4th Annual GCC Mental Health Research Conference

September 21-22, 2022
Houston, Texas

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Gulf Coast Consortia - Research

Gulf Coast Consortia
QUANTITATIVE BIOMEDICAL SCIENCES

The Gulf Coast Consortia (GCC), located in Houston, Texas, is a dynamic, multi- institution collaboration of basic and translational scientists, researchers, clinicians, and students in the quantitative biomedical sciences, who benefit from joint training programs, topic-focused research consortia, shared facilities and equipment, and exchange of scientific knowledge. Working together, GCC member institutions provide a cutting-edge collaborative training environment and research infrastructure beyond the capability of any single institution. GCC research consortia gather interested faculty around research foci within the quantitative biomedical sciences, and currently include Antimicrobial Resistance, Cellular and Molecular Biophysics, Innovative Drug Discovery and Development, Immunology, Mental Health Research, Regenerative Medicine, Single Cell Omics, Theoretical and Computational Neuroscience, and Translational Pain Research. GCC training programs currently focus on Biomedical Informatics, Computational Cancer Biology, Molecular Biophysics, Pharmacological Sciences, Precision Environmental Health Sciences and Antimicrobial Resistance. Current members include Baylor College of Medicine, Rice University, University of Houston, The University of Texas Health Science Center at Houston, The University of Texas Medical Branch at Galveston, The University of Texas M. D. Anderson Cancer Center, The Institute of Biosciences and Technology of Texas A&M Health Science Center and Houston Methodist Research Institute.

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Agenda

Sept. 21, 2022
Day 1

12:30	Registration and poster setup
12:50	GCC welcome, Suzanne Tomlinson, Gulf Coast Consortia
12:55	Welcome and keynote speaker introduction: Fernanda Laezza, Univ. of Texas Medical Branch
1:00	Keynote Presentation *Cell Types of Adult Mouse Brain: Definition and Experimental Access* **Bosiljka Tasic,** Allen Institute
Session 1:	**Translational Building Circuits**
Convener:	Elizabeth Zuniga-Sanchez, Baylor College of Medicine
1:45-2:05	*Adult Human Hippocampal Neurogenesis and Depression: Are We Closer to Solving the Puzzle?* **Mirjana Maletic-Savatic,** Baylor College of Medicine
2:05-2:25	*Brain-periphery Axis, Establishing Connections for Better Treatments* **Sonia Villapol,** Houston Methodist
2:25-2:45	*Brain Circuits for Silencing Fear* **Stephen Maren,** Texas A&M Univ.
2:45-3:00	Break
Session 2:	**Bioinformatics**
Convener:	Chelo Walss-Bass, Univ. of Texas Health Science Center Houston
3:00	Keynote Presentation *Array-Based Protein Kinase Activity Profiling in Disorders of Cognition* **Robert McCullumsmith**, Univ. of Toledo
3:45-4:05	*A Multi-omics Perspective on Substance Use Disorders* **Cristian Coarfa***,* Baylor College of Medicine
4:05-4:25	*Developing Technology to Improve Access to Biobehavioral Health and Social Services* **Benson Irungu,** Univ. of Texas Health Science Center Houston
4:25	**Rapid Fire Talks**
4:55	Closing remarks, **Chelo Walss-Bass**, Univ. of Texas Health Science Center Houston **Thomas Green**, Univ. of Texas Medical Branch
5:00-6:30	Poster Session and Reception 5:00-6:00 Poster presenters will be at posters

Sept. 21, 2022
Day 2

8:30 AM Registration

8:55 AM Welcome and keynote speaker introduction: Anil Pillai, Univ. of Texas Health Science Center Houston

9:00-9:45 Keynote Presentation
Psychological Stress and Prolonged Anxiety: Key Neuroimmune Interactions between Microglia, Monocytes, and Endothelia
Jonathan Godbout, Ohio State College of Medicine

Session 3: Neuroinflammation

Convener: Anil Pillai, Univ. of Texas Health Science Center Houston

9:45-10:05 *Systemic Factors That Contribute to Neuroinflammation*
Louise McCullough, Univ. of Texas Health Science Center Houston

10:05-10:25 *PET Imaging of Neuroinflammation in Psychiatry*
Sudhakar Selvaraj, Univ. of Texas Health Science Center Houston

10:25-10:40 Break

Session 4: Clinical Science: Suicide Biology & Prevention

Convener: Sanjay Mathew, Baylor College of Medicine

10:40-11:25 Keynote Presentation
Peripheral Neural-Derived Exosomal microRNAs as Biomarkers for Suicidality and Treatment Response
Yogesh Dwivedi, Univ. of Alabama, Birmingham

11:25-11:40 *Time Course of Suicidal Behavior and Risk*
Alan Swann, Baylor College of Medicine

11:40-11:55 *Using Wearables and Remote Technologies to Evaluate Risk for Suicide*
Michelle Patriquin, Baylor College of Medicine

11:55-12:30 Lunch

12:30-1:30 Networking, Workgroup booths, and final remarks

Workgroup and Consortia Booths:

Workgroups:
Addiction Research
Francesco Versace, MD Anderson Cancer Center
Heather Webber, UT Health Science Center Houston

Behavioral Medicine
Chris Fagundes, Rice Univ.

Brain Computer Interface
T. Dorina Papageorgiou, Baylor College of Medicine

Combinatorial Drug Discovery Program, TAMHSC
Cliff Stephan, TAMHSC
Nghi (Ivy) Nguyen, TAMHSC

Connecting Circuits: From Genes to Molecules to Cells
Elizabeth Zuniga-Sanchez, Baylor College of Medicine

IMC/CAMII
Michael Mancini, Baylor College of Medicine

Neuroimmunology
Anilkumar Pillai, UT Health Science Center Houston

Neurotherapeutics
John Allen, UTMB
Fernanda Laezza, UTMB

Noninvasive Brain Stimulation (NIBS)
Francesco Versace, MD Anderson Cancer Center
Heather Webber, UT Health Science Center Houston

Consortia:
Single Cell Omics
Rui Chen, Baylor College of Medicine

Translational Pain Research
Michael Lacagnina, MD Anderson Cancer Center

Cristian Coarfa, PhD
Associate Professor
Molecular and Cellular Biology
Baylor College of Medicine

A Multi-omics Perspective on Substance Use Disorders

Dr. Cristian Coarfa is currently an Associate Professor in the Molecular and Cellular Biology, and Co-Director for Multi-Omics Data Analysis in the Biostatistics and Informatics Shared Resource (BISR) of the Dan L Duncan Comprehensive Cancer Center and the Advanced Technology Cores at Baylor College of Medicine. His research focuses on achieving biological insight via integrative analysis, interpretation, and visualization of deep multi-omics profiling data. He has developed methods for integration of genetic and epigenetic variation, reference pipelines for epigenetic assays, and bioinformatic tools for high-throughput reads mapping and structural variants detection.

Dr. Coarfa earned his B.Sc in 1998 from POLITEHNICA University in Bucharest in Computer Science, and a Ph.D. in 2007 in Computer Science from Rice University, with additional Postdoctoral training from Baylor College of Medicine. He co-authored over 250 publications in the field of computational biology and high-performance computing. His work yielded new insights into the prostate cancers transcription regulators SPOP and GATA2, CPT1B as a driver of metabolic dysregulation in bladder cancer, regions of systemic methylation in human genome, and disease endotypes with clinical relevance in Tuberculosis.

Abstract: To understand mechanisms and identify potential targets for intervention in the current crisis of opioid use disorder (OUD), postmortem brains represent an under-utilized resource. To refine previously reported gene signatures of neurobiological alterations in OUD from the dorsolateral prefrontal cortex (Brodmann Area 9, BA9), we explored the role of microRNAs (miRNA) as powerful epigenetic regulators of gene function. Building on the growing appreciation that miRNAs can cross the blood-brain barrier, we carried out miRNA profiling in same-subject postmortem samples from BA9 and blood tissues. miRNA-mRNA network analysis showed that even though miRNAs identified in BA9 and blood were fairly distinct, their target genes and corresponding enriched pathways overlapped strongly. Among the dominant enriched biological processes were tube development and morphogenesis, and pathways related to endothelial cell function and vascular organization. Using correlation network analysis we identified cell-type specific miRNA targets, specifically in astrocytes, neurons, and endothelial cells, associated with OUD transcriptomic dysregulation. Our

miRNA-mRNA networks enabled identification of novel pharmacotherapeutic interventions for OUD, particularly targeting the TGFß-p38MAPK signaling pathway. Leveraging a collection of control brain transcriptomes from the Genotype-Tissue Expression (GTEx) project, we identified correlation of OUD miRNA targets with TGFß, hypoxia, angiogenesis, coagulation, immune system and inflammatory pathways. These findings support previous reports of neurovascular and immune system alterations as a consequence of opioid abuse and shed new light on miRNA network regulators of cellular response to opioid drugs. Single nuclei analysis in postmortem BA9 tissue revealed a global reduction in cell-cell communication in opioid users, with NRXN-NLGN identified as a common decreased L/R pair. Interestingly, endothelial cells appeared to be the only cell type gaining communication as revealed by incoming ligand/receptor pairs (Figure 6B), with APP-CD74 identified as a L/R pair gained from multiple source cell types. Overall, our work reveals the discovery potential of combining post-mortem brains as a biological source with rich multi-omic profiling in elucidating dysregulation mechanisms and potential interventions in OUD.

Yogesh Dwivedi, PhD
Elesabeth Ridgely Shook Professor
Director, Division of Behavioral Neurobiology
University of Alabama at Birmingham

Peripheral Neural-Derived Exosomal microRNAs as Biomarkers for Suicidality and Treatment Response

Dr. Dwivedi received his Ph.D. from Central Drug Research Institute, India, a premier research institution focused on developing novel drugs. He did his post-doctoral training at the Illinois State Psychiatric Research Institute, Chicago. He then joined the University of Illinois at Chicago as Assistant Professor and reached the rank of tenured Professor. He joined the Department of Psychiatry and Behavioral Neuroscience, the University of Alabama at Birmingham, in August 2013 as the Elesabeth Ridgely Shook Endowed Chair in Psychiatry and tenured Professor and Director of Translational Research, UAB Mood Disorders Program. He is also the Division Director of Behavioral Neurobiology and Director of the UAB Depression and Suicide Center. Dr. Dwivedi is an internationally recognized molecular neuroscientist who has significantly contributed to the understanding of fundamental molecular mechanisms associated with stress biology and mood disorders, and suicide. He has received numerous awards and is a member of the US National Institute of Mental Health study section, Chair of PMDA NIMH study section, and member of the Scientific Council of American Foundation of Suicide Prevention and Genetics and Neurobiology Task Force associated with the International Association of Suicide Prevention. He has been consistently funded by the National Institute of Mental Health and the American Foundation for Suicide Prevention. He has published 160 peer-reviewed papers and numerous book chapters and has edited a book: The Neurobiological Basis of Suicide. He serves on the editorial Board of several scientific journals and has been invited worldwide for various talks and symposia.

Dr. Dwivedi's research primarily focuses on understanding the neurobiological mechanisms associated with major depression and suicidal behavior. To increase the understanding of these disorders and identify new therapeutic targets and treatment approaches, Dr. Dwivedi's lab examines the molecular and cellular nature of events in the brain that may lead to suicidal and depressive behavior. To achieve this, he is utilizing various approaches using human postmortem brain studies, peripheral blood cell studies from the patient population, rat brain studies involving manipulation of the stress axis, rodent models of depression and post-traumatic disorder, and gene knock-out mice. His primary area of research includes neurotransmitter receptors, cytokines, neurotrophins, cellular signaling, neural plasticity, and gene regulation in depression and suicide risk using gene expression, RNA sequencing, microRNAs, and epigenetic approaches.

Abstract: Suicide is the 10th leading cause of death in the US. Thus, there is a desperate need for identifying risk factors and for non-invasive, reliable biomarkers that can be used for early detection of suicidality and treatment response. MicroRNAs (miRNAs) have emerged as an important class of small non-coding RNAs that suppress the translation and stability of specific target genes. Since miRNAs show a highly regulated expression, they contribute to developing and maintaining specific transcriptomes and thus have the unique ability to influence physiological and disease phenotypes. Using preclinical and clinical studies, I will provide evidence of the role of miRNAs in stress resiliency and susceptibility to developing depression phenotype. I will also discuss the role of synaptosomal miRNAs in depression. Recently, we found that a subset of miRNAs is specifically altered in the brain of suicide subjects regardless of psychopathology. Neural miRNAs are responsive to environmental and pathological changes and can be actively secreted by cells such as exosomes from the brain into blood. Using a neural-specific surface marker, we successfully isolated neural-derived exosomes from blood plasma and found that these exosomes are enriched with miRNAs expressed in the brain. Using this novel approach, we have examined whether neural-derived exosomal miRNAs can be used as a diagnostic tool to identify suicidality and treatment response. I will discuss our preliminary data on neural-derived exosomal miRNAs in depressed suicidal patients and their response to acute ketamine treatment.

Jonathan Godbout, PhD
Professor
Neuroscience
Ohio State Univ.

Psychological Stress and Prolonged Anxiety: Key Neuroimmune interactions between Microglia, Monocytes, and Endothelia

Dr. Godbout is a Professor of Neuroscience at the Ohio State University Wexner Medical Center. He is the Faculty Director of the Chronic Brain Injury Program, the Co-Director of a NINDS T32 Training grant (Neuroimmunology) and a member of the Institute for Behavioral Medicine Research. Dr. Godbout has a B.S. (1996) and a Ph.D. (2001) from the University of Illinois-Urbana and was a NRSA supported post-doctoral fellow with Dr. Rodney Johnson. Dr. Godbout's background is in neuroscience, immunology, and behavior with specific expertise in aging, neuroimmunology (e.g., microglia, astrocytes, and cytokines) and affective behavior (anxiety, sickness, depression). As a Principal Investigator, Dr. Godbout aims to determine the degree to which the bi-directional communication between the immune system and brain is affected by aging, psychological stress, and traumatic brain injury. In addition, he aims to delineate the mechanism by which inflammatory cytokine signaling causes long-lasting complications (e.g., anxiety, cognitive decline and depression). Dr. Godbout is an author on over 100 publications and his research is/has been supported by grants from the NIH (NIA, NINDS & NIMH), AFAR, DOD, Abbott Nutrition, and OSUMC. The Godbout laboratory has been productive and published several relevant and impactful "Neuroimmunology" and "Neurotrauma" papers, including reports in Journal of Neurotrauma, Brain, Behavior, and Immunity, Journal of Neuroscience, Glia, Biological Psychiatry, Molecular Psychiatry and Immunity. Dr. Godbout is active in the scientific community with membership in the Society for Neuroscience, National Neurotrauma Society and PsychoNeuroImmnology research Society (PNIRS). He serves on the Editorial Boards for the Journal of Neuroinflammation and Brain Behavior and Immunity. In addition, Dr. Godbout is a standing member of the BNRS NIH study section and serves on the President's council for PNIRS. Last, Dr. Godbout has received several awards including the PNIRS New Investigator Award (2009), the Siddens Award for Distinguished Faculty Advising (2012), the Neuroscience Faculty Research Award (2013 & 2017) and OSU Excellence in Research Award (2018).

