0900

USU Cafeteria

Please join our small group discussions from 0800–0900 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: Israel Liberzon, MD
Contextual Processing in PTSD in Humans and in the Animal Model

Table 2: Alexander D. Crawford, PhD
High-throughput Behavioral Assays in Zebrafish: A New Tool in the Search for Effective PTSD Therapies?

Table 3: Joshua G. Corbin, PhD
Genetic and Cellular Development of the Amygdala

Table 4: Joel Gelernter, MD
PTSD and Genetics: GxE and GWAS PTSD Studies

Table 5: Joel E. Kleinman, MD, PhD
Genetic Neuropathology in Human Brain Development and Schizophrenia: A Road Map for PTSD

AGENDA

0800–0900:	Registration, Small Group Discussions and Poster Review
0900–0905:	Conference Announcements, **Gary H. Wynn, MD**
0905–0915:	Welcome and Introduction, **Robert J. Ursano, MD**
0915–1000:	**Israel Liberzon, MD** *Contextual Processing in PTSD in Humans and in the Animal Model*
1000–1045:	**Alexander D. Crawford, PhD** *High–throughput Behavioral Assays in Zebrafish: A New Tool in the Search for Effective PTSD Therapies?*
1045–1115:	Coffee Break and Poster Review in Lobby
1115–1145:	Discussion Panel 1 Moderator, **LTC Dennis McGurk, PhD**
1145–1245:	Lunch
1245–1330:	**Joshua G. Corbin, PhD** *Genetic and Cellular Development of the Amygdala*
1330–1415:	**Joel Gelernter, MD** *PTSD and Genetics: GxE and GWAS PTSD Studies*
1415–1445:	Coffee Break and Poster Review in Lobby
1445–1530:	**Joel E. Kleinman, MD, PhD** *Genetic Neuropathology in Human Brain Development and Schizophrenia: A Road Map for PTSD*
1530–1600:	Discussion Panel 2 Moderator, **LTC Christopher G. Ivany, MD**
1600–1615:	Closing Remarks and Presentation of Travel Award, **Robert J. Ursano, MD**

Conference Speakers

Joshua G. Corbin, PhD

Dr. Corbin is a Principal Investigator at the Center for Neuroscience Research at Children's National Medical Center with academic appointment as Associate Professor of Pediatrics, Pharmacology and Physiology at George Washington University's School of Medicine and Health Sciences. He holds a BA from Rutgers University and PhD in neuroscience from the University of North Carolina, Chapel Hill. He completed a postdoctoral program at Mt. Sinai School of Medicine in neuroscience and another postdoctoral program at New York University School of Medicine in developmental neuroscience. With more than 22 years of experience in the field of research, Dr. Corbin's lab is focused on the genetic and cellular basis governing normal and abnormal development of the mammalian amygdala using the mouse as a model. He also currently serves as a consultant for public and private organizations focused on understanding and treating a variety of neurodevelopmental disorders. He has served as a panel reviewer for the NIH, NSF, Autism Speaks and Department of Defense. Dr. Corbin also had the pleasure of presenting his work to Prince Philip, Duke of Edinburgh, during the Royal visit to the US in 2007.

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Websites
www.childrensnational.org/research/faculty/bios/cnr/corbin_j.aspx

www.gwumc.edu/smhs/facultydirectory/profile.cfm?empName=Joshua%20Corbin&FacID=2062669303&show=1

Alexander D. Crawford, PhD

Dr. Crawford is Principal Investigator of the Chemical Biology Group at the Luxembourg Centre for Systems Biomedicine (Esch-sur-Alzette, Luxembourg), and Senior Scientist at the Laboratory for Molecular Biodiscovery at the University of Leuven (Leuven, Belgium). He is also Project Manager of PharmaSea, a European Union-funded research consortium focusing on drug discovery from marine microorganisms, and is the founding CEO of Theracule, a spin-off company focusing on personalized drug discovery and orphan drug development for genetic CNS disorders. Dr. Crawford was previously the founding CEO of two drug discovery companies in Germany that raised more than $100 million in private equity, and held research positions at the Flanders Institute for Biotechnology (Leuven, Belgium) and the Whitehead Institute for Biomedical Research (Cambridge, Massachusetts). He earned a PhD in pharmaceutical sciences at the University of Leuven, an MPhil in neuroscience at the Max Planck Institute for Developmental Biology (Tübingen, Germany), and an SB in biology at the Massachusetts Institute of Technology.

Website: crawfordlab.org

Joel Gelernter, MD

Dr. Gelernter is Foundations Fund Professor of Psychiatry and Professor of Genetics and Neurobiology and Director, Division of Human Genetics (Psychiatry), at Yale University School of Medicine. He studied music and biology as an undergraduate at Yale University and completed his MD at SUNY-Downstate. Dr. Gelernter began his psychiatry residency at Western Psychiatric Institute and Clinic (Pittsburgh) and completed his residency and fellowship at the NIMH. He returned to Yale in 1988 to join the psychiatry faculty.

