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A Mouse-to-Human Approach to Understand the Role of the Extended Amygdala in Stress and Alcohol Use Disorder

And

Towards Mapping the Cell Type-Specific Regulome of Stress Disorders

And

Neural Mechanisms of PTSD and Their Implications for Treating PTSD

An insula-bed nucleus of the stria terminalis (BNST) circuit in the brain is associated with anxiety/depression during alcohol abstinence. The endocannabinoid system is a potential therapeutic target in alcohol use disorder (AUD). Animal model studies suggest that attention to therapeutic windows may be of importance in future AUD therapeutic approaches.

The gene-regulatory landscape of the brain is highly dynamic in health and disease, coordinating many biological process across distinct cell types. Here we present a multi-omic single nuclei study of 1.6M nuclei in PTSD and Major Depressive Disorder, profiling chromatin accessibility and gene expression in the same biological samples and uncovering vast cellular heterogeneity. We identified cell-type-specific, disease-associated candidate cis-regulatory elements and their candidate target genes. We describe cis-regulatory relationships in specific cell types at a subset of PTSD risk loci defined by genome-wide association studies, demonstrating the utility of this multi-omic single-nucleus approach. Finally, we introduce single-nucleus consensus weighted gene coexpression analysis to perform systems level analysis of the PTSD transcriptome.

Although neural models of post-traumatic stress disorder (PTSD) have predominantly focused on fear circuitry, there is increasing evidence that other networks are also involved. This review outlines a series of studies conducted by our team on neural mechanisms underpinning traumatic stress. This will include neural studies of differential diagnoses of PTSD with related conditions, including prolonged grief and mild traumatic brain injury. It will also outline genetic and neural predictors of response to psychotherapy using emotional and non-emotional paradigms during neuroimaging. It will also consider how trauma-focused psychotherapy impacts on neural functioning. The studies reported will focus on structural and functional MRI using a range of paradigms, connectome analyses, and diffusion tensor imaging.

Target Audience: Health care professionals who work with civilian and military trauma-exposed populations.

Instructional Level: Intermediate

Learning Objectives:

Attendees will be able to:

- Evaluate the potential roles of the insula and BNST in alcohol abstinence relevant behaviors
- Assess the potential value for timing-dependent interventions as an avenue in AUD treatment
- Distinguish between neuronal and non-neuronal cell types in the prefrontal cortex
- Assess how stress disorders such as PTSD and depression affect gene expression in the brain
- Evaluate genetic risk results in molecular pathology of stress disorders
- Evaluate the key genetic and neural factors that predict response to psychotherapy for PTSD
- Differentiate between PTSD and related psychiatric conditions with reference to neural mechanisms

Agenda:

12:45 – 1:30 PM ET:	A Mouse-to-Human Approach to Understand the Role of the Extended Amygdala in Stress and Alcohol Use Disorder
1:30 – 2:15 PM ET:	Towards Mapping the Cell Type-Specific Regulome of Stress Disorders
2:15 – 2:45 PM ET:	Break
2:45 – 3:30 PM ET:	Neural Mechanisms of PTSD and Their Implications for Treating PTSD

Location Information

Address:

Online via Zoom

4/19/2022, 12:45 – 3:30 PM ET

Participate

Registration Information:
To register for this training, please visit:
https://usuhs.zoom.us/webinar/register/WN_jSR65M6yQwyzEaTY1TBksQ

Cost/Refunds: Free

Special Accommodations:

If you require special accommodations due to a disability, please contact Julia Petrini at julia.petrini.ctr@usuhs.edu FOUR weeks prior to the training so that we may provide you with appropriate service.

Presenter

Danny G. Winder, Ph.D., is a Professor of Molecular Physiology and Biophysics, Psychiatry and Behavioral Sciences and Pharmacology at Vanderbilt University. Dr. Winder received his B.S. from North Georgia College, and his Ph.D. in Neuroscience from Emory University in 1995. After completing a postdoctoral fellowship with Nobel Laureate Eric Kandel, M.D., at Columbia University College of Physicians & Surgeons, he joined the Vanderbilt faculty in 1999 as assistant professor of Molecular Physiology and Biophysics. He was promoted to full professor in 2010.