Abstract: Psychological stress contributes to the development of anxiety and depression. Recent clinical studies have reported increased inflammatory leukocytes in circulation of individuals with stress-related psychiatric disorders. Parallel to this, our work with repeated social defeat (RSD) in mice shows that this stressor causes release of inflammatory monocytes into circulation. In addition, RSD caused the

development of prolonged anxiety that was dependent on microglia activation and the accumulation of inflammatory monocytes within the brain vasculature. Therefore, we hypothesize that chronic stress drives unique immune to brain signaling events that augment neuroinflammatory signaling and prolong anxiety. We provide evidence of threat appraisal activation that spatially coincided with microglial activation and endothelial facilitation of monocyte recruitment. Moreover, microglial depletion with a CSF1R antagonist prior to stress prevented the recruitment of monocytes to the brain and abrogated anxiety. Transcriptional profiling revealed unique mRNA signatures of monocytes in the blood, monocytes in the brain and microglia in the brain after RSD. For example, microglia selectively enhanced the expression of key chemokines, while monocytes highly expressed IL-1β, MMP9 and Ly6C. Moreover, the monocyte inflammatory profile was also dependent on IL-6. Consistent with these profiles, the recruited inflammatory monocytes with stress adhered and activated IL-1R1+ neurovascular endothelia through an IL-1β (caspase-1 dependent) signaling mechanism. Cell specific RiboTag capture revealed an endothelial mRNA profile that was enriched in cyclooxygenase (COX) and prostaglandin signaling pathways after this IL-1β mediated activation with stress. Intervention with the COX-2 inhibitor, Celecoxib (CCB), reduced PGE2 production and blocked anxiety-like behavior in response to RSD. Collectively, prolonged anxiety following RSD was caused by microglial recruitment of IL-1β-producing monocytes that activated brain endothelia.

Benson M. Irungu, PhD
Assistant Professor
Psychiatry and Behavioral Sciences
University of Texas Health Science Center
Houston

Developing Technology to Improve Access to Biobehavioral Health and Social Services

Benson Mwangi Irungu, PhD, graduated with a Bachelor's degree in Computer Science from Uganda, East Africa in 2005. He continued with a two year European Erasmus Mundus MSc in Computer Vision and Robotics at Heriot-Watt University- United Kingdom, University of Girona- Spain, and University of Burgundy- France. In August 2012, he completed a PhD in Neuroimaging from the University of Dundee – Scotland. For his doctorate, Irungu focused on predictive modelling of neuroimaging data in major depressive disorder. His thesis work had a specific focus on the role of advanced machine learning algorithms in predicting outcomes in major depression using structural neuroimaging scans. In December 2012, he joined the Center of Excellence on Mood Disorders, part of the Department of Psychiatry and Behavioral Sciences, as a postdoctoral research fellow.

Irungu, currently an assistant professor, researches the development and application of novel big data and machine learning tools to multimodal neuroimaging and clinical data that may help elucidate the pathophysiology of neuropsychiatric disorders. This will result in new and novel biomarkers with potential clinical applications in diagnosis, prognosis and therapeutic interventions. Irungu has published over 45 articles and presented internationally.

Abstract: Access and participation in community resource programs such as transportation, housing and medication assistance - also known as social determinants of health (SDOH) is inextricably linked to successful treatment and recovery in mental health and substance use disorders (SUD). Therefore, health and social service providers dedicate a significant amount of time to curate local community resource listings often known as - "referral binders". These community resource listings are often highly duplicated and fragmented across agencies and by using expensive non-scalable solutions technology vendors in this domain have not fully addressed this problem. Therefore, our lab has developed and translated a novel natural language processing (NLP) powered software tool that helps behavioral health providers to curate mental health and SUD related resources in the community and in turn make patient referrals to such resources. As a result, we have developed a novel NLP algorithm known as the Community Experts Routing Algorithm (CERA) and translated

it into a web-based software tool that is heavily utilized by mental health and SUD services providers in the larger Houston Metroplex region. This presentation will introduce the CERA algorithm as well as showcase how it's currently used to locate and curate critical resources to support treatment and recovery for patients with behavioral health challenges.

Mirjana Maletic-Savatic, MD, PhD, FAAP
Associate Professor
Pediatrics, Neurology, and Neuroscience
Baylor College of Medicine

Adult Human Hippocampal Neurogenesis and Depression: Are We Closer to Solving the Puzzle?

Dr. Mirjana Maletic-Savatic is the Investigator at the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and Associate Professor of Pediatrics, Neurology, and Neuroscience at Baylor College of Medicine. She is a Board- certified neurologist specialized in Child Neurology. Born in Belgrade, Serbia, Dr. Maletic-Savatic earned her medical degree and started her PhD at the University of Belgrade. Due to the outbreak of war in then Yugoslavia, she immigrated to the United States and completed her PhD degree in biophysics and neurobiology at Stony Brook University. Following a brief but very productive postdoctoral fellowship at Cold Spring Harbor Labs (her work on activity-dependent brain plasticity was a runner up for the Best Publication of the Year in Science), she pursued residency in child neurology at Stony Brook Hospital. Shortly after, she received a prestigious Phillip R. Dodge Young Investigator Award from the Child Neurology Society and was subsequently recruited by Dr. Huda Zoghbi to Baylor College of Medicine and the Duncan Neurological Research Institute. Dr. Maletic-Savatic has made important discoveries in the fields of learning and memory, adult neurogenesis, and NMR-based biomarker discovery. She has been recognized with many honors including the Neuroscience Brain Research Award from the McKnight Foundation, Brain Immuno-imaging Award from the Dana Foundation, NASA/TRISH Human Tissue Avatars grant, and Best Doctors in America among others. She is an avid supporter of women in science, technology, engineering and math, and actively mentors young women across the globe as part of the New York Academy of Sciences (Next Global Scholars, 1000 Girls, 1000 Futures).

Abstract: Adult hippocampal neurogenesis has been strongly associated with mood control in animal models. However, in the human brain, the extent and the functional significance of neurogenesis continues to be debated, in large part because the field has lacked a non-invasive method to measure the phenomenon in living organisms. Using magnetic resonance spectroscopy (MRS), we identified a fatty acid-related biomarker that is highly enriched in neuroprogenitors and visible on the MRS spectrum. We discovered, using a panel of biophysical, chemistry, and pharmacological tools, that neuroprogenitors are particularly abundant in mono-unsaturated fatty acid, one of which is an endogenous ligand for nuclear receptor NR2E1, required for their self-renewal, proliferation, and neurogenesis. We then developed an automated algorithm that allows objective quantitation of the fatty-acid

enriched neurogenic biomarker in the live human brain. The MRS neurogenic biomarker distinguishes neurogenic and non-neurogenic areas (N=35 subjects; Wilcoxon V=55, p=0.01) and is positively associates with pattern separation and response to antidepressant treatments (N=34; p=0.0029), while it declines with age (N=300; Rpartial=-0.23, p=0.004; df=224). In depressed individuals receiving electroconvulsive treatment (N=20), an early two-fold signal increase predicts subsequent hippocampal plasticity (R=0.70, p=0.0026) and clinical outcome (R=-0.53, p=0.036). We thus now have the means to study neurogenesis in the live human brain and in patients who suffer from depression. Moreover, we have a new druggable target that may lead to development of more effective therapies for depression, as we can stratify patients in whom pathology may depend on the rate of hippocampal neurogenesis.

Steve Maren, PhD
Distinguished Professor and
Charles H. Gregory Chair of Liberal Arts
Dept. of Psychological and Brain Sciences
Texas A&M University

Brain Circuits for Silencing Fear

Dr. Maren is a University Distinguished Professor and Charles H. Gregory Chair of Liberal Arts in the Department of Biological Sciences at Texas A&M University. He is an internationally recognized scientist exploring the neural basis of emotional learning and memory and its relevance to psychiatric disorders, including post-traumatic stress disorder. Research in his laboratory seeks to understand the brain circuits and cellular mechanisms underlying the encoding, storage, retrieval, and extinction of aversive memories, and how dysfunction in these circuits and processes contributes to anxiety disorders. He focuses on the neurobiology of fear conditioning and extinction in rodent models. He is the recipient of the American Psychological Association Distinguished Scientific Award for an Early Career Contribution to Psychology (2001) and the D. O. Hebb Distinguished Scientific Contributions Award (2017). He is a Fellow of the American Psychological Association and Association for Psychological Science, Past-President of the Pavlovian Society. He has been continuously funded by the National Institutes of Health since 1995 and is a recipient of the 2015 McKnight Memory and Cognitive Disorders award.

Abstract: Memories for emotional, particularly fearful, events are vivid, visceral, and enduring. Emotional memories enable us to predict and avoid potential threats, as well as respond to immediate danger. But dysfunction in this system can result in anxiety, panic and post-traumatic stress disorder. Extinction learning is critical for the suppression of pathological fear and is central to exposure-based therapies in humans. Here I will describe research in rats exploring the brain circuits regulating extinction learning and fear suppression. Importantly, in recent work we have shown that the thalamic nucleus reuniens is a critical hub for the suppression of fear memories. Specifically, the nucleus reuniens interconnects the medial prefrontal cortex and hippocampus, two brain areas essential for extinction learning, and enables the prefrontal cortex to silence hippocampal-dependent fear memories. Silencing hippocampal-dependent fear memories may be the essential neural mechanism underlying effective behavioral therapies for pathological fear in humans.

Louise McCullough, PhD
Roy M. and Phyllis Gough Huffington
Distinguished Chair and
Professor of Neurology
Univ. of Texas Health Science Center
Houston

Systemic Factors That Contribute to Neuroinflammation

Dr. Louise McCullough is the Roy M. and Phyllis Gough Huffington Distinguished Chair and Professor of Neurology at McGovern Medical School at UTHealth and Chief of Neurology at Memorial Hermann Hospital – _Texas Medical Center. She is a physician-scientist and a practicing vascular neurologist with clinical expertise in sex/gender disparities, the microbiome, stroke and aging, and acute stroke treatments. A renowned investigator, she is well recognized for her work in cerebral vascular disease and is known for her research identifying sex differences in cell death pathways during stroke, which have now been shown to be a major factor in the response to an ischemic insult. Working closely with the Society for Women's Health Research (SWHR) and the Office of Research on Women's Health (ORWH), she was instrumental in the National Institute of Health's_ _requirement to include female animals in basic and translational studies.

Among Dr. McCullough's_ _many honors and awards are the prestigious National Institute of Neurological Disorders and Stroke (NINDS) Javits Neuroscience Investigator Award, the NINDS Landis Award for Outstanding Mentorship, the Inaugural American Heart Association (AHA) Outstanding Stroke Research Mentor Award and the AHA Merit Award. She completed her PhD in Neuroscience and her MD from the University of Connecticut. She continued her training at Johns Hopkins completing a neurology residency in 2000. Her residency was followed by a fellowship in cerebrovascular disease and stroke (2000-2002). After completing her training, she joined the faculty at Johns Hopkins Hospital and began her translational research career.

Dr. McCullough returned to Connecticut in 2004 and rose to the rank of Professor in the Departments of Neurology and Neuroscience at The University of Connecticut Health Center and at the John Dempsey Hospital in Farmington, Connecticut. She became the Director of Stroke Research and Education at Hartford Hospital, and helped develop one of the largest stroke centers in New England. In 2015, she relocated to the University of Texas Health Science Center in Houston 2015 as the Chair of Neurology. The Neurology Department at UT Health has very active educational, clinical, and research programs, and is ranked highly in NIH funding.

Abstract: Over the past decade, there has been a growing recognition that stroke and other sterile brain injuries cause dramatic changes in peripheral tissues. In addition to focal brain damage, acute ischemic stroke (AIS) provokes systemic abnormalities across peripheral organs. AIS profoundly alters the autonomic nervous system, hypothalamic-pituitary-adrenal axis, and immune system, which further yield deleterious organ-specific consequences. Poststroke systemic pathological alterations in turn considerably contribute to the progression of ischemic brain injury, which accounts for the substantial impact of systemic complications on stroke outcomes. One increasingly important signaling pathway is the microbiota-gut-brain-axis (MGBA). The MGBA is a bidirectional communication network between gut microbes and their host. Many environmental and host-related factors affect the gut microbiota. Dysbiosis is defined as compositional and functional alterations of the gut microbiota that contribute to the pathogenesis, progression and treatment responses to disease. Dysbiosis occurs when perturbations of microbiota composition and function exceed the ability of microbiota and its host to restore a symbiotic state. Dysbiosis is seen with both aging and stroke, and is linked to the development of common stroke risk factors such as obesity, diabetes, and atherosclerosis. This talk will focus on the relationship between the MGBA in both aging and after stroke.

Robert McCullumsmith, MD, PhD
Chair
Neurosciences
University of Toledo College of Medicine

Array-Based Protein Kinase Activity Profiling in Disorders of Cognition

Dr. Robert McCullumsmith completed his BS degree with highest distinction and Honors in biochemistry from Indiana University in 1990. He completed his MD and PhD degrees from the University of Michigan in 1997, and he completed a research track residency in Psychiatry in 2002. He is a recipient of numerous awards, including the prestigious ACNP travel award, the ACP Laughlin Fellowship, the ECNP Rafaelsen Scholar, as well as the Kempf Fund award from the APA. He has been continuously funded for the past 16 years by NIMH, with work focusing on the pathophysiology of complex brain disorders, including schizophrenia. His recent work includes using bioinformatics approaches to test hypotheses using large publicly available databases, with the goal of repurposing or first-purposing FDA approved drugs or library-sourced compounds, respectively. Dr. McCullumsmith is currently the Chair of the Neurosciences department at the University of Toledo College of Medicine and the Research Director of the ProMedica Neurosciences Center, Toledo, OH, USA.