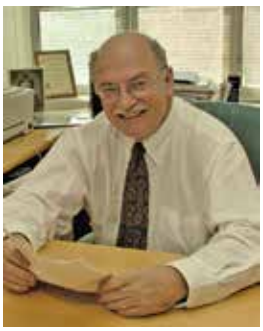
The research focus of his laboratory is genetics of psychiatric illness. This includes a range of behavioral phenotypes including posttraumatic stress disorder (PTSD), cocaine, opioid, nicotine, and alcohol dependence, panic and other anxiety disorders, schizophrenia, and affective disorders. In addition, the lab studies a range of intermediate phenotypes, such as neuroimaging measures; and basic issues in population and complex trait genetics.

The overall approach involves study of genetic polymorphism and sequence variation, on a molecular level, and from the perspective of population genetics. Current projects include NIDA, NIAAA, and VA-funded multicenter studies with the goal of identifying genes predisposing to cocaine, opioid, nicotine, and alcohol dependence, and PTSD (using genomewide association analysis, whole exome and whole genome sequencing, and other approaches); and an international drug dependence genetics training project in collaboration with Chulalongkorn Faculty of Medicine (Bangkok, Thailand).

In the past year, Dr Gelernter's laboratory has published the first genomewide association studies (GWAS) for cocaine and opioid dependence, the second (and largest to date) for PTSD, as well as the largest such study for alcohol dependence. All of these studies have resulted in the identification of novel risk loci.

Website: psychiatry.yale.edu/people/joel_gelernter.profile

Joel E. Kleinman, MD, PhD



Dr. Joel Kleinman is Associate Director, Clinical Sciences, Lieber Institute for Brain Development (LIBD), Johns Hopkins University, Baltimore, MD. Dr. Kleinman received three degrees from the University of Chicago (BS, 1966, MD, 1973 and PhD, 1974). He completed an internship at San Francisco General Hospital and residencies in psychiatry at Harvard University and neurology at George Washington University, respectively. He subsequently was a tenured Section Chief in the NIMH. Dr. Kleinman has spent the last 36 years in the NIH amassing what is widely regarded as one of the best collections of postmortem human brains for the study of the molecular biology of brain development and related disorders, especially schizophrenia. He has been both a pioneer and leader in this area of research with over 200 peer-reviewed papers on postmortem human brain. Recently, his research has focused on allelic variation, alternative transcripts and epigenetic modifications in both human brain development and schizophrenia. His laboratory has published a dozen papers that focus on prenatal brain development and its importance in risk for schizophrenia. Dr. Kleinman and his group at LIBD have also established one of the first, if not largest collections of postmortem brains of patients with post traumatic stress disorder.

Website: www.libd.org

Israel Liberzon, MD

Dr. Liberzon is Professor of Psychiatry, Psychology and Neuroscience at the University of Michigan. He is also an Associate Chair for Academic Development and Director of the Psychiatric Residency Research Track at the Department of Psychiatry, University of Michigan. After graduating from Sacklers Medical School, Tel Aviv University, Dr. Liberzon completed his post-doctoral training in physiology at Rappaport Institute, Israeli Institute of Technology in Haifa. He then completed the Psychiatry Residency Program at the University of Michigan. Since 1992, Dr. Liberzon has been on the faculty of the University of Michigan's Department of Psychiatry, Department of Psychology and Neuroscience programs.

In 1992, Dr. Liberzon established the PTSD program at the University of Michigan and Ann Arbor VAMC, a program that has since grown and remained on the forefront of biological research of PTSD worldwide. Dr. Liberzon co-founded the Trauma, Stress, and Anxiety Research Group (TSARG) at the University of Michigan, which includes the Psychiatric Affective Neuroimaging Laboratory, a basic science (wet bench) laboratory, a MiRRR genetic repository and a clinical research group. Dr. Liberzon's primary research interest centers on emotions, stress and stress related disorders like PTSD, and regulation and dysregulation of stress response systems. His work integrates cognitive, functional neuroimaging, neuroendocrinological and genetic approaches to study stress, emotions, cognitive-emotion interactions and the effects of emotions on decision making. In the last fifteen years, under Dr. Liberzon's leadership, the TSARG had be continuously funded with multiple NIMH RO1 grants, VA Career development and NIH K awards, VA merit awards, Army and DOD grants, and more. Currently there are over ten active federally funded grants of various kinds awarded to Trauma Stress and Anxiety Research Group members.