A neuroscientist focused on stress and addiction, Dr. Winder has been particularly interested in determining mechanisms that modulate synaptic plasticity, and how and when these processes are disrupted by stress and during Alcohol/Substance Use Disorder. To accomplish these goals, he and his colleagues have pioneered the use of whole cell patch clamp and extracellular recordings in ex vivo brain slice preparations containing key stress circuits.

In 2013, Dr. Winder received a NARSAD Distinguished Investigator Award and in 2016 a MERIT Award from NIAAA. In 2017, he was awarded the F. Peter Guengerich award in the School of Medicine for postdoctoral mentoring, as well as the Bixler-Johnson-Mayes Endowed Chair. He is founding director of the Vanderbilt Center for Addiction Research, which was established in 2016 to define events that drive addictive behavior and develop new treatments to sustain recovery. At the national level, he has served as an associate editor of The Journal of Neuroscience, section editor of Neuropharmacology and on the editorial board of Molecular Pharmacology.

Matt Girgenti, Ph.D., is an Assistant Professor of Psychiatry at Yale University. Dr. Girgenti received his B.S. in Molecular Engineering from Fairfield University in 2002, and his Ph.D. from University of Connecticut in 2015. As a graduate student, he received extensive research training in molecular and cell biology, in projects examining the epigenetic basis of schizophrenia (SCZ) using neural stem cells to demonstrate a role for the SCZ-risk gene ZNF804a as a gene transcription regulator.

Dr. Girgenti is a molecular neuroscientist by training with a strong history of genomic-centric research focused on the neurobiology of stress-related disorders. His research at Yale has focused on the functional genomics of neuropsychiatric disorders, specifically

PTSD, major depression, and suicide using frozen postmortem brain tissue. His lab is identifying convergent biological pathways in PTSD and depression combining single-cell molecular levels (epigenomic, transcriptomic, and proteomic) across discrete brain regions. This large multi-omics dataset is being used to identify novel neuronal and non-neuronal cell types and discovery of shared neural biomarkers harboring clinical significance in PTSD and MDD.

Dr. Girgenti has been recognized with a number of awards, including a VA VISN1 Career Development Award, a NARSAD/BBRF Young Investigator Award, and an American Foundation for Suicide Prevention Young Investigator Award. Dr. Girgenti is an expert in the field of traumatic stress, from genetics to physiology and imaging in human subjects to rodent models examining the molecular biology of prefrontal cortical and amygdala function. He has published the first studies on the genomic organization of the PTSD brain using postmortem tissue. Dr. Girgenti is also a Research Scientist at the VA National Center for PTSD and a scientific advisor for the Traumatic Stress Brain Research Group, the steering committee that oversees the NCPTSD VA Brain Bank where he co-directs the Genomics and Epigenetics Working Groups. He is also a member of the International Psychiatric Genomics Consortium (PGC) PTSD Group and the PGC Systems Biology Working Group.

Richard Bryant, Ph.D., is a Scientia Professor of Psychology at the University of New South Wales, Sydney, and Director of the Traumatic Stress Clinic in Sydney, Australia. Dr. Bryant earned his B.A. in Psychology and Religious Studies from University of Sydney and his M.Clin. and Ph.D. from Macquarie University.

Dr. Bryant has focused on the nature and treatment of PTSD for 30 years. He has conducted many longitudinal, experimental, and treatment studies in PTSD and grief, including investigating the mechanisms of PTSD using cognitive, neural, emotional, and social paradigms. Dr. Bryant has identified some of the core neural factors underpinning PTSD, grief, and mild traumatic brain injury. In recent years, his team has focused on neural and genetic factors associated with treatment response to trauma-focused psychotherapy.

Dr. Bryant has written 6 books, including *Treating PTSD in First Responders* (2021) and *Acute Stress Disorder: What It Is, and How to Treat It?* (2016), 78 book chapters, and 690 journal articles. He is an Institute for Scientific Information (ISI) Highly Cited Researcher.

**There is no commercial support or conflict of interest to report for these presenters.

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