Abstract: *Where are the final frontiers in biomedical research?* In this age of sequenced genomes, CRISPR, and organoids, how can there be any truly unexplored spaces? Surprisingly, there are dozens (more than 140!) of understudied protein kinases in the human genome. Many of these have ZERO or very few annotations for downstream substrates, lack knockdown and/or overexpression signatures, and have no identified small molecule inhibitors. Many of these understudied, or “dark” kinases, are present in the NIH Illuminating the Druggable Genome (IDG) program, along with many other non-kinase proteins.

What is the best way to study protein kinases? Interestingly, only ~40% of protein abundance can be explained by mRNA expression levels, while the rest is explained by other factors including post-translational modifications (PTMs). Extending this example, protein abundance does not necessary reflect protein activity. A recent study analyzed 150 tumor samples and found that phosphorylation at specific phospho-sites and overall kinase abundance were generally uncorrelated. Taken together, these concepts highlight how assumptions about biological regulation may confound protein research. What is needed is a *functional* understanding of the cellular mechanisms that drive the disorder.

Peptide activity array profiling of brain substrates. We have deployed complementary approaches to study protein kinase activity changes in disorders of cognition,

anchored by a kinome array platform that permits simultaneous assessment of protein kinase activity at 100s of reporter peptides. Combined with RNAseq, LCMS, and standard biochemical assays, we have detected changes in protein kinase signaling networks in schizophrenia (SCZ), Alzheimer's dementia (AD), and major depressive disorder (MDD). Substrates include iPSCs differentiated into astrocytes and frontal cortical neurons, as well as postmortem brain and animal models.

Major findings are providing new leads for drug development. Alterations in specific protein kinases identified as signaling nodes in SCZ (SGK kinase) and AD (AMPK kinase) are being confirmed using standard biochemical approaches. We are also using in silico bioinformatics approaches to identify library compounds and repurposed drugs that may be advanced for development of novel treatment strategies for these often devastating disorders.

Michelle Patriquin, PhD, ABPP
Director of Research and Senior Psychologist, The Menninger Clinic Associate Professor, Psychiatry and Behavioral Sciences, Baylor College of Medicine

Using Wearables and Remote Technologies to Evaluate Risk for Suicide

Dr. Michelle Patriquin is the Director of Research and a Senior Psychologist at The Menninger Clinic and Associate Professor in the Department of Psychiatry and Behavioral Sciences at Baylor College of Medicine. She is board certified by the American Board of Professional Psychology (ABPP). The Menninger Clinic in an inpatient and outpatient mental health hospital that has been a nationally ranked in the top 10 by US News for over 30 years. She has authored over 120 publications or presentations on the subjective (e.g., trauma) and objective (e.g., heart rate/heart rate variability, sleep) precursors of mental illness. Her work is funded by federal (NIH, NSF) and foundation grants. She has been honored with multiple awards for her research and mentorship, including the New Investigator Award by the American Society of Clinical Psychopharmacology and the Rising Star Award by the Association for Psychological Science. She is has served as a standing reviewer for over 3 years on a NIH SBIR/STTR panel reviewing grants at the intersection of novel technology (apps, AI, sensors) and psychiatry/biobehavioral areas. At The Menninger Clinic, she leads a large, diverse team of faculty and staff to better understand mental health diagnoses and treatment outcomes. She is particularly interested in how we can develop and leverage new technologies to improve mental health in intensive treatment settings.

Abstract: The initial 90-days post-discharge from an inpatient psychiatric hospital is the highest risk period for suicide (Chung et al., 2017). Our research team has published a theory that hypothesizes that noctural inpatient safety precautions might be contributing to this high-risk period and generate an effect, the Safety-Sleep-Suicide Spiral (Gazor et al., 2020). Given the critical role that sleep plays in the mitigation of suicide risk, reducing the nighttime sleep disturbances related to noctural safety precautions, using alternative methods could interrupt the compounding effect of the Safety-Sleep-Suicide Spiral. Herein, one highly promising alternative method that may not disturb sleep will be discussed: continuous monitoring via wearable technology. Data will be presented from an ongoing study (N = 24 at present) examining objective and subjective sleep measures and their relationship with suicide risk (measured via the Suicide Behaviors Questionnaire-Revised, SBQ-R). Objective sleep is measured

via actigraphy (ActiGraph wGT3X-BT) continuously for a patient's entire length of stay (4-6 weeks) in an inpatient psychiatric hospital. Subjective sleep is measured through weekly self-report of nighttime sleep disturbance on the Pittsburgh Sleep Quality Index (PSQI), Insomnia Sleep Index (ISI) and daytime sleepiness on the Epworth Sleepiness Scale (ESS). Initial results demonstrate that increased suicide risk on the SBQ-R is associated with significantly shorter objective total sleep time (TST) measured via the actigraph ($p < .05$) and that increased suicide risk is related to more subjective sleep disturbance ($p < .05$). We will discuss the promise, as well as importance, of translating wearables data in order to improve inpatient outcomes monitoring and provide a less invasive real-time nocturnal safety assessment. Prior to this clinical translation, significant research is needed to improve the predictive power of wearable-based metrics as they relate to suicide risk and safety, as well as the development of clinically actionable visualization of these data. These challenges will also be discussed.

Sudhakar Selvaraj, PhD
Associate Professor
Psychiatry & Behavioral Sciences
Univ. of Texas Health Science Center Houston
PET Imaging of Neuroinflammation in Psychiatry

Sudhakar Selvaraj is an Associate Professor at the Department of Psychiatry & Behavioral Sciences at UTHSC-Houston (UTHealth). He directs the depression research program focusing on the underlying pathophysiology of depressive disorders to identify biomarkers to stratify and individualize treatment. His research utilizes multimodal brain imaging (MRI, positron emission tomography, PET), psychopharmacology, and neuromodulation. His research is funded by NIH, foundation, and industry grants. He has >85 papers, a neuroimaging-focused book titled "Mood Disorders: Brain Imaging and Therapeutic Implications", book chapters and he is an Editorial Board Member, Journal of Affective Disorders. He is a Fellowship, Royal College of Psychiatrists, member of the Society of Biological Psychiatry, American Society of Clinical Psychopharmacology and American College of Neuropsychopharmacology.

Alan C. Swann, MD
Professor
Psychiatry and Behavioral Sciences
Baylor College of Medicine
Time Course of Suicidal Behavior and Risk

Alan C. Swann M.D., Professor, Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston.

I attended the University of Texas Southwestern Medical School at Dallas, straight medicine internship at Columbia-Presbyterian Medical Center in New York, research fellowship at the National Institute of Neurological Disorders and Stroke, Psychiatry Residency at Yale University School of Medicine, and initial faculty appointment as assistant professor there. I was in the Department of Psychiatry, University of Texas Medical School at Houston, from 1980-2013, followed by Baylor College of Medicine and Michael E. DeBakey VAMC.

Committees and organizations have included the National Advisory Council on Alcoholism and Alcohol Abuse, and NIH and VA grant review committees, including past Chair of the VA Merit Review Board on Mental Health and Behavioral Sciences. I was a co-founder, and past president, of the International Society for Research on Impulsivity; am a Fellow of APA and American College of Neuropsychopharmacology; and a member of relevant societies including the American Association of Suicidology (Scientific Advisor) and ISCTM.

In the community, I serve on the Scientific Advisory Board of reMIND (DBSA Houston), have made presentations or taken part in programs on crisis with police and clergy, and on suicidality with DBSA, Alliance for Mentally Ill, and AFSP Survivors of Suicide programs.

Academic activities combine teaching, clinical, administration, and research. Teaching includes didactics, supervision, and mentoring of medical and graduate students, residents, and postdoctoral fellows, community education and support activities, resulting in Teaching Awards at UT and Baylor. Clinical responsibilities have included setting up an outpatient program, supervising inpatient and outpatient clinical units, and caring for patients directly and for consultations or second opinions. Administratively, I served on the IRB at UT Houston for 25 years and was Vice-Chair and Chair, and on Health Science Center, Medical School, Graduate School, and

Departmental committees. I was Vice Chair for Research at UT Houston from 1990-2013, also serving on or chairing other committees and work groups. At Michael E. DeBakey VAMC I have served on the Research & Development Committee

Research (over 300 refereed publications, 66 chapters, invited reviews or commentaries) focuses on interactions between long-term and short-term mechanisms in the immediate regulation of behavior, especially regarding mechanisms of disease progression and of suicidal behavior. Preclinical human research includes impulsivity, sensitization, and regulation of action. Clinical research includes relationships of preclinical mechanisms to clinical characteristics and treatment of psychiatric, especially affective, disorders; interactions between episode characteristics and illness course; and related topics including suicide, substance abuse, mixed states, and combinations of addictions with other illnesses. Basic research includes pharmacological and developmental aspects of behavioral sensitization to stimulants or stressors, a potential model for the influence of long term behavioral processes on immediate action. Mechanisms in sensitization overlap with those regulating initiation of action. Strategies include extensive collaboration to combine neurophysiological, behavioral laboratory, psychopharmacological, and clinical studies. Our goals include understanding mechanisms of initiation of action and of disease progression that cut across current diagnostic entities. My aim is to link basic and preclinical research to clinical research and observation to develop clinically relevant indices of brain function that will enable us to identify and treat severe psychiatric illness in a physiologically-based manner. Research support has included NIMH, NIAAA, Centers for Disease Control, American Heart Association, American Foundation for Suicide Prevention, private foundations, and industry.

Abstract: The regulation of action requires interactions between immediate regulation of action and long-term behavioral adaptation. These interactions can result in apparently complex, chaotic patterns of behavior. We will discuss the manner in which this is related to suicidal behavior. Suicide is the most common cause of fatal trauma. People who have made medically severe suicide attempts have increased subsequent suicide and non-suicide mortality regardless of diagnosis. However, we cannot rely on past suicide attempts to predict risk because most suicides were first attempts. Many characteristics associated with long-term suicide risk have been identified, but the actual behavior is notoriously difficult to predict. We will discuss interactions between long-term mechanisms of behavioral sensitization and the immediate, pre-attentive regulation of action in suicidal behavior. The resulting characteristics cross clinical diagnoses. There may be a transdiagnostic condition characterized by impaired control of action associated with sensitization to stress- or reward-related stimuli. The expression of this behavior may be difficult to predict, but identification of mechanistic and diagnostic properties could generate effective preventive strategies. We will address practical approaches to these questions.

Bosiljka Tasic, MD, PhD
Director, Molecular Genetics
Allen Institute for Brain Science

Cell Types of Adult Mouse Brain: Definition and Experimental Access

Bosiljka Tasic joined the Allen Institute for Brain Science in Seattle in late 2011, where she is currently the Director of Molecular Genetics. There, she leads an effort toward comprehensive molecular analysis of cellular identity in the mouse brain. She is also interested in integrative cellular phenotyping, where different cellular properties (e.g., molecular, physiological, and morphological) are obtained for single cells and used to derive multimodal cell-type taxonomies. She has a long-standing interest in the development of novel genetic tools to enable access to specific cell populations for their functional characterization. Before joining the Allen Institute, Bosiljka completed her postdoctoral training with Liqun Luo at Stanford University, obtained her Ph.D. with Tom Maniatis at Harvard University, and received a Bachelor's degree from the University of Belgrade, Serbia.

Abstract: Single-cell genomics has fundamentally changed the way we define and experimentally access cell types and assess changes in their states or identity. One of the major team efforts at the Allen Institute for Brain Science is to define all cell types in the mouse brain by single-cell/single-nucleus transcriptomics (RNA-sequencing and spatial transcriptomics). I will present our current definition of cell types in mouse brain based on single cell transcriptomics as well as its correlation with other cellular properties which suggest specific cell type functions. Establishing causality relationships between specific properties and cell type function requires highly specific and temporally regulated perturbations combined with integrative phenotyping. I will present the development of new viral genetic tools that can be delivered systemically to the whole mouse brain to specifically label, monitor, perturb, or treat a cell class or type. The new viral genetic tools perform well across rodents and primates and have the potential to enable systematic analysis of brain cell type function and become precursors for highly specific neural circuit therapeutics.

Sonia Villapol, PhD
Assistant Professor
Neurosurgery
Houston Methodist Research Institute

Brain-periphery Axis, Establishing Connections for Better Treatments

Dr. Sonia Villapol graduated from the University of Santiago of Compostela (Spain) with a bachelor's degree in Molecular Biology and Biotechnology in 2003. She received her master's degree and Ph.D. in Neuroscience from the Autonomous University of Barcelona (Spain) in 2007. She worked as a postdoctoral fellow at CNRS in the University Pierre and Marie Curie VI and at INSERM in Paris, France (2007-2010) and at the National Institutes of Health, Center for Neuroscience and Regenerative Medicine, and Uniformed Services University (USUHS) in Bethesda, Maryland from 2010 to 2014. Following her postdoctoral research work, Villapol joined the Department of Neuroscience at Georgetown University in Washington, D.C. as a Research Assistant Professor in May 2014. In July 2018, she started as a faculty member at the Center for Neuroregeneration at Houston Methodist Research Institute as Assistant Professor of Neurosurgery. Dr. Villapol has received extramural research funding as Principal Investigator from NIH, and she serves as a standing member at Molecular Neurogenetics NIH Study Section (MNG). She is also an Associate Editor for Cellular and Molecular Neurobiology (Springer Journal). She has published over 60 articles in peer-reviewer journals and book chapters.

Currently, our lab is exploring the role of the gut microbiome and brain damage and studying biomimetic nanoparticles as a theranostic tool for brain injury and neurodegenerative diseases. We currently develop preclinical and clinical projects. We are also using our resources and expertise to focus on understanding the role of microbiome on acute and long-COVID-19.

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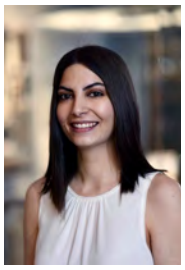
Holly Chapman, University of Texas Medical Branch at Galveston
Hold That Thought: Uncovering A Biosignature Of Impulsivity
Poster 7

Jessica Di Re, University of Texas Medical Branch at Galveston
Neurodevelopmental Changes in Rodent Behaviors Induced by Early-Life Exposure to Deltamethrin
Poster 9

Rachele Lipsky, Duke Univ,
The Association Between Severe Cases of Gulf War Illness and Suicidal Thoughts and Behaviors Among Gulf War Era Veterans
Poster 21



Sirena Soriano, Houston Methodist Research Institute
Restoring the Gut Microbiota of Alzheimer's Disease Mice may Facilitate Recovery from Brain Injury
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Xu Zhang, University of Texas Health Science Center Houston
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Poster 1

Can 3DCNN Decoders Capture More Accurately The Classification Of Neurological And Psychiatric Disorders In The Individualized fMRI-Brain Computer Neurofeedback Interface?