Dr. Liberzon has mentored twelve doctoral candidates, more than twenty post-doctoral research fellows, and fourteen junior faculty members. He has published over 150 articles, and has authored and edited numerous book chapters and reviews. Until recently Dr. Liberzon served as a Chief of Mental Health Service at the Ann Arbor VA Health System. He is a Fellow of American College of Neuropsychopharmacology. Dr. Liberzon is past President of Psychiatric Research Society. He is an editorial Board member for Biological Psychiatry, Neuropsychopharmacology and other journals, and is also a member of an NIMH study section.

Website: sitemaker.umich.edu/panlab/home

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.

Lieutenant Colonel Dennis McGurk, PhD

Dr. McGurk is Deputy Director of the Research Area Directorate (RAD3), Fort Detrick, Maryland. The RAD3 is responsible for managing research to develop effective medical countermeasures against combat and operational stressors to maximize warrior health and performance. Dr. McGurk was born in New Jersey. He earned a bachelors degree in Psychology from the University of Delaware. He began his military career in 1989 as an Infantryman in the Army Reserve. Dr. McGurk earned a Masters Degree in Clinical Psychology and completed ROTC at Loyola College in Maryland. He was commissioned in 1994. Dr. McGurk's early assignments include treatment platoon leader at Schofield Barracks, Hawaii and Company Commander at Walter Reed. He completed his PhD in Experimental Psychology from Texas Tech University in 2002. Dr. McGurk commanded the U.S. Army Medical Research Unit-Europe and was the Chief of the Research Transition Office (RTO), Walter Reed Army Institute of Research. While deployed he was the Senior Science Officer on Mental Health Advisory Team IIb (MHAT IIb) in Afghanistan, MHAT IV in Iraq, MHAT V in Afghanistan, and Team Lead on the 2012 J-MHAT 8 in Afghanistan.

Dr. McGurk has published in peer-reviewed journals and presented at scientific and military conferences. He has briefed many senior military leaders including the Under Secretary of Defense for Personnel and Readiness and the Secretaries of the Army and Navy. His military awards include the Meritorious Service Medal, the Army Commenda-

Continued

Dennis McGurk, PhD, Continued

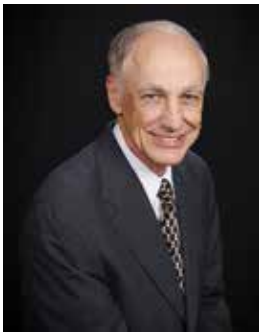
tion Medal, the Joint Achievement Medal, the Army Achievement Medal, the Humanitarian Service Medal, the Armed Forces Expeditionary Medal, the NATO Kosovo Medal, the Kosovo Campaign Medal, the Afghanistan Campaign Medal, the Iraq Campaign Medal, the Global War on Terrorism Medal, the Overseas Ribbon, the Air Assault Badge, and the Airborne Badge.

Conference Leadership

Lieutenant Colonel Gary H. Wynn, MD

Dr. Wynn is Assistant Chair of Research and Assistant 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 in 2000 from the Uniformed Services University (USU) in Bethesda, MD. Dr. Wynn completed a combined 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 numerous book chapters and journal articles. His presentations at numerous 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 of the Health Sciences, Bethesda, Maryland. He is founding Director of 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 of 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. He is 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

Continued

Robert J. Ursano, MD, Continued

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, and 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 member of the National Academies of Science, Institute of Medicine, Committee on Psychological Responses to Terrorism, Committee on PTSD and Compensation 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 is a member of scientific advisory boards to the Secretary of Health and Human Services and the Centers for Disease Control. In 2012, Dr. Ursano was awarded the William C. Menninger Memorial Award for distinguished contributions to the Science of Mental Health by the American College of Physicians. Dr. Ursano has more than 300 publications. He is co-author or editor of eight books.

Conference Posters

Presented in Lobby

Travel Award Winner

Posters

TRAVEL AWARD WINNER

Impaired Extinction Retention in Patients Who Developed PTSD Following a Single Traumatic Event

Authors

Heather L. Rusch, MS[1,2,3], Erel Shvil, PhD[1,4], Miriam Campeas, BS[1], Emily D. Joyner, BS[1], Jessica M. Gill, PhD[2], Mohammed R. Milad, PhD[5], Gregory M. Sullivan, PhD[1,4], Yuval Neria, PhD[1,4]

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2. National Institute of Nursing Research, National Institutes of Health, Bethesda, MD
3. Henry M Jackson Foundation for The Advancement of Military Medicine, Bethesda, MD
4. Department of Psychiatry, Columbia University Medical Center, New York, NY
5. Department of Psychiatry, Harvard Medical School & Massachusetts General Hospital, Boston, MA

Abstract

Background: While the risk for posttraumatic stress disorder (PTSD) increases with multiple traumatic exposures, a swubstantial proportion of trauma exposed individuals demonstrate a heightened vulnerability to trauma by developing PTSD after a single, time limited, traumatic incident. To advance research on putative biomarkers of this increased vulnerability, the current study investigated whether PTSD patients reporting a single traumatic event exhibited greater extinction retention deficits compared to PTSD patients who endured multiple traumatic events before developing PTSD.

Method: Thirty-eight participants diagnosed with PTSD were classified into one of two groups—Single Trauma (n=19) or Multiple Trauma (n=19)—based on self-reported trauma exposure history prior to PTSD onset. A 2-day Pavlovian threat-conditioning procedure with skin conductance response (SCR) was used to examine differences in threat conditioning, extinction learning, and extinction retention between the two groups.

Results: No significant demographic (i.e., gender, education, and age), clinical (i.e., depression and PTSD symptom severity), or shock level differences were found between the two groups, with the exception of ethnicity. On Day 1, both groups acquired the CS-US contingency and achieved comparable extinction learning. During the early extinction recall phase on Day 2, the Multiple Trauma group exhibited lower SCR (i.e., less startle) to the previously extinguished stimulus (CS+E) compared with the non-extinguished stimulus (CS+NE), thus demonstrating intact retention of extinction learning. Meanwhile, the Single Trauma group evinced comparable responses to both the CS+E and CS+NE, suggesting impaired extinction retention.

Conclusion: The study results suggest for the first time that while PTSD patients with multiple trauma exposures exhibit intact extinction retention, those who developed PTSD following a single traumatic incident revealed impaired extinction retention. The findings underscore the complex nature of PTSD, and warrant further examination of whether patients with a lower threshold for developing PTSD have a decreased capacity to process traumatic experiences.

Posttraumatic Stress MicroRNA Signatures in Serum and Amygdala of Rats: Potential Role in Fear Mechanism(s) and Biomarker Development

Authors

Nagaraja S. Balakathiresan[1], Raghavendar Chandran[1,2], Manish Bhomia[1,2], Anuj Sharma[1], Min Jia[3], He Li[3] and Radha K. Maheshwari[1]

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2. Biological Sciences Group, Birla Institute of Technology and Science, Pilani, Rajasthan 333031, India
3. Department of Psychiatry, Uniformed Services University, Bethesda, MD

Abstract

The molecular mechanism(s) underlying fear response due to acute traumatic stress and anxiety disorder is not clearly understood. MicroRNAs are post-transcriptional regulators of gene expression including genes of the serotonergic system. The primary aim of this study was to identify the candidate miRNA(s) as diagnostic biomarker in the serum and their involvement in fear memory formation in the amygdala. MiRNA expression in serum and amygdala of rats was studied which were exposed to traumatic stress for three days, using a restraint and tail shock model. Global miRNA expression at day 0 and day 14 of serum and amygdala was analyzed using Taqman low-density real time PCR arrays. A panel of nine stress-responsive miRNAs viz., miR-142-5p, miR-19b, miR-1928, miR-223-3p, miR-322*, miR-324, miR-421-3p and miR463* and miR-674* were identified as potential biomarker candidates for PTSD. Most miRNAs were found to be downregulated at day 0 immediatley after the cessation of stress in amygdala. An increase in total miRNAs was observed at day 14 amygdala which suggest a substantial alteration of the posttranscriptional machinery and indicate that the newly formed fear memories are being consolidated into stable long-term memories in the amygdala during PTSD development. Further validations by bioinformatics and system biology approaches identified five miRNAs, miR-142-5p, miR-19b, miR-1928, miR-223 and miR-421-3p, which may play a role in the regulation of genes associated with delayed and exaggerated fear. To the best of our knowledge, this is the first report demonstrating the plausibility of using circulating miRNAs as biomarkers of PTSD.

The views presented here are of the authors and should not be construed as that of DMRDP, USUHS or BITS Pilani. These studies were supported by funding form DMDRP (PI: Radha K.Maheshwari)

Individual Differences in Morphine Self-Administration Predict Body Weight Change, Acoustic Startle Reflex and Drug Seeking Behavior During Spontaneous Withdrawal from Morphine

Authors

Kwang Choi[1,2,3], Thien Le[1,2], Mercedes Xia[1,2], Min Jia[1,2], He Li[1,2,3] and Robert J. Ursano[1,2,3]

Affiliations

1. Department of Psychiatry, Uniformed Services University, Bethesda, MD
2. Center for the Study of Traumatic Stress, Department of Psychiatry, Uniformed Services University, Bethesda, MD
3. Program in Neuroscience, Uniformed Services University, Bethesda, MD

Abstract

Rationale: Although chronic use of and withdrawal from opiates can cause undesirable side effects such as weight loss, anxiety and craving for drugs, potential individual differences contributing to these effects are largely unknown.