Allam A[1], Huynh D[2], Froudarakis E[4], Patel A[3,5], Papageorgiou TD[2,3,5,6,7]

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Background: The Papageorgiou lab has developed an fMRI-BCI, referred to as individualized real-time fMRI neurofeedback(iRTfMRI-nFb) for the neurorehabilitation of neuropathic pain following supra- or infra-nuclear cranial nerve(CN), IX(glossopharyngeal) and XII(hypoglossal) lesions, which affects speech and swallowing. Decoding brain activity with increased sensitivity and specificity, meaning enhanced classification accuracy and capturing networks that reflect the anatomical and physiological underpinnings of a function is of utmost importance to provide effective neurofeedback to induce neurorehabilitation. Linear SVMs, the most common algorithm used in the field did not generate activation of the medulla oblongata, the region where the nuclei of the CNs originate. This important caveat suggests the need to assess whether a deep learning algorithm, such as 3D Convolutional Neural Networks(3DCNNs) can decode brain feature maps more successfully than Linear SVMs.

Goal/Hypothesis: 3DCNNs will achieve higher classification accuracies, and brain maps with greater physiological interpretability when compared to Linear SVMs.

Methods: We decoded participants' brain networks generated during tongue-motor-control in four directions(up; down; left; right) using both Linear SVMs and 3DCNNs. The architecture used for the 3DCNN was a deep network consisting of 152 layers with an additional integration layer consisting of a multilayer perceptron. The cortical activation maps were derived using: 1. the sum of the SVM training weight vectors for the Linear SVM; and 2. a derivative of a linear saliency map(SmoothGrad) for the 3DCNN. Random gaussian noise was added to the inputs and averaged over 50 maps to produce a cortical map with increased sharpness while maintaining interpretability. The models were trained to distinguish across all cortical direction selectivities of the tongue versus baseline-tongue-at-rest for the individualized iRTfMRI nFb and control-no neurofeedback conditions. We decoded 30 participants' tongue-motor-control networks with a 20/10 training/test split. Within the training dataset, we used a five-fold cross-validation procedure: in each iteration, the models were trained on data from 16 participants and validated on data from 4 participants.

Results: To decode our brain maps, we averaged the conditions for the control runs and neurofeedback runs for SVMs and 3DCNNs, separately. As we expected the 3DCNN generated higher classification accuracies for the control(81%) and neurofeedback(84%) runs compared to the SVM, which generated 71% and 80% classification, respectively. This suggests the increased consistency of the 3DCNN to predict tongue motor control direction. Most importantly, 3DCNN elucidated activity in the medulla oblongata where CNIX and CNXII nuclei originate, while SVM did not reveal medulla oblongata activation, when we decoded each tongue direction cortical selectivity and across all directions.

Conclusions: 3DCNNs achieve higher classification accuracies and more accurate cortical neural networks that reflect the function associated with tongue sensorimotor control with greater sensitivity compared with Linear SVMs. Immediate future goals include the optimization of hyperparameters for the 3DCNN with the goal to use this decoder in the iRTfMRI-nFb environment to optimize the neurorehabilitation of neurological and psychiatric disorders.

Acknowledgements: This study is funded by grants to T.D. Papageorgiou: McNair Medical Institute, Robert and Janice McNair Foundation, TIRR/Mission Connect, Baylor College of Medicine Junior Faculty Award, NIH-T32.

Poster 2

Modulation of Individualized Sensorimotor Networks Through Individualized Real-Time fMRI Neurofeedback Towards the Alleviation of Radiation-Induced Cranial Neuropathy

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Background: Brain-computer interfaces(BCIs) have revolutionized the rehabilitation of neurological and psychiatric disorders. The Papageorgiou lab has developed a closed-loop fMRI-BCI neurofeedback interface, we call individualized real-time fMRI neurofeedback(iRTfMRI-nFb) to increase efficiency, and efficacy of the neuromodulation. Our long-term goal is to neuromodulate tongue motor and sensory control(TMSC) to neuro-rehabilitate neuropathic pain, in particular radiation-induced cranial neuropathy, as the patients become refractory to current pharamacotherapeutic regimens due to drug-drug interactions. Here we elucidate the cause-effect spatiotemporal mechanisms involved in the brain's modularity when targeting sensorimotor networks. By targeting individualized networks that regulate TMSC, we decoded the tongue's cortical direction selectivity, and uncovered a probabilistic framework of the mechanisms involved in the brain's modularity.

Methods: Healthy volunteers(n=30) participated in a two-day iRTfMRI-nFb study. On study-day one, we decoded the cortical spatial patterns and amplitude generated by TMSC in four directions(up; down; left; right), interleaved with periods of tongue-rest(baseline) and swallow. Our innovation is based on the delineation of individualized networks, as a function of the BOLD's magnitude and spatial extents. The individualized networks associated with each participant's TMSC cortical direction selectivity were extracted and targeted for nFb delivery. On study-day two, participants underwent iRTfMRI-nFb and control-no nFb conditions. Linear support vector machine(SVM) classified cortical direction selectivity patterns versus tongue-at-rest generated via nFb and control. We quantified the BOLD magnitude for each network's areas separately, as a function of time by computing the sensitivity index(d'), area under the curve(AUC), and variance. We performed dynamic causal modeling after modifying Pitkow's ECoG Markov model to fit the fMRI's spatiotemporal scale.

Results: We found the mechanisms associated with **sensorimotor** iRTfMRI-nFb-induced modulation are: 1. 45% increase in the BOLD's magnitude d' and AUC ($p<0.001$); 2. 14% decrease in the BOLD's intensity variance($p<0.01$); and 3. 20% increase in the networks' spatial expansion ($p<0.001$). We elucidated the dynamic brain states during the TSMC task performance: 1. a dominant state, which shows tongue movement occurred in 95% of the nFb trials, while it occurred in only 76% of the control trials; and 2. a non-dominant state (noise) identified as swallowing, occurred in 5% of the nFb trials, and 24% of the control trials. The dominant state induced by nFb was driven by: 1. within(60%) motor(M1, motor cerebellum, basal ganglia) areas and motor to sensory(54%) networks; and 2. within(47%) sensory (intraparietal lobule, insula, claustrum, sensory cerebellum, thalamus, cingulate, ACC) areas and across sensory to motor (52%) networks. iRTfMRI nFb increased the consistency in the decoded networks' spatial extents reflected by significantly greater accuracies compared to the control(94.3% vs. 89.6%, $p<0.001$).

Conclusion: This study shows that iRTfMRI-nFb enhances TMSC and establishes spatiotemporal causality between the sensorimotor tongue task and the cortical networks involved. These findings show that modularity of the individualized networks via iRTfMRI-nFb can serve as a valuable tool in modulating not only neuropathic pain disorders, but also other neurologic and psychiatric disorders.

Acknowledgements: This study is funded by grants to T.D. Papageorgiou: McNair Medical Institute, Robert and Janice McNair Foundation, TIRR/Mission Connect, Baylor College of Medicine Junior Faculty Award, NIH-T32.

Poster 3

iFGF14 Peptide Derivative Differentially Regulates $Na_v1.2$ and $Na_v1.6$

Arman P[1], Haghighijoo Z[1], Xue Y[1], Wang P[1], Chen H[1], Zhou J[1], Laezza F[1]

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Background: Voltage-gated Na^+ channels (Na_v) are the molecular determinants of action potential initiation and propagation because of their role in mediating ionic flow (Na^+). Out of the nine voltage-gated Na^+ channels ($Na_v1.1$-$Na_v1.9$), $Na_v1.2$ and $Na_v1.6$ are of particular interest because of their expression and distribution within the central nervous system (CNS). Although the α-subunit can sufficiently confer transient Na^+ currents (I_{Na}), *in vivo* these channels exist alongside β-subunits and in addition are modulated by auxiliary proteins like intracellular fibroblast growth factor 14 (FGF14) through protein:protein interactions (PPI). Previous studies have identified ZL0177, a peptidomimetic derived from a short peptide sequence thought to mediate the FGF14:$Na_v1.6$ PPI, as a functionally active modulator of $Na_v1.6$ mediated I_{Na}.

Goals: To that end, we assessed the isoform selectivity and mechanism of action of ZL0177 in heterologous cells stably expressing the α-subunit of either $Na_v1.2$ or $Na_v1.6$. Lastly, we complemented our electrophysiology studies with *in silico* docking of ZL0177 to $Na_v1.2$ and $Na_v1.6$ homology models.

Methods: Automated planar-patch electrophysiology was utilized to study the selectivity of ZL0177 against HEK-293 cells stably expressing either $Na_v1.2$ or $Na_v1.6$ Na^+ channels. Homology modeling was done to build $Na_v1.2$ and $Na_v1.6$ Na^+ channels structures. Using these models, *in silico* docking was performed to predict the possible binding sites of ZL0177.

Results: We observed statistically significant changes in peak I_{Na} density as well as polarizing shifts in both activation and steady-state inactivation that were isoform specific. ZL0177 statistically decreased both $Na_v1.2$ and $Na_v1.6$ mediated peak I_{Na} density at 1 μM and 10 μM. However at 10 μM, ZL0177 caused a statistically significant depolarizing shift in $V_{1/2}$ of activation for $Na_v1.6$. In addition, ZL0177 (10 μM) caused a selective hyperpolarizing shift in $V_{1/2}$ of steady-state activation and inactivation for $Na_v1.2$. *In silico* docking revealed that ZL0177 binds strongly to residue Glu^{1884} in $Na_v1.2$ and Asp^{1846}, Ala^{1875}, and Ser^{1876} in $Na_v1.6$ via H-bonds. Subsequently, there are various hydrophobic and π-π interactions with Lys^{1891}, Tyr^{1883}, and Thr^{1887} for $Na_v1.2$ and Asp^{1833}, Val^{1837}, and His^{1843} for $Na_v1.6$.

Conclusions: ZL0177 reduced both $Na_v1.2$ and $Na_v1.6$ mediated peak I_{Na}, but exhibited opposite selectivity towards voltage-sensitivity of activation and steady-state inactivation. These ZL0177 isoform-specific modulations of $Na_v1.2$ and $Na_v1.6$ might be driven by the ligand interacting with Glu^{1884} ($Na_v1.2$) and Met^{1869} ($Na_v1.6$) residues. This study could provide useful information for the development of novel isoform-specific probes and future neurotherapeutics against Na_v channels.

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Poster 4

Targeting the Nav1.6:GSK3β Protein:Protein Interaction Complex to Alleviate Hippocampal Hyperexcitability

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Background: A vast array of neurological disorders are facilitated by aberrant hippocampal network activity. The hippocampus plays a critical role in learning, memory formation, social cognition, and emotional processing. A multitude of recent studies indicate a causative relationship between hippocampal hyperexcitability and memory impairment, cognitive deficits, and epileptiform activity. Voltage-gated Na^+ channels (Nav channels) have critical regulatory roles in synaptic function and neuronal firing. Of the three Nav channel isoforms expressed in the adult human brain, (Nav 1.1, 1.2, and 1.6), Nav1.6 is the most densely expressed and plays a critical role in action potential initiation due to its subcellular localization at the axon initial segment. Thus, targeting the Nav1.6 macromolecular complex represent a promising strategy for modulation of neuronal excitability. Recent studies from our laboratory have revealed that glycogen synthase kinase 3β (GSK3β) binds the Nav1.6 C-terminal tail and phosphorylates the T1938 residue of its C-terminal domain (CTD), indicating that GSK3β regulates the Nav1.6 channel via a dual-function scaffolding and phosphorylation mechanism. Functionally, genetic silencing of GSK3β suppresses Nav1.6-encoded currents, while overexpression produces opposing phenotypes. This evidence suggests that the Nav1.6:GSK3β Protein-Protein Interaction (PPI) interface represents a promising target for alleviation of aberrant hippocampal hyperexcitability.

Hypothesis/Goals: The goals of this study are to identify the critical residues conferring Nav1.6:GSK3β complex formation, optimize a chemical probe identified to inhibit the PPI complex, and evaluate this compound for functional modulation of Nav1.6-mediated hyperexcitability and other disease-related phenotypes in hippocampal neurons. We hypothesize that pathological hippocampal hyperexcitability can be diminished through small-molecule modulation of the Nav1.6:GSK3β PPI complex.

Methods: Split-luciferase complementation assay (LCA), surface plasmon resonance (SPR), whole-cell patch clamp electrophysiology, ex-vivo whole-cell voltage clamp recordings

Results: We have identified a chemical probe that exhibits inhibition of Nav1.6:GSK3β complex assembly in the LCA and appreciable binding to both proteins using SPR. A mutagenesis screen of GSK3β and the Nav1.6 CTD has revealed putative regions of the PPI interface that we predict are critical for conferring the functional effects of our representative ligand. Initial studies have revealed that our compound decreases Nav1.6 channel activity *in vitro* in a manner reminiscent of genetic silencing GSK3β and reduces hippocampal excitability *ex vivo* in a neurodegenerative disease rodent model.

Conclusions: The Nav1.6:GSK3β PPI complex is a key regulatory element contributing to hippocampal excitability, and further elucidation of the molecular determinants of this interaction will guide optimization of our representative ligand for modulation of the Nav1.6:GSK3β complex.