Objectives: We investigated whether individual differences in intravenous morphine self-administration (MSA) are associated with body weight change, acoustic startle reflex (ASR) and drug seeking behavior during spontaneous withdrawal from morphine.

Methods: Male Sprague Dawley rats self-administered either morphine (0.5 mg/kg/infusion) or saline for 3 weeks (4 hours/day, 5 days per week) and body weight and drug intake were monitored daily. The ASR and drug seeking were measured during the spontaneous withdrawal from chronic MSA.
Results On average, morphine animals did not gain weight (101%±0.69) while the saline control animals did (115%±1.06) after 3 weeks of self-administration. However, individual differences in initial morphine intake (first 10 minutes), but not total intake (4 hours), were positively correlated with the weight change in morphine animals (r: 0.428, p: 0.033). Although the average ASR were not significantly different between the morphine and the control animals, the initial morphine intake was negatively correlated with the ASR in morphine animals (r: -0.544, p: 0.005). On the contrary, the initial morphine intake was positively correlated with drug seeking behavior during the spontaneous withdrawal (r: 0.424, p: 0.035).

Conclusions: We found that individual differences in initial morphine intake can predict weight change, acoustic startle (anxiety) and craving for drug during the spontaneous withdrawal. A subgroup of animals appear to be more sensitive to reinforcing effects while more tolerant to aversive effects of morphine. Identifying individual differences in opioid responses may provide a novel treatment strategy for anxiety and substance use disorders.

Supported by the CSTS.

Transcriptome Analysis of Discrete Microdissected Amygdala and other Regions of Fresh and Frozen, Intact non-Human Primate Brain

Authors

Clifton L. Dalgard, PhD[1], Harvey B. Pollard, MD[1], Vijay Singh, PhD[2], Kadharbatcha S. Saleem, PhD[3], Robert J. Ursano, MD[4], David M. Jacobowitz, PhD[1]

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4. Department of Psychiatry and Center for the Study of Traumatic Stress, Uniformed Services University School of Medicine, Uniformed Services University, 4301 Jones Bridge Rd, Bethesda, MD 20814

Abstract

Genomic and proteomic profiling of subcortical regions from intact human and non-human primate brain present specific technical problems that limit accuracy and sensitivity. In situ hybridization, while maintaining spatial precision, is low throughput, non-parallel and not optimal for low abundance transcripts. Here, we have implemented a workflow to obtain discrete areas of either fresh or frozen non-human primate brain by targeted sectioning and micropunching to isolate high integrity RNA for profiling by massive parallel sequencing. We have utilized this strategy to prepare sequencing libraries from orbital-frontal cortex, medial frontal cortex (Area 25), anterior cingulate cortex, insular cortex, amygdala, hippocampus and entorhinal cortex from non-human primate brain. In each of these anatomical regions, we have determined the complete transcriptome at high sequencing depth (up to 60 million reads). Comparative transcript expression analysis of multiple subjects identified previously known and candidate novel transcript features with increased or specific expression in distinct brain regions. These transcripts are enriched in known functions for energy metabolism, neurotransmitter signaling, and neuronal morphology. This developed microdissection technique provides a workflow to permit experimental access to central brain regions that may be analyzed in context of acquired or endogenous injury or disease. This simple methodology may be utilized to provide a transcriptomic data complement to behavioral or connectomics studies that store disease-specific brains in biological repositories.

Cytokine and Chemokine Profiling of Plasma and CSF Identifies the MCP-4/MCP-1 Ratio as a Novel Diurnal Candidate Plasma Biomarker for Chronic Post-Traumatic Stress Disorder

Authors

Clifton Dalgard[1,2], Ofer Eidelman[1,2], Catherine Jozwik[1,2], Yvonne K. Eudy[1,2], Meera Srivastava[1,2], Roopa Biswas[1,2], Stephen W. Rothwell[1,2], Gregory P. Mueller[1,2,] Peixiong Yuan[3], Wayne Drevets[3,4], Husseini K. Manji[3,4], Meena Vythilingam[3,5], Dennis S. Charney[3,6] , Robert J. Ursano[7,8], David M. Jacobowitz[1,2], Harvey B. Pollard[1,2], and Omer Bonne[3,9]

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7. Department of Psychiatry, Uniformed Services University School of Medicine, Bethesda, MD
8. Center for the Study of Traumatic Stress, Uniformed Services University School of Medicine, Bethesda MD
9. Department of Psychiatry, Hadassah Medical Center, Jerusalem, Israel

Abstract

Background: Post-traumatic stress disorder (PTSD) is a psychiatric disorder, which occurs following exposure to traumatic events. PTSD may be acute or chronic, and can have a waxing and waning course of symptoms. It has been hypothesized that proinflammatory cytokines and chemokines in the CSF or plasma might be biomarkers, surrogates, or drivers for the psychophysiological mechanisms relating a history of trauma exposure to changes in behavior and mental health disorders and medical morbidity.