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Poster 5

Interaction of Sex and Stress Hormones on the Neurodegenerative Effects of Binge Alcohol

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Background Binge alcohol exposure causes cell loss and neuroimmune activation, in humans and animal models. Our lab has shown significant cell loss and microglial activation from once-weekly binge exposure in rats, and we are now investigating potential contributions of sex and stress hormones. Circulating gonadal hormones are known to underlie sex-specific outcomes in other types of brain injury, such as stroke, but their contribution to binge-induced damage is not fully understood. Female sex hormones seem to provide protection from brain injury in the case of edema or stroke, but may increase susceptibility to damage under conditions of stress and inflammation. Alcohol is a known stressor that invokes neuroinflammation and activates the Hypothalamic-pituitary-adrenal-axis (HPA) responsible for the body's stress response. Sex hormones organize the HPA-axis during development and differentially modulate stress hormones in adulthood. Estrogens have been shown to present an increased stress response while androgens seem to inhibit the HPA. **Hypothesis/Goals** It is possible that the interaction between sex hormones and the stress hormone cortisol (CORT) from the HPA-axis plays a role in neuronal damage from binge alcohol. We believe androgens may be protective from alcohol exposure while estrogens present a risk factor. **Methods** In the present study, male and female rats were gavaged once weekly for 5 weeks with either 5 g/kg alcohol or isocaloric control solution. To assess the influence of sex hormones, gonadectomy (GDX) or sham surgery was performed in early adulthood prior to binge alcohol exposure. Outcome measures included behavioral intoxication, corticosterone output, hippocampal cell loss and neuroimmune activation. **Results** Preliminary data suggest a role of circulating androgens in protection from binge-induced damage, as binged GDX males had fewer remaining DG neurons than intact binged males. Binged GDX females did not show a difference from binged intact. GDX binged males showed increased behavioral intoxication across binge exposures, whereas intact males showed decreased. These findings suggest circulating androgens buffer the negative effects of repeated binge exposure. Interestingly, our current data shows GDX binged males to have higher CORT levels than intact binged males at week 1, but similar CORT levels week 5. **Conclusions** Overall, our results to date suggest a protective role for androgens in the neurobehavioral effects of repeated binge alcohol exposure. **Acknowledgements** This study was supported by NIAAA R01AA025380.

Poster 6

Alterations in the Mouse Brain Lipidome Induced by Early-life Exposure to Deltamethrin

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Background: Pyrethroid pesticides have been commonly used for the past 30 years due to their low toxicity in adults and favorable safety profile. However, recent studies have found an association between early-life exposure to pyrethroids and neurodevelopmental disorders. One pyrethroid, deltamethrin (DM), may be linked to attention deficit hyperactive disorder (ADHD), as children who have detectable pyrethroid metabolites in urine are twice as likely to be diagnosed with ADHD.

Hypothesis/Goals: Research in animals has shown that exposure to DM alters levels of dopamine transporters, impulsivity, attention, and memory formation, all of which are hallmarks of ADHD in humans and have been associated with dysfunction of the striatal circuit. DM is a highly lipophilic molecule, which can permeate the plasma membrane of neurons. However, the potential consequences of DM accumulation in the brain during development have not been assessed yet.

Results: On this basis, the effect of DM exposure on the lipidome of the striatum was examined using an early-life exposure mouse model in which dams are exposed to the NOAEL dose (1 mg/kg/day) of DM through pregnancy and lactation. Using LC-MS/MS, the lipidomic analysis of the striatum was compared between DM-exposed and control pups at 30- and 60- PN days following cessation of DM exposure at weaning. Exposure to DM through development resulted in alterations in several key lipid species, including ceramides, diacylglycerols (DAG), and triacylglycerols (TAG). Further, it was shown that DM accumulation in the striatum persists following the cessation of DM exposure.

Conclusions: Differences were observed between treated cortex and treated striatum samples. Some of the changing lipid species in treated samples included glycerophospholipids (phosphatidylserines and phosphatidylethanolamines) and glycerolipids. Clear differences were observed in samples where DM was detected. Some of the changing lipid species in these samples included free fatty acids (FFA), monoacylglycerols (MAG), diacylglycerols (DAG), and triacylglycerols (TAG). Additionally, sex-specific differences were observed between treated female and male mice. Taken together, these results indicate potential harmful effects of DM on the brain lipidome that might underlie increased risk for ADHD associated with pyrethroid exposure.

Poster 7

Hold That Thought: Uncovering A Biosignature of Impulsivity

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Abstract: One in 14 individuals in the U.S. report experiencing a substance use disorder (SUD) and use drugs to help cope with stress, trauma, or mental health issues. Memories of the intense reward feelings of being high, anticipation of negative feelings, and impaired impulse control of behaviors combine with drug-associated environmental triggers to increase the urge to use (craving) and vulnerability to relapse. We propose that a loss of inhibitory control, or high impulsivity, may serve as a relapse vulnerability biosignature, a personalized marker used to inform clinical decisions about diagnosis and treatments, for at-risk individuals with SUD. Impulsivity is a complex behavior that is regulated by the medial prefrontal cortex (mPFC), a brain region critical for decision-making and goal-directed behaviors. Neurons in the mPFC are highly structured into bundles which project to the nucleus accumbens (NAc). A misalignment of this architecture can affect the function of the mPFC and its communication with the NAc. In particular, reduced function of the corticoaccumbens circuit may drive high impulsivity. We tested the hypothesis that the density and branching of neurons in the mPFC to NAc circuit is reduced in animals with high trait impulsivity, supporting these neuroanatomical features as a unique marker for disorders characterized by a loss of impulse control.

METHODS: Male, Sprague-Dawley rats were phenotyped using the one choice serial reaction timed (1-CSRT) task, a behavioral measure of impulsive action, as high impulsive (HI) or low impulsive (LI). HI and LI rats then received a bilateral microinfusion of a retrograde virus in the NAc (AAVr2) to trace mPFC to NAc neurons. Immunohistochemical analyses of microtubule associated protein 2 (MAP2), a cytoskeletal marker of dendrites and somas associated with synaptic strengthening was performed. Fluorescent images were taken of brain sections, with respect to 3-dimensional space (z-stacks), in the mPFC and processed to identify properties of dendrites such as length, number of branches, number of dendrites that bundled together, distance between bundles of dendrites and number of spines. Additionally, levels of MAP2 protein in the mPFC of HI rats were quantified using capillary electrophoresis immunoblotting vs LI rats.

RESULTS: HI rats made greater premature responses, a marker of impulsive action, in the 1-CSRT task vs LI rats ($p<0.05$). MAP2 protein levels were lower in HI vs LI rats ($p<0.05$). The density of mPFC dendritic bundles was lower in HI vs LI rats ($p<0.05$). Data analyses of corticoaccumbens projection neurons and spine densities are ongoing.

CONCLUSIONS: Behavioral measures of trait impulsivity associate with reduced bundling of dendritic processes and decreased MAP2 protein. Taken together, underlying neuroanatomical differences in dendritic structure and decreased markers of synaptic strengthening may associate with high trait impulsivity. Our data highlight the necessity for future investigations into cortical structure correlations with impulsive behaviors to further the identification of a SUD relapse vulnerability biosignature.

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Poster 8

Enhancing Associative Learning in Rats with a Computationally Designed Training Protocol

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Background. Associative learning requires the activation of protein kinases with distinct temporal dynamics. Learning protocols with computationally designed intertrial intervals (ITIs) that maximize the interaction between fast-activated protein kinase A (PKA) and slow-activated extracellular signal-regulated kinase (ERK) enhance nonassociative learning in *Aplysia*.

Goals. Here, we examined whether a computationally designed protocol based on PKA and ERK dynamics in rat hippocampus would enhance associative learning in mammals. We simulated ~1000 training protocols with varying ITIs and identified an optimal protocol predicted to induce stronger learning than those with fixed ITIs.

Methods. Male adult Long-Evans rats were exposed to an auditory fear conditioning paradigm where conditioned stimuli (CS, 3 kHz tone, 30 s) co-terminated with unconditioned stimuli (US, footshock, 0.7 mA, 0.5 s). Rats in the full conditioning (FC, n = 14) and partial conditioning (PC, n = 12) groups received 8 or 4 CS-US pairings with fixed ITIs of 4.5 min respectively, whereas rats in the optimal partial conditioning (OPC, n = 14) group received 4 CS-US pairings with ITIs of 8, 8 and 16 min. In a separate experiment, we compared the OPC protocol with an equally spaced partial conditioning (SPC, n = 10) protocol consisting of 4 CS-US pairings with ITIs of 11 min and 10 s.

We also examined whether the optimized ITIs would enhance fear extinction. Conditioned suppression of reward-seeking behavior was used as a measure of fear memory as it is more sensitive than freezing during extinction. Fear conditioned rats were assigned to three groups: full extinction (FE, n = 12) and partial extinction (PE, n = 11) groups received 12 and 4 CS trials with 2.5 min ITIs respectively, whereas the optimal partial extinction (OPE, n = 13) group received 4 CS trials with ITIs of 8, 8 and 16 min.

Results. After conditioning, FC and OPC groups exhibited reduced locomotion speed compared to the PC group, suggesting stronger fear memory retrieval. FC and OPC groups also showed impaired extinction learning characterized by sustained freezing compared to the PC group. In comparison to the SPC group, rats in the OPC group showed stronger fear acquisition and retrieval, suggesting that the memory facilitating effects of the optimal protocol are specific for the irregular intervals and not the training duration.

In addition, when compared to FE and PE groups, the OPE group showed increased lever pressing during the pre-CS periods during both extinction and spontaneous recovery tests, suggesting enhanced extinction of contextual fear memory.

Conclusions. Together, our findings demonstrate enhanced associative learning in mammals with a behavioral protocol designed using a computational model of memory-related signaling pathways.

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Poster 25

Diet-Induced Negative Selection of SCFA-Producing Taxa Among Maternal Gut Microbiota Impairs Descendant Social Behavior

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Abstract.

Background: There is growing consensus behind a two-hit model in which environmental exposures can promote disease in genetically predisposed individuals. Among environmental factors, Western diet is implicated in the growing prevalence of metabolic disorders and obesity, and epidemiological studies likewise identify maternal obesity is a significant risk factor for neurodevelopmental disorders, including autism spectrum disorder (ASD). Specifically, diet-induced disruption, or 'dysbiosis,' of the maternal gut microbiome during pregnancy is associated with long-lasting behavioral alterations in offspring. Previously, we showed that maternal high-fat diet (MHFD), modeling a Western pattern diet, induces gut dysbiosis, social dysfunction, and underlying synaptic plasticity deficits in male offspring (F_1).

Hypothesis: Here, we hypothesized that MHFD would likewise induce dysbiosis in *female* offspring (F_1), thereby recapitulating the adverse *in utero* environment experienced by the F_1 males and resulting social dysfunction in the F_2 generation, even in the absence of a dietary challenge.

Methods: We analyzed social, locomotor, and anxiety-like behavior in 6–8 weeks-old F_2 MRD *vs*. MHFD descendants using a mixed-effects model and nested *t*-tests to account for litter effects. Gut microbiome community structure was determined by 16S rRNA gene amplicon (metataxonomic) sequencing. Briefly, beta diversity was assessed based on both unweighted and weighted UniFrac distances, visualized by principal coordinate analysis (PCoA), and analyzed using permutational multivariate analysis of variance (PERMANOVA). Differentially abundant bacterial taxa were determined by Linear Discriminant Analysis (LDA) Effect Size (LEfSe).

Results: Metataxonomic sequencing revealed a significant reduction in microbial richness among female F_1 MHFD offspring, with a specific decrease in the abundance of short-chain fatty acid (SCFA)-producing taxa. Despite recovery of richness in the F_2 generation, F_2 social behavior remained impaired, implicating dysbiosis of the *maternal* gut microbiome in offspring social deficits. Post-weaning supplementation with *Limosilactobacillus* (*L.*) *reuteri* was sufficient to rescue F_2 generation social deficits. Unexpectedly,

probiotic treatment with *L. reuteri* led to sexually dimorphic remodeling of the host gut microbiome, thus identifying the maternal gut microbiome and its remodeling during pregnancy as promising therapeutic targets for improving long-term neurobehavioral outcomes in descendants. Therefore, we developed a 7-strain probiotic cocktail consisting of immunomodulatory taxa and administered it to control and HFD-fed dams during pregnancy and lactation. Antenatal targeting of the maternal gut microbiome was sufficient to restore neurotypical social behavior in the MHFD-descendant F_1 generation.

Conclusions: Our results link maternal lineage HFD to instability of descendant microbial communities and maladaptive social behavior. Moreover, they highlight the potential for therapeutic targeting of the maternal gut microbiome to improve neurobehavioral outcomes in descendants.

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Poster 9

Neurodevelopmental Changes in Rodent Behaviors Induced by Early-Life Exposure to Deltamethrin

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Background: Pyrethroid pesticides, one of the most common classes of pesticides for agricultural and home use, have been favored in recent years due to their low toxicity in adults. Recent concerns have been raised about an association between increased exposure to pyrethroid pesticides and the occurrence of neurodevelopmental disorders, including attention deficit hyperactivity disorder (ADHD), autism spectrum disorder and developmental delay. For example, children with detectable urinary metabolites of pyrethroids are twice as likely to be diagnosed with ADHD. Animal research indicates that exposure to deltamethrin (DM), a type of pyrethroid pesticide, alters dopamine signaling in the striatum, locomotor activity, impulsivity, attention, and memory, all of which have been associated with neurodevelopmental disorders in humans. However, the impacts of early-life DM exposure during gestation and lactation on additional behaviors have not been well-characterized.

Hypothesis: Based on these data, we sought to characterize behaviors associated with the striatal circuit that are disrupted by early-life exposure to DM, including locomotor activity and habituation to an open field, palatable food neophobia and intake, and activity in an elevated plus maze.

Methods: Pregnant dams were exposed to 3 mg/kg/72 hours DM or vehicle through pregnancy and lactation and the behavior of pups were examined beginning between PND 45-60. Locomotor activity, habituation to an open field, and elevated plus maze activity were recorded and scored using AnyMaze behavioral software. All other behaviors were scored manually by blinded experimenters.

Results: No change in locomotor activity was seen on initial exposure to an open field, however on subsequent days, there was a decrease in the locomotor activity of DM-exposed animals and a decrease in the time spent in the center of the open field, a measure of anxiety-like behavior. However, there was no observed change in the time spent in the open arm of an elevated plus maze. DM-exposed animals also showed a decrease in intake of peanut butter chips, a palatable food, upon initial exposure, indicating a decrease in food neophobia. Intake of palatable food remained increased in DM-exposed animals over an additional two days of testing.

Conclusions: Several behaviors associated with dysfunction of striatal circuitry are disrupted after exposure to DM during development. Taken together, these results may indicate a critical period of vulnerability to the neurotoxic effects of pyrethroid pesticides such as DM and further supports that exposure to DM may be a contributing factor to the occurrence of neurodevelopmental disorders.

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Poster 10

Expanding the Druggable Genome: Pharmacologically Targeting Protein:Protein Interaction Interfaces for Neuropsychopharmacological Probe Development

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Background: Current neuropsychopharmacological agents are associated with delayed therapeutic onset and deleterious side effects, which leads to patience nonadherence. Thus, there is an unmet need to identify novel surfaces that could be targeted to develop improved neuropsychopharmacological agents. Whereas protein:protein interaction (PPI) interfaces have been targeted in oncology to develop anti-neoplastic agents with improved selectivity profiles, they have not yet been explored in the context of central nervous system drug discovery.

Hypothesis/Goals: On account of its profound regulation of the output of medium spiny neurons (MSN) of the nucleus accumbens (NAc), the PPI between the voltage-gated Na^+ (Na_v) channel isoform 1.6 and its auxiliary protein fibroblast growth factor 14 (FGF14) represents a promising surface to target to ameliorate perturbed neuronal activity underlying neuropsychiatric disorders.

Methods: The split-luciferase complementation assay (LCA); surface plasmon resonance (SPR); patch-clamp electrophysiology; *in vivo* single-unit electrophysiological recordings; reward cue task.

Results: To develop probes targeting the FGF14:Na_v1.6 PPI interface, we screened ~45,000 small molecules against the complex using the LCA. This screening, in tandem with a Lipinski's analysis, potency studies, and selectivity studies, identified 4 non-toxic compounds with favorable drug-like properties that had potent and selective effects on the FGF14:Na_v1.6 complex. SPR analyses revealed that the 4 compounds had binding to FGF14 or Na_v1.6. Then, a combination of patch-clamp electrophysiology and molecular docking was used, which revealed that the 4 ligands had conserved effects on Na_v1.6 channel inactivation, effects on MSN firing, and predicted interactions with residues at the FGF14:Na_v1.6 PPI interface with established roles in regulating Na_v1.6 channel inactivation. On account of its superior potency, 1028 was selected as a representative ligand from this class for mechanism of action studies. Consistent with our molecular docking studies and models of Na_v channel inactivation, 1028 was shown to bind to FGF14, modulate FGF14:Na_v1.6 complex assembly, and manipulate Na_v1.6 channel inactivation through a mechanism dependent upon an intact interaction between $FGF14^{R117}$ and the $Na_v1.6^{D1846:R1866}$ salt bridge. *Ex vivo*, 1028 was shown to potentiate MSN firing through a mechanism dependent upon FGF14. Based upon its *in vitro* and *ex vivo* performance, coupled with its determined blood-brain barrier permeability, 1028 was selected for *in vivo* studies. Consistent with our *ex vivo* studies, 1028 was shown to potentiate firing rates of accumbal neurons *in vivo*. At the behavioral level, these electrophysiological changes were found to correlate with sustaining motivation in satiated states.

Conclusions: We show that small molecule modulation of the FGF14:Na_v1.6 complex increases Na_v channel availability through manipulating the interaction between $FGF14^{R117}$ and $Na_v1.6^{D1846:R1866}$, which increases MSN firing and leads to maintenance of motivation in satiated states. Furthermore, our studies demonstrate that PPIs represent tractable targets for the development of an entirely new class of neuropsychopharmaoclogical agents.

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Poster 11

Neural Correlates of Ultrasonic Vocalizations in the Prelimbic Cortex of Rats

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Background: Rodents emit ultrasonic vocalizations (USVs) to establish communications with their conspecifics. In rats, USVs can be divided into two main types: *i)* 22 KHz aversive calls that communicate negative emotional states, and *ii)* 50 KHz appetitive calls that communicate positive emotional states. It has been shown that the emission of aversive vs. appetitive calls by an emitter rat can bidirectionally regulate the behavioral response of a receiver rat. However, which brain regions encode both types of USVs and how different frequencies of vocalization result in opposite behavioral outcomes remains unknown. One candidate region is the prelimbic subregion of the prefrontal cortex (PL), a structure implicated in the regulation of social behaviors and decision-making processes.

Hypothesis: USV valences are encoded by specific areas of the brain and have an effect on rodent behavior.

Methods: To explore whether PL neurons encode USVs of different valences, male Long-Evans rats with single-unit recording electrodes implanted in PL were exposed to pre-recorded aversive and appetitive USV playbacks during the same session. A 22 KHz artificial sound was used as a control stimulus.

Next, to check whether aversive and appetitive USV playbacks can affect animal's behavior, a different group of rats previously trained to press a lever for sucrose during the presentation of a light cue was exposed to the USV playbacks (22 KHz or 50 KHz) or the artificial 22 KHz sound either 10 s before or 10 s during the sucrose cue presentation.

Results: An offline analysis of 474 neurons recorded from 19 rats revealed two subpopulations of PL cells that responded exclusively to either aversive USVs (14.4%, 7.4% excited and 7% inhibited) or appetitive USVs (11.8%, 4.6% excited and 7.2% inhibited), indicating that PL neurons can discriminate appetitive and aversive USVs. Interestingly, ~65% of PL neurons that changed their firing rates in response to 22 KHz USVs did not respond to 22 KHz artificial sound, suggesting that distinct populations of cells in PL encode social calls vs. ordinary sounds of the same frequency.

We found that the presentation of aversive or appetitive USV playbacks did not change cued sucrose-seeking responses. The playback of aversive or appetitive USVs also did not affect cued sucrose-seeking responses in separate groups of rats that had previously observed a conspecific receiving electrical foot shocks or received the foot shocks themselves. Moreover, exposure to USV playbacks did not alter motor activity assessed in an open field arena.

Conclusions: Together, our results establish a role for PL neurons in the discrimination of social cues of different valences, and reveals that the communicative function of distinct USVs may require a richer social context to elicit behavioral changes in the receiver animals.

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Poster 12

Dexamethasone Nanoparticles Treatment Reduces Neuroinflammation Following Traumatic Brain Injury in Mice

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Background: Traumatic Brain Injury (TBI) elicits a robust inflammatory response which causes further neurodegeneration leading to long-term disabilities. Despite improving rehabilitative care, there is a lack of effective neuroprotective treatments for TBI patients. Current delivery mechanisms cannot quickly target inflamed brain areas and deliver the drug efficiently.

Hypothesis/Goals: Dexamethasone (Dex) is a promising anti-inflammatory drug that we pair with liposomal nanoparticles (NPs) to target the brain.

Methods: Dex-NPs were administered to young control C57BL/6 (wild-type, WT) male and female mice after they underwent controlled cortical impact (CCI) injury as a model of TBI. Due to the TBI, the blood-brain barrier (BBB) is already breached, allowing the nanoparticles to cross and accumulate in the brain's vasculature. This accumulation is visualized and quantified via in vivo microscopy imaging.

Results: Our results demonstrate selective targeting of Dex-NPs to the injured brain and decreased astrogliosis, neutrophil infiltration, microglial density, and apoptotic cells compared to vehicle-treated mice.

Conclusions: These results suggest that Dex-NPs represent a promising future theragnostic tool for TBI treatment.

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Poster 13

Individual Differences in LPP Amplitude and Theta Power Predict Cue-induced Eating Behavior

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Background

A body of research has demonstrated that individuals who attribute higher levels of incentive salience to food-associated cues than to pleasant images (C>P group) are more vulnerable to cue-induced eating, or eating in the presence of cues that signal food availability, than those individuals who attribute higher incentive salience to pleasant images than food cues (P>C group). Meanwhile, a separate body of research has demonstrated that cognitive control also regulates eating by enabling top-down attentional control.

Hypothesis & Goals

The present study is aimed at elucidating how both incentive salience and cognitive control act in tandem to regulate cue-induced eating. A central question of this research is: do individuals in the C>P group also show attenuated cognitive control? Considering the animal literature demonstrating that individuals who attribute high incentive salience to reward-associated cues also show attenuated top-down attentional control, I hypothesized that the C>P group would also show attenuated cognitive control relative to the P>C group.

Methods

I analyzed electroencephalogram (EEG) data collected during a controlled cued food delivery task, in which participants viewed images and were dispensed food rewards (candy) and non-food objects (beads, control condition) that they could eat or discard. From these EEG recordings, I calculated the amplitude of the late positive potential (LPP) and power in the theta (θ, 4-8 Hz) frequency band as metrics of affective and cognitive processing, respectively. To identify individual differences in affective and cognitive processing, I conducted two separate K-means ($k = 2$) cluster analyses using LPP and theta power data.

Results

The LPP-based cluster analysis reproduced previous findings: C>P individuals ate significantly more candies during the experiment than P>C individuals (Wald $X^2[1] = 43.1$, $p<0.001$). However, I found no significant differences in theta power between P>C and C>P groups ($F[2, 114] = 0.667$, $p = 0.515$). Meanwhile, the theta-based cluster analysis found that some individuals show higher theta during the candy condition than the bead condition (θCA>θBE), while others show the opposite response pattern (θBE>θCA). Furthermore, the θCA>θBE group ate significantly more during the experiment than the θBE>θCA group (Wald $X^2[1] = 41.5$, $p < 0.001$). Finally, I crossed group assignments from both cluster analyses to create four groups: those with no risk factors (P>C & θBE>θCA group), those with only an LPP risk factor (C>P & θCA>θBE), those with only a theta risk factor (P>C & θCA>θBE), and those with both risk factors (C>P & θCA>θBE). I found that, although individuals with no risk factors ate the least of all four groups (Wald $X^2[3] = 106.2$, $p < 0.001$), the three remaining groups showed similar levels of eating behavior on average (Wald $X^2[2] = 0.825$, $p = 0.662$).

Conclusions

These results indicate that both cognitive and affective brain systems regulate cue-induced eating. However, the finding that P>C and C>P individuals do not show significant differences in theta power suggests that

these mechanisms act independently in humans. Because an individual with an affective vulnerability to cue-induced eating may not also have cognitive deficits, this underscores the need for targeted, individualized treatments for maladaptive behaviors.

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Poster 14

Investigating Voltage-gated Na+ Channels Cell Surface Trafficking via Kinase Activity

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Background: Voltage-gated sodium (Nav) channels are responsible for the initiation and propagation of action potentials in excitable systems such as neurons. In response to changes in membrane potential, Nav channels undergo conformational changes that lead to shifts between resting, activated, and inactivated states. Phosphorylation plays an essential role in regulating Nav channels and excitability. Yet, a surprisingly limited number of kinases have been identified as regulators of Nav channels. In previous studies we showed that glycogen synthase kinase 3 (GSK3), a critical kinase found associated with numerous brain disorders, directly phosphorylates Nav1.2 and Nav1.6 channels producing opposite effects on Na+ current amplitudes. However, whether these changes are associated with corresponding changes in channel cell surface expression is not known. Understanding how regulation of GSK3 confers changes in Nav channel cellular trafficking and neural activity has important implications for unraveling the complex signaling cascades that fine-tune neuronal excitability.

Hypothesis/Goals: The goal of this study was to determine the effect regulating the GSK3 signaling pathway on surface expression of Nav1.6 and Nav1.2 channels. We hypothesize that altering activity of GSK3 by Akt-mediated disinhibition would alter the surface expression of Nav1.6 and Nav1.2 channels.

Methods: Cell surface biotinylation and Western blotting.

Results: Using cell surface biotinylation, we treated HEK-293 cells stably expressing Nav1.6 or Nav1.2 with the Akt inhibitor, triciribine or vehicle; labeled the cells with biotin and performed pulldown of the labeled fraction with neutravidin. Treatment with triciribine led to a statistically significant increase in the surface expression of Nav1.6 and a decrease in surface expression of Nav1.2.

Conclusion: These findings provide evidence for a signaling mechanism by which the Akt/GSK3 pathway modulates Nav channel cell surface expression that might be critical for regulating neuronal activity in several brain disorders associated with dysfunction of Nav channels.

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Poster 15

Computational Insights into the Structural Properties of iFGFs:Nav Channel Complexes

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Background:
Voltage-gated Na+ channels (Na_v) are distributed throughout the body and play an important role in the generation and propagation of action potential. There are nine different alpha subunits of Na_vs (Na_V1.1-Na_v1.9), and mutations in these proteins can cause diseases known as channelopathies.
Among them Na_v1.1, Na_V1.2, Na_v1.6 and Na_v1.7 are of particular importance due to their links to pathologies such as epilepsy, schizophrenia, bipolar disorder and pain. Despite the tremendous progress in the past decades towards understanding the mechanisms regulating the fundamental properties governing channel voltage sensitivity, pore opening, activation, and inactivation, there are still many properties of these channels that are not yet known. Furthermore, because of limited structural information and high homology among Na_v channels subtypes, therapeutic compounds that selectively target individual isoforms remain a major challenge. The potential protein:protein interaction (PPI) interface between the Nav channel C-terminal tail domains (CTD) and the intracellular fibroblast growth factors (iFGFs; FGF11-14) provides a divergent and rich framework for structure-based drug design.

Hypothesis/Goals: The goals of this study were to build homology models for various iFGFs:Na_v channel complexes and to use small molecules, peptides and peptidomimetics to probe for potential structural differences at their PPI interfaces.

Methods: *in silico* drug discovery approaches such as homology modeling, molecular docking, and binding site analyzing studies were used.

Results: Using available crystal structures, we built twelve homology models for Nav1.1, 1.2, 1.5, 1.6 and 1.7 in complex with either FGF14, FGF13 or FGF12. We then evaluated the binding mode actions of various ligands to these homology models using the Schrödinger's GLIDE module. Our findings suggest the presence of critical hydrogen bonds and salt bridges between the CTD of all Nav isoforms and the β-12 strands of iFGFs. Subsequent docking analysis using available ligands revealed structural divergence at these PPI interfaces.

Conclusions: These studies provide computational insights into the structural properties of iFGFs:Nav channel complexes, revealing PPI interfaces that are sufficiently divergent to enable the design of selective ligands for each complex.

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Poster 16

Functional Analysis of Rare Genetic Variants in SATB2 using Drosophila melanogaster

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Background: SATB2-associated syndrome (SAS, a.k.a. Glass syndrome: OMIM #612313) is a rare genetic disorder with around 550 known cases worldwide. This condition is characterized by developmental delay, intellectual disability with severe speech impediment, autistic tendencies, psychiatric disturbances, and craniofacial dysmorphisms with variable expressivity and penetrance. Most cases are caused by rare *de novo* variants in *SATB2*. This gene encodes for an evolutionarily conserved DNA binding protein that regulates chromatin remodeling. In the mammalian central nervous system, SATB2 has been shown to regulate the formation of the cortical layers and the corpus callosum during embryonic and postnatal stages.

Hypothesis/Goals: Because genotype-phenotype relationships in SAS have not been clearly established, we assessed the functional consequences of disease associated variants in *SATB2* using fruit flies.

Methods: By generating transgenic flies that express human *SATB2* under the control of a binary expression (GAL4/UAS) system, we compared the phenotypes induced by tissue-type or cell-type specific ectopic overexpression of reference or variant SATB2 *in vivo*. We selected to study two nonsense (p.R239*and p.R459*) and three missense variants (p.R389C, p.E436V, p.G515S) previously reported in SAS patients. Based on *in vitro* studies, p.R239* was proposed to produce a truncated protein that acts in a dominant negative manner, whereas p.R459* has not been functionally studied. p.R389C and p.G515S are located in the first and second DNA binding CUT domains of SATB2, respectively, and have been reported to have different effects on the mobility of SATB2 within the nucleus. Finally, p.E436V is a recently identified variant found in a unique SAS patient showing neurological symptoms without major dysmorphology.

Results: We found that overexpression of reference and variant human SATB2 in the wing, dorsal thorax, eye, or neurons of *Drosophila melanogaster* permits the classification of disease associated genetic variants into different functional classes. First, p.R239* and p.R459* behaved as strong loss-of-function (LOF) alleles *in vivo*, rather than as dominant negative alleles. Second, p.R389C behaved as a milder LOF allele compared to the nonsense variants. Last, p.E436V and p.G515S behaved as gain-of-function (GOF) alleles.

Conclusions: In conclusion, some *SATB2* variants found in SAS patients that we examined in this study behave as LOF alleles whereas others behave as GOF variants. Understanding the functional consequence of each patient's variant has clinical implications because therapeutic design should be different for patients with LOF variants (e.g., gene therapy) and GOF variants (e.g., antisense oligonucleotide). Using newly generated genetic tools using CRISPR, we are actively analyzing the precise expression pattern and function of the orthologous fly gene in the central and peripheral nervous systems, and further attempting to 'humanize' this gene in *Drosophila*. In addition, we are actively investigating how LOF and GOF of SATB2 alter neuronal and glial function to further understand the role of this gene in the nervous system *in vivo*.

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Poster 17

Automated Detection and Analysis of GFAP-labeled Astrocytes in Micrographs Using YOLOv5

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Background

Astrocytes, a subtype of glial cells with a complex morphological structure, are active players in many aspects of the physiology of the central nervous system (CNS). However, due to their highly involved interaction with other cells in the CNS, made possible by their morphological complexity, the precise mechanisms regulating astrocyte function within the CNS are still poorly understood. This knowledge gap is also due to the current limitations of existing quantitative image analysis tools that are unable to detect and analyze images of astrocyte with sufficient accuracy and efficiency.

Goals

To address this knowledge gap, we introduce a new deep learning framework for the automated detection of GFAP-immunolabeled astrocytes in brightfield or fluorescent micrographs.

Methods

Our novel approach is based on the applications of YOLO, a sophisticated deep learning platform for object detection, that we optimized to derive highly efficient classification models for the task of astrocyte detection.

Results

Extensive numerical experiments using multiple image datasets show that our method performs very competitively against both conventional and state-of-the-art methods, on both images from brightfield and fluorescent microscopy and including the case of images where astrocytes are very dense. In the spirit of reproducible research, our numerical code and annotated data are available open source and freely available to the scientific community.

Conclusions

The ability to automatically detect astrocytes and extract reliable information about their morphology has important practical implications including the development of efficient algorithms for astrocyte analysis and classification that will advance the understanding of the role of astrocytes in the physiology of the CNS and its pathologies.

Acknowledgements

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Poster 18

Greater Exercise Distance is Associated with Better 5-choice Serial Reaction Time Task Performance in Middle Aged Female Rats

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Background. Midlife in women is accompanied by a decrease in circulating ovarian hormones, increasing the risk of cognitive and affective impairments. While interventions such as hormone replacement therapy have been shown to be neuroprotective, they come with a risk for adverse side effects. Exercise has been shown to improve brain health and cognition and as such is a possible intervention. However, there is a lack of research on its efficacy in mid-life females.

Hypothesis/Goals. Voluntary wheel running in young males and hormone replacement therapy in midlife have both independently been associated with improved performance on cognitive tasks. Given past studies, we predicted that midlife VWR would enhance task performance in female rats.

Methods.11-month-old female rats were randomly assigned to two conditions: sedentary (locked wheels, n=16), or exercise (unlocked wheels, n=16). Animals underwent 9 weeks of voluntary wheel running 2h/d, Mon-Fri, before undergoing 10 weeks training and testing in the 5-Choice Serial Reaction Time Task – a choice discrimination task that assesses behavioral control.

Results. Rats in the exercise condition naturally split into two groups: high runners (M=2.39±0.14 km/wk) and low runners (M=1.06±0.15 km/wk). This split was not due to estrous cyclicity as analysis of vaginal cytology showed no relationship between running distance and estrous stage (χ^2 (2)=1.42, p =.49). The effect of exercise on task acquisition (**Figure 1**) was shown to be significant, (H(2)=8.17, p=. 017). A Kruskal-Wallis test showed high runners reaching criterion quicker than both low runners (z=2.52, p=.035) and sedentary rats (z=2.48, p=.039). High runners significantly outperformed sedentary rats in specific tasks. A repeated measures ANOVA revealed interactions between exercise performance and errors of omission made (F(12,156)=1.88, p=.04) and correct response times (F(12,156)=4.10, p<.0001)..

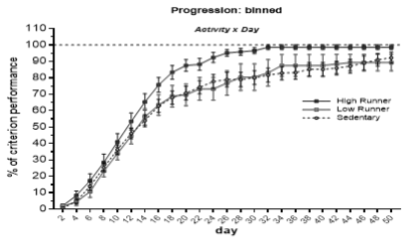

Figure 1. Rate of task acquisition on the 5-Choice Serial Reaction Time Task in middle-aged female rats. Kruskal-Wallis showed high runners reaching criterion faster than both low runners (z=2.52, p=.035) and sedentary rats (z=2.48, p=.039).

Conclusion. Our results provide preclinical evidence for the potential of voluntary exercise as a midlife intervention to promote cognitive performance and brain health in females. Ongoing efforts are assessing neuronal plasticity in the prefrontal cortex, a region of the brain that is a key determinant of 5-CSRTT performance, in order to determine if differences in dendritic morphology are associated with cognitive status.

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Poster 19

A Comprehensive Application for Detection and Treatment Prediction of Alzheimer's Disease

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Background:
Most automated Alzheimer's disease detection systems are found to focus on one of the indications of the disease; however, a comprehensive medical analysis, history, and visuals of the brain are all important indicators of the disease progression and growth. There is a need to not only include the biomarkers with significance but also remove the less related markers, thus making the system efficient. The brain volume change depicted in radiographs, the blood and urine profile, glucose and protein profile, and genetic history are all worthwhile, and we cannot ignore any of these to diagnose the disease manifestation. What often gets bypassed in these systems is the role of monitoring the response of an individual with AD to the medicines and treatment being provided to him/her. An initial detection is not enough. Further, Alzheimer's disease is heterogeneous in nature, manifesting differently in different patients, showing varied symptoms, and often depicting inconsistent responses to medicine from patient to patient. Therefore, continuous monitoring of the outcomes of therapy, medicines, and procedures is what defines the healing path to be followed. In order to fully facilitate the doctors, it is important to keep track of the entire patient journey, starting from the diagnosis to the journey itself. Detection and classification of AD into its types/stages is good to assist the medical officials but not good enough in a sense that they lack the proper and interactive visualization of the results produced by such algorithms, adding an additional overhead for the doctors to go through the imagery and pathological profiles separately, matching them with the system and so on.

Goals:
Our target here is to put forth a system inclusive of all major markers implying the occurrence of disease, severity, visual localization, and response to treatment (for returning patients). This is expected to assist the medical personnel the most. We aim to input all important readings and output the most apprehendable results, evident enough to predict a tailored treatment course per patient for the doctors to verify.

Methodology:
In order to develop this extensive method for Alzheimer's disease detection and assistance in treatment, we propose a *three-step system* with the inclusion of most visual and pathological biomarkers, thorough and explanatory visualization of the results, and a grouping mechanism for tailored treatment for the AD patients. We propose an end-to-end system where an individual's complete medical profile, including his/her genetic background and general medical history, a series of radiological imagery, and their healing associated with treatment (in case of returning patients), will be utilized to learn a machine/deep-learning-based algorithm. The first step will indicate the possible presence of the disease accompanied by proposing the type and stage of the AD occurrence in the patient. This step is hoped to work for all first-time and returning patients and acts as a starting point for the steps to follow. Additionally, the importance of radiological imagery such as MRI, PET-scans, and fMRI maintains itself in this research. A major step of the algorithm is expected to contain an interactive visualization of the results produced by categorizing and identifying the disease. At this step, we hope to input the remarks of the doctors as added input for the next steps.
The last step of the proposed algorithm is expected to group the individuals that respond similarly to several treatments from others. We expect to attain at least three sets of readings, some time apart, associated with the same person for the system to identify the pattern and predict the group he/she belongs to. This is expected to aid the healthcare professionals in their procedures.

Results and Conclusion:
The end product of this research will be an end-to-end system, assisting in diagnosing the disease and predicting tailored treatment for the AD patient for psychologists and psychiatrists. This system is hoped to include most of the important biomarkers and symptoms, process them through and produce some perceivable results for the professionals.

Poster 20

Leung E

Polysubstance use is a common and underrecognized health condition that leads to additional health and psychiatric risks. There have been extensive efforts to characterize the pathways that are altered in individual substance use but understanding the mechanisms and pathways that are altered in polysubstance use has been more limited, particularly in alcohol and opioid co-use. Epidemiological data demonstrate that in this population of polysubstance users, there are far more fatal outcomes due to the hypoxic respiratory failure that comes from the additive and synergistic effects of opioids with alcohol. As such, understanding the neural changes that occur in this subpopulation of users is important to prevent deaths and develop better methods for treating this population. Using postmortem brain samples from individuals with substance misuse disorders (n=29), including alcohol (n=11) and opioid misuse disorder (n=12), or co-use with both disorders (n=6), compared to controls (n=12), we performed proteomic analysis and show that these substances affect both common and different biological pathways compared to controls. Alcohol misuse affects primarily protein translation, rRNA processing, and energy metabolism pathways, while opioid influences G-protein signaling, protein translation, rRNA processing, energy metabolism, and angiogenesis pathways. Alcohol and opioid misuse combined appears to have a synergistic effect on protein expression of the TCA cycle, respiratory transport, mitochondrial function, LGI-ADAM interactions, interleukin signaling, neuronal system changes, and actin polymerization. These findings offer new insights into how substance misuse leads to protein alterations and how combined substance misuse leads to different protein changes compared to single substance misuse.

Poster 21

The Association Between Severe Cases of Gulf War Illness and Suicidal Thoughts and Behaviors Among Gulf War Era Veterans

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Background: About 25% of the 700,000 Gulf War Era veterans deployed to the Persian Gulf theater in 1990-1991 (GWV) remain afflicted with chronic unexplained symptoms, known as Gulf War Illness (GWI) and attributed to neurotoxicant exposures encountered during this deployment. However, not everyone with neurotoxic exposures goes on to develop GWI, which is suggestive that genetic liability likely also plays a role in the pathogenesis of GWI. Additionally, chronic symptoms (e.g., pain and others seen in GWI) have been associated with an increased risk of suicidal thoughts and behaviors (STB). Associations between STB and presumed neurotoxicant damage due to deployment or the chronic symptoms of GWI are plausible and of concern to GWV advocates, but have not been studied.

Hypothesis/Goals: This study examined the association between deployment and presence of severe GWI and STB outcomes (history of suicidal thoughts, history of suicide attempts, and suicidal thoughts in the past 12 months). We hypothesized that, controlling for measured potential confounders, overall, deployment to Persian Gulf in 1990-1991 and severe GWI would be associated with STB and among the deployed GWV subset, severe GWI would be associated with STB.

Methods: A national sample of GWV (N=966) completed a survey of demographic, military, and health information. Logistic regression models assessed bivariate associations between STB, demographic characteristics, combat exposure history, and presence of severe GWI for the entire sample and the deployed (N=385) subset. Multivariate logistic regression models identified the associations between deployment and severe GWI and STB outcomes for the entire sample and the deployed subset controlling for age, race, sex, combat exposure, marital status, income level, and education.

Results: In the adjusted models of the entire cohort, deployment was not associated with any STB outcome. However, severe GWI was associated with a history of suicidal thoughts (p=0.03; OR 1.814; CI 1.225-2.685) and with suicidal thoughts in the past 12 months (p=0.002; OR: 1.967; CI: 1.277-3.030). In the deployed subset, severe GWI was associated with a history of suicidal thoughts (p=0.045; OR 1.778; CI 1.102-3.124).

Conclusions: Our findings suggest that severe GWI is independently associated with two measures of STB among GWV, and, among the deployed, GWI is independently associated with a history of suicidal

thoughts. The burden and negative impact of the chronic symptoms of GWI may play a role in STB. Healthcare team awareness of the presence of severe GWI may be important to identify GWVs at risk of STB and ensure access to effective therapies. Future research should more closely investigate potential gene-by-environment (GxE) interactions between neurotoxicant exposure while deployed and genetic risk in relation to STB.

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Poster 22

C1q Deletion Attenuates Chronic Stress-Induced Glial Activation and Behavioral Deficits in Mice

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Background
Chronic stress and underlying inflammatory changes are the major risk factors for neuropsychiatric disorders including depression. A growing body of evidence suggests an important role of complement system in the development of depressive-like symptoms. In our previous studies, we have observed the role of C3, a central complement component, in neuroinflammation and behavioral deficits under chronic stress conditions. In the present study, we investigated the role of C1q, the initiator of the classical complement pathway, in chronic stress-induced depressive-like behavior and neuroinflammation in mice.

Hypothesis/Goals
We hypothesize that inhibition of classical complement pathway attenuates chronic stress-induced depressive-like behavior and neuroinflammation in mice.

Methods
We used C1q knock-out (C1q KO) mice. chronic unpredictable stress (CUS) model to test our hypothesis. Three-chamber test and the Sucrose preference test were used to study the social behavior and anhedonia-like behavior, respectively. mRNA expression analysis was determined by qRT-PCR. Microglia (M1/M2) and astrocyte (A1/A2) activation status (were determined using specific markers.

Results
We found that the deletion of C1q attenuates CUS-induced depressive-like behavior in mice. Further, chronic stress-induced increases in microglia, as well as astrocyte activation in the pre-frontal cortex (PFC), were attenuated by C1q inhibition.

Conclusions
Our findings show an important role of classical complement pathway in mediating chronic stress-induced neuroinflammation and depressive-like behavior.

Acknowledgments
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Poster 23

Impact of Early Life Exposure to Deltamethrin in Parvalbumin Interneurons of Nucleus Accumbens

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Background: Growing evidence from epidemiological studies identifies early-life exposure to pyrethroids, the largest category of pesticides used in households, schools, and agriculture, as a risk factor for attention-deficit hyperactivity disorder (ADHD), autism spectrum disorders, and anxiety. In support of the epidemiological studies, an animal model of early-life exposure to the pyrethroid pesticide deltamethrin (DM) recapitulates ADHD-like behavior through disruption of neuronal circuitry in the nucleus accumbens (NAc), a brain region within the mesocortical and mesolimbic pathway implicated in the human disease. The cellular and circuit mechanisms underlying the ADHD-like behavior are still not fully clarified.

Hypothesis/Goals: Based on previous evidence showing that DM exerts a toxic effect on the sodium voltage-gated channel $Na_v1.1$ subtype, we hypothesized that parvalbumin (PV) interneurons, a subtype of inhibitory cells controlling the NAc circuit output and expressing the $Na_v1.1$ subtypes, could be a potential target in our mice model of early-life exposure to DM. A disruption on PV firing may cause an increase in risk of neurodevelopmental disorders.

Methods: Acute brain slices, prepared from male mice, were exposed to vehicle or DM throughout gestation and weaning. Whole cell patch-clamp recordings were performed from PV interneurons in the NAc. Taking advantage of PV-TdTomato transgenic mouse line we were able to identify and target PV^+ interneurons. We focused our study on the basic intrinsic biophysical and action potential (AP) firing properties of these PV interneurons.

Results: In both the control and the DM groups, we recorded from a heterogeneous population of PV^+ interneurons which are characterized by variable value of input resistance and distinct firing patterns. Early life exposure to DM appeared to selectively affect a subpopulation of PV^+ interneurons with relatively low input resistance (< 250 MOhm) and with an adapting firing pattern, causing a reduction in their input-output curve dynamic range.

Conclusions: Early-life exposure to DM might alter the computational ability of selected PV^+ interneurons in the NAc by either a cell-autonomous or a network-based mechanism contributing to neuronal circuit phenotypes associated with neurodevelopmental disorders.

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Poster 24

Elucidating the Role of Protocadherin 9 in Synaptic Connectivity

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Background: Loss of synaptic connections between neurons is one of the early events that precede cell death in neurodegenerative diseases. However, the molecular events involved in the loss of synapses are poorly understood. Cell adhesion molecules are key molecules involved in assembling neural circuits, where they play multiple roles at the synapse during development. Although cell adhesion molecules are critical for synapse formation in the developing nervous system, their function in neurodegenerative diseases and mental health disorders is unclear. Protocadherin 9 (Pcdh 9) is a cell adhesion molecule that is a member of the nonclustered Protocadherin family. Pcdh9 is highly expressed in the retina and brain during development and continues to be expressed throughout the adult stages. Disruption of Pcdh9 results in a decrease in the number of synapses within the hippocampus, and defects in neuron morphology in the somatosensory cortex. However, the cellular and molecular mechanisms of how Pcdh9 functions at the synapse during development and degeneration are relatively unknown.

Hypothesis/Goals: Here we use the mouse retina to uncover the function of Pcdh9 at the synapse, with the overall goal of identifying how this cell adhesion molecule is implicated in neurological diseases. We hypothesize that Pcdh9 is an essential cell adhesion molecule required to form and maintain proper synaptic connections in neural circuits.

Methods: To determine the role of Pcdh9 in synaptic connectivity, we generated a floxed allele of Pcdh9 (*Pcdh9*$^{flox/flox}$) as Pcdh9 null mouse mutants are embryonically lethal. We crossed a retinal-specific cre line (*Chx10cre*) to *Pcdh9*$^{flox/flox}$ transgenic animals to generate *Chx10cre; Pcdh9*$^{flox/flox}$ mice. We refer to this cross as Pcdh9 CKO. Retinas were isolated and fixed from Pcdh9 CKO and controls at adult stages (i.e. P30) to evaluate for synaptic defects. Several cell-type specific antibodies and synaptic markers were used to assess retinal defects. Imaris confocal software was used for quantification and GraphPad Prism 9 for statistical analysis.

Results: Loss of Pcdh9 presents several distinct laminations and synaptic connectivity defects in the retina. First, Pcdh9 CKO mice show a decrease or loss of the outer synaptic layer (i.e. OPL) in regions where Pcdh9 protein expression is absent. Second, cone photoreceptors present a misshapen axon terminal or pedicle. Third, the presynaptic marker Bassoon presents sparse protein expression in Pcdh9 CKO compared to controls, indicating a decrease in synaptic transmission. Additionally, disruption of Pcdh9 in bipolar neurons affects the inner synaptic layer (i.e. IPL) and shows synaptic changes between bipolar neurons and amacrine/retinal ganglion cells.

Conclusions: Our preliminary data supports Pcdh9 playing a critical role in synaptic connectivity of retinal circuits. Future experiments will decipher the developmental mechanisms of how Pcdh9 mediates synapse formation as well as the later roles of Pcdh9 in synapse maintenance. The significance of this work is that Pcdh9 may have a conserved function in the brain and may reveal new mechanisms that disrupt synaptic wiring in neurological disorders.

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Poster 26

Agonist Activation of the Schizophrenia Risk Gene GPR52 Results in Antipsychotic Activity and Neuronal Excitation

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Background: GPR52 is an orphan G protein-coupled receptor and recently identified GWAS schizophrenia risk gene. GPR52 is a $G_{s/olf}$-class receptor that activates cAMP signaling and is located primarily in the ventral striatum of the human brain in dopamine D2 medium spiny neurons. This unique brain expression profile of GPR52 suggests the receptor may functionally regulate cAMP signaling to oppose the neural signaling of dopamine D2 receptors. This distinguishes GPR52 as an attractive, druggable target for psychiatric disorders, including schizophrenia and substance use disorders. **Goal:** Here we report our efforts to elucidate GPR52 neuronal signaling and to create and evaluate selective activators for this receptor. **Methods/Results:** In molecular signaling studies, expression of human GPR52 in wildtype HEK293 cells elevated basal cAMP levels by over 100-fold, with further elevation of cAMP in response to the activator PW0787, which was eliminated by stable knockout of $G_{s/olf}$ G proteins using CRISPR/Cas9 genome editing. Medicinal chemistry and pharmacology were used to create novel GPR52 agonists resulting in an optimized agonist PW0787. PW0787 had superior efficacy to increase GPR52 cAMP signaling with good potency (EC50: 135nM), while retaining excellent target selectivity, brain penetrance, and serum concentration. Molecular docking of PW0787 into the GPR52 crystal structure suggested compound binding with extracellular loop 2 (ECL2) and an allosteric mode of action. In a whole cell patch clamp study using mouse brain slices, PW0787 increased the frequency and number of evoked action potentials in D2, but not D1, medium spiny neurons of the nucleus accumbens. Dose-dependent testing of the optimized agonist PW0787 revealed 3 and 10 mg/kg treatments in mice significantly reduced amphetamine-induced hyperlocomotion, indicating antipsychotic-like activity. **Conclusions:** Taken together, these findings indicate the schizophrenia risk gene GPR52, via $G_{s/Golf}$ cAMP signaling, is an excitatory receptor selectively expressed in D2 medium spiny neurons. Our drug discovery effort has resulted in novel GPR52 activators with PW0787 being a potent, selective, orally bioavailable, brain-penetrant agonist that excites D2 medium spiny neurons and shows antipsychotic-like activity. Functional alterations in striatal GPR52 cAMP signaling in D2 neurons may also help explain why GPR52 is a schizophrenia risk gene. These findings further support that GPR52 is a druggable target with therapeutic potential for treating neuropsychiatric disorders.

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Poster 27

Striatal Orphan G Protein Receptors as Therapeutic Targets for Neuropsychiatric Disorders

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Background: The striatum is a subcortical brain region which plays a vital role in dopaminergic circuits involving motor control, decision-making, motivation, and reward. Disrupted striatal function is associated with numerous neurological and psychiatric disorders, including dyskinesia, schizophrenia, substance use disorders, Parkinson's disease, and Huntington's disease. **Goal:** We sought to identify proteins within the striatum that could serve as new druggable targets for the modulation of disrupted dopaminergic circuits. G protein-coupled receptors (GPCRs) are proven druggable proteins and are targeted by ~35% of current FDA approved medications. However, for over 120 GPCRs, considered orphan receptors, no endogenous ligands have been discovered. These orphan receptors are understudied both physiologically and pharmacologically. **Methods/Results:** Using the human RNAseq tissue dataset from the Genotype-Tissue Expression Project (GTex), we identified seven orphan GPCRs with at least 8-fold enriched transcript expression in the caudate, putamen, and nucleus accumbens of the human striatum. We found robust constitutive activity for the excitatory cAMP signaling pathway by three of these receptors (GPR6, GPR52, and GPR101) in the GloSensor cAMP assay. By simply expressing these receptors in HEK293 cells, cAMP levels increased more than 100-fold. We validated G protein signal transduction for GPR6, GPR52, and GPR101 through the G_s/G_{olf} proteins, which was eliminated in GPR52, and nearly eliminated in GPR6 and GPR101 by CRISPR/Cas9 knockout of G_s/G_{olf}. With the Cisbio IP-One assay, we also identified signal transduction by GPR101 through coupling to G_q/G_{11}, which was eliminated by CRISPR/Cas9 knockout of G_q/G_{11}. In striatal neurons, GPR6, GPR52, and GPR101 are co-expressed with the $G_{i/o}$-coupled D2 dopamine receptor (D2R), the site of action for typical antipsychotics. To examine the effects of the observed high levels of constitutive cAMP signaling by GPR6, GPR52, and GPR101 on D2R signaling, each orphan receptor was co-expressed in HEK293 cells with D2R. D2R expression alone produced low cAMP levels comparable to the empty vector control, and treatment with the D2R agonist quinpirole yielded a moderate decrease in cAMP (~3000 light counts/sec). Co-expression of D2R with each of GPR6, GPR52, and GPR101 greatly increased basal cAMP levels, as well as substantially increasing the effect of quinpirole on cAMP signal (decrease of ~200,000-600,000 light counts/sec). Pre-treatment of D2R/GPR52-expressing cells with novel GPR52 agonist PW0787 yielded an even larger decrease of cAMP by quinpirole (~1,500,000 light counts/sec). **Conclusions:** We hypothesize that the high constitutive signaling by GPR6, GPR52, and GPR101 may set the basal tone of cAMP in striatal neurons to allow for more robust, dynamic inhibition of the cAMP signaling cascade by $G_{i/o}$-coupled receptors, such as the D2R. These findings also suggest potential for these orphan receptors as pharmacological targets for modulating D2R-mediated cAMP signaling in the striatum, with therapeutic possibilities for psychosis, substance use disorders, and motoric diseases.

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Poster 28

Microglia and Macrophage Gene Editing via CRISPR-Cas9 using Nanoparticles Reduces Inflammation After Traumatic Brain Injury in Mice

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Background: Traumatic brain injury (TBI) is a health problem that affects 6 million people in the USA each year who suffer short and long-term disabilities. One of the first physiological and cellular events after brain damage is *inflammatory-driven progressive neurodegeneration*. The major players in this process are the brain resident immune microglia/macrophage cells (MG/Ma). One of the limitations of pharmacological drugs is the slight effectiveness in reaching the injured brain. Lipid Nanoparticles (LNP) have been used in multiple diseases with remarkable success due to their rapid diffusion and small containers targeting specific cell types and locally delivering drugs. We will design and optimize a circulating LNP with the CRISPR editing system (CRISPR-LNP) targeting MAPK9/SOCS3 signaling synthetic lipids to polarize the resident MG/Ma anti-inflammatory properties.
Hypothesis/Goals: We will test the *hypothesis* that CRISPR-LNP is an affinity to bind MG/Ma using Iba-1 conjugated antibody and effectively reduce the inflammatory and degenerative processes after TBI. In this proposal, our goal is to investigate the best formulation of CRISPR-LNP to reach the injured brain by intravenous or intranasal routes of administration. We suggest that the LNP will have high effectiveness and be considered a potential candidate for TBI therapies.
Methods: Here, we create Iba-1Ab-CRISPR-LNP as a tool to directly assess inflamed regions in a TBI model using an adult male C57BL/6J mice. We also evaluated the delivery efficacy of CRISPR-LNP targeting MG/Ma using two routes of administration in a mouse model of TBI. The CRISPR-LNP was visualized using an advanced *in the vivo* imaging system (IVIS), immunofluorescence analysis, and immunohistochemical staining with *in situ* hybridization.
Results: We identified and planned to target mitogen-activated protein kinase 9 (MAPK9/JNK2) signaling and suppress cytokine signaling 3 (Socs3) to reverse MG/Ma polarization after TBI in *vivo*. We optimized the size, synthesis, biocompatibility, and stability of the CRISPR-LNP. Intranasal administration of Iba-1Ab-CRISPR-LNP produces greater specificity in binding compared to systemic administration. IVIS indicates that systemic administration led to a more significant accumulation of LNPs in the injured cortex. We found that Iba-1 shows decreased hypertrophic MG/Ma morphology in CRISPR-treated brains, indicating that the treatment reduces the MG/Ma activation. We also found a decrease in the number of pro-inflammatory cytokines (IL-1β and TNFα) and TUNEL-positive cells following CRISPR-LNP treatment compared with the vehicle group after 1day post-TBI.
Conclusions: Our results show that the Iba-1Ab-CRISPR-LNP reduces the MG/Ma activation and cell death after TBI. This work lays the foundation for developing a specific transformational therapeutic approach for TBI patients.
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Poster 29

Deciphering the Cellular and Molecular Mechanisms of Neural Circuit Assembly in the Developing Retina

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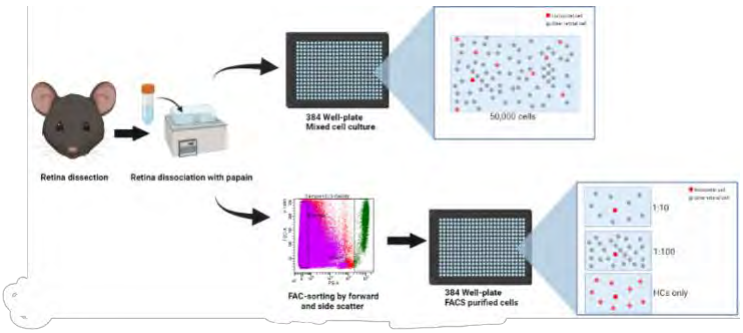
Background Defects in neural circuit formation and synaptogenesis have been implicated in many psychiatric disorders, yet the