Hypothesis: Here, we further test the cytokine/chemokine hypothesis for PTSD by examining levels of 17 classical cytokines and chemokines in CSF, sampled at 9 AM, and in plasma sampled hourly over a 24 hour period.

Methods: The PTSD and healthy control patients are all from the chronic PTSD (N = 12) and Healthy Control (N=11) cohort, initially described by Bonne et al (2011). We quantitatively measured cytokines and chemokines using a MesoScale multiplexed electrochemiluminescent ELISA platform.

Results: We find that in plasma, collected hourly over a 24 hour period, the bivariate MCP4/MCP1 *ratio* significantly discriminates between PTSD and Healthy Control patients at all time points. At the 9 AM time point, the MCP-4/MCP-1 ratio in PTSD plasma is elevated 66% ($p = 0.004$; AUC = 0.84). In CSF, collected at 9 AM from the same patients, we find that the MCP-4/MCP-1 ratio is not informative.

Conclusion: The ratio of MCP-4/MCP-1 in plasma may be a biomarker for PTSD in civilian PTSD patients that is invariant over a 24 hour period.

Neuronal Morphology and Cell Signaling Transcripts are Differential Markers in Hippocampal Transcriptomes of Fear-Resilient Mice During Fear Conditioning

Authors

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Abstract

Post traumatic stress disorder (PTSD) affects approximately 8.6% of veterans returning from conflicts in Iraq and Afghanistan. Intrusive fearful thoughts and memories are one of the hallmarks of PTSD. Accordingly, animal models of fear memory are utilized to investigate this component of PTSD in a controlled setting. To study the mechanisms of fear conditioning, which mimics certain symptoms of PTSD, an animal model was developed to create a divergent mouse intercross line displaying high and low levels of fear. These fear susceptible and fear resilient mice were previously utilized to identify candidate genes that contribute to baseline susceptibility or resilience to fear establishment. Functional imaging in these mice demonstrated differential activity in the hippocampus of the fear susceptible mice, which amygdala activity was non-significantly different. To investigate the mechanisms underlying this difference in activity we performed complete transcriptome profiling using next generation sequencing of hippocampal tissue from these mice and performed differential expression analysis to identify candidate transcripts which are associated with functional activity differences observed. An enrichment of transcripts associated with neuronal morphology, GSK-3b associated cellular signaling and axonal transport. Comparative analysis of transcriptomes as a function of fear conditioning exposure revealed a distinct subset of transcript features enriched for neuronal function. We anticipate that functional analysis of these candidate transcripts for fear phenotypes will elucidate novel strategies to mitigate deleterious mechanisms contributing to developing PTSD.

Spontaneous Withdrawal from Chronic Morphine Self-Administration Reduces *in vivo* Brain Glucose Metabolism (^{18}FDG-PET) and Facilitates Fear Extinction in Rats

Authors

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Abstract

Background: Chronic use of opiates may lead to abnormal brain energy metabolism which contributes to increased anxiety and stress responses. However, *in vivo* regional glucose metabolism and fear-related behavior following chronic use of morphine are largely unknown. Previous studies reported that withdrawal from repeated experimenter-administered morphine was associated with impaired fear extinction in rats.

Method: Using an intravenous morphine self-administration (MSA) paradigm, we investigated the effects of chronic morphine on *in vivo* brain glucose metabolism and fear extinction in rats. Male Sprague-Dawley rats self-administered intravenous morphine (0.5 mg/kg/injection) for 3 weeks (4 hr/day, 5 days/week). During the spontaneous withdrawal from the MSA, animals were tested with Pavlovian fear conditioning and extinction. *In vivo* regional glucose uptake was measured using a combined [18F]fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG-PET) and computed tomography (CT) scan before and after the MSA.

Results: Morphine animals did not show differences in fear learning but showed facilitated fear extinction when compared to the control animals. During the withdrawal, *in vivo* glucose uptake was decreased in the brainstem as compared to the pre-MSA baseline. A morphine challenge (0.5 mg/kg) induced a robust behavioral sensitization and increased *in vivo* glucose uptake in the nucleus accumbens, the amygdala and the brainstem of morphine-dependent animals.

Discussion: Spontaneous withdrawal from chronic opiate use may have drastic effects on brain energy metabolism and fear/anxiety behavior. This may partially explain the mechanisms of abnormal fear extinction observed in morphine self-administered animals. By combining a clinically relevant animal model and a non-invasive brain imaging, we demonstrated the utility of studying important relationship between *in vivo* brain function and psychiatric behavior. The current findings have important clinical implications because opioid drugs are increasingly used as analgesics and have high abuse potential.

Mitochondrial Gene Expression Profiles and Metabolic Pathways in the Amygdala Associated with Exaggerated Fear in an Animal Model of PTSD

Authors

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Abstract

The metabolic mechanisms underlying the development of exaggerated fear in post-traumatic stress disorder (PTSD) are not well defined. In the present study, alteration in the expression of genes associated with mitochondrial function in the amygdala of an animal model of PTSD was determined. Amygdala tissue samples were excised from 10 nonstressed control rats and10 stressed rats, 14 days post stress treatment.. Total RNA was isolated, cDNA was synthesized, and gene expression levels were determined using a cDNA microarray. During the development of the exaggerated fear associated with PTSD, 48 genes were found to be significantly upregulated and 37 were significantly downregulated in the amygdala complex based on stringent criteria ($p<0.01$). Ingenuity Pathway Analysis (IPA) revealed up or down regulation in the amygdala complex of four signaling networks – one associated with inflammatory and apoptotic pathways, one with immune mediators and metabolism, one with transcriptional factors, and one with chromatin remodeling. Thus, informatics of a neuronal gene array allowed us to determine the expression profile of mitochondrial genes in the amygdala complex of an animal model of PTSD. The result is a further understanding of the metabolic and neuronal signaling mechanisms associated with delayed and exaggerated fear.

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Sex Differences in the Single Prolonged Stress (SPS) Model of Posttraumatic Stress Disorder (PTSD)

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Abstract

Women are more than twice as likely to develop PTSD as men; however, the reasons for this sex difference are not understood. To our knowledge, this is the first study to systematically examine the sex-specific effects of SPS, a validated PTSD animal model, in adult rats. Used to detect disruption of the hypothalamic-pituitary-adrenal (HPA) axis, the dexamethasone (DEX) suppression test indicates that patients with PTSD typically exhibit exaggerated suppression of cortisol in the stress response, suggesting a hypersensitivity to HPA negative feedback. In rats, exaggerated DEX suppression of corticosterone has also been demonstrated in the SPS model, but as with the clinical reports, this generalization was formed with evidence from predominately male populations. While our data replicate the expected effect in male rats, our data indicate that females exposed to SPS do not show the enhanced stress-induced CORT suppression typical of SPS-exposed males. This lack of an enhanced DEX suppression is akin to a "DEX non-suppression" phenotype typically associated with depression. Thus, enhanced DEX suppression of CORT (in males) and no DEX suppression of CORT (in females) may represent two core phenotypes of PTSD that may be segregated by gender. The acoustic startle response (ASR) measures the enhanced arousal associated with PTSD and, as expected, we found to be exaggerated in SPS-exposed males. However, we find that females normally become more reactive with repeated exposure to the startle stimulus, regardless of wehther they have been exposed to SPS. These data indicate that female rats do not respond to SPS with the *same* phenotype established in male rats, indicating that the traumatic stress response manifests differently in male and female rats. Understanding the mechanisms underlying different types of PTSD response patterns is crucial in determining effective diagnostic measures and individual treatment.

Synaptic Potentiation in Medial Amygdala Related to Anger

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Abstract
Introduction: Anger is a devastating component of post traumatic stress disorder (PTSD). High frequency stimulation of the medial amygdala (MeA) peaking at 200 pps accelerates aggressiveness in experimental animals. This aggressiveness at least appears to be a manifestation of anger and has a time course comparable to that of short term synaptic potentiation (STP).

Hypothesis: High frequency stimulation evokes STP in MeA.

Methods: Under urethane anesthesia, the MeA of the rat is electrically stimulated (0.2–1.0mA, 0.2msec) via basomedial amygdala (BAM) afferents or accessory olfactory bulb (AOB) afferents. The excitatory postsynaptic field potential (fEPSP) evoked by each stimulation is recorded. The stimulus is given at a slow enough rate (1 pulse / 10 sec) such that it in itself does not produce synaptic potentiation. After a baseline is collected, a brief (5 sec) burst of 200 pps is given, after which a return baseline is collected, again at 1 pulse/10 sec.

Results: 200 pps stimulation of BAM or AOB afferents to the MeA potentiates excitatory synaptic transmission with a time course corresponding to STP.

Conclusion: High frequency stimulation of the MeA such as accelerates aggression in rats also evokes STP in MeA.

Multimodal *in vivo* Imaging Reveals Structural and Functional Changes in the Amygdala of a Controlled Cortical Impact Small Animal Model of Traumatic Brain Injury

Authors

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Abstract

Objectives: The amygdala is a region of particular interest in the study of both traumatic injury (TBI) and post-traumatic stress disorder (PTSD) among military services members. Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) and magnetic resonance (MR) imaging was utilized to characterize rat brain injury using FDG uptake, apparent diffusion coefficient (ADC), and T2-relaxation time (T2).

Methods: A moderate controlled cortical impact (CCI) brain injury was conducted on male Sprague Dawley (SD) rats with imaging performed prior to injury (baseline) and at one other time point between 3-6 hours and 21 days post-injury. FDG-PET scans were acquired for 30 minutes on a Siemens PET/CT scanner following 45 minutes of FDG uptake. Scatter and attenuation-corrected PET sinograms were reconstructed as a single high resolution static frame. Multi-echo T2-weighted and diffusion-weighted MRI data were acquired using a Bruker Biospec 7T/20 scanner. Quantitative T2 and ADC maps were generated using non-linear with constant (Levenberg-Marquardt) and linear (OLS) least squares estimations, respectively. A robust image processing technique was developed to evaluate 13 brain regions for coregistered PET/CT/MR images. Normalized FDG uptake and the average T2 and ADC values were determined for the whole amygdala, ipsilateral, contralateral, and the ratio of ipsilateral to contralateral (I/C) amygdala was calculated.

Results: Cross-sectional, repeat measures analysis of each post-injury time point relative to baseline revealed a significant decrease ($p \leq 0.01$) in FDG uptake at days 3 and 7, corresponding to significant decreases in ADC and increases in T2 values. In addition, the ratio of ipsilateral/contralateral for FDG uptake and T2 values were highly correlated (Pearson r=-0.937, p=0.006). Taken together, these parameters indicate cytotoxic edema at sub-acute time points and not swelling of extracellular space or cellular infiltration.

Conclusion: When combined, FDG-PET and MR imaging provide a remarkably sensitive method for detecting structural and functional changes in the amygdala after TBI.

Characterization of Psychological and Biological Factors in an Animal Model of Warrior Stress

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Abstract

For over a decade, American service members have been vigorously defending this nation and, in the process, have been exposed to death or the threat of death, explosive blasts, debilitating injuries, and other environmental stressors (*e.g.,* noise, heat), not to mention separation from loved ones and unpredictable deployment schedules. Because service members are exposed to physical and psychological stressors, it is important to understand the effects of stress on psychobiological processes to better prevent and/or treat resulting illness or injury. Despite increased awareness that Warriors exposed to stress and blast may experience cognitive effects (*e.g.,* memory and attention problems) and other post-deployment symptoms (*e.g.,* chronic pain) mechanisms underlying psychological effects of stress and blast injury have yet to be identified. Therefore, basic research must be conducted to understand the complex response to injury and stress.

The purpose of this project was to characterize psychological and biological responses in a rodent model of Warrior Stress using males and female rats. A comprehensive and sophisticated multivariate data analytic strategy examined complex relationships among behavioral and biological responses to physical and psychological stress. Data were gathered from an experimental investigation of blast overpressure induced traumatic brain injury and psychological stress in male and female rats (N=96). Exploratory factor analysis, multivariate analysis of variance, and multiple discriminant analysis were performed to: (a) reveal underlying dimensions in the data; (b) use those dimensions to try to identify the mechanisms of differential effects of four levels of stress; and (c) determine whether there were sex differences for psychobiological variables.

Multivariate analyses revealed that ***males and females differed on dimensions that represented neurochemical function*** of: (a) serotonin among the prefrontal cortex, hippocampus, insula cortex, and basolateral amygdala, and (b) dopamine activity among the prefrontal cortex and the amygdala. There were no apparent differences among stress groups on combinations of the psychobiological variables. This project highlights the need for considering sex differences in psychobiological responses and for including males *and* female participants in all injury and stress research.

Roles of p11 in Memory Retrieval: A Behavior Test of p11 Knock-Out Mice

Authors

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Abstract

Stress increases expression of p11, a member of the S100 family of proteins and influences learning and memory. Patients with PTSD, a traumatic stress associated disorder, have over-expressed p11 and experience fixed memory on a traumatic event so that the processing of non-trauma-related memories is often impaired. However, the role of p11 in memory, particularly in memory retrieval is still unknown. In this study, we examined p11 knock-out mice in the water-maze spatial test to elucidate the role of p11 in memory retrieval. There were two sets of results: control data and experimental data sets. The controls were wild-type and p11 knockout mice, pharmacological controls (i.e., mice received saline injection) and stress controls (yoked foot shock). The experimental groups were wild-type or p11 knockout mice, which received pharmacological treatment (corticosterone injection) and foot shock exposure. We found that the latency to find platform was shorter in p11 knockout mice than that in wild type mice during training day 1-3, although the latency for both wild and knock-out was not different on the final day of training or probe test. We also found that corticosterone resulted in significant decreases in the time spent in quadrant and number of island crossing in both p11 knockout and wiled type control. Our data indicate that p11 knock-out enhances memory retrieval and corticosterone induced-impairment of memory retrieval is independent of the p11 expression.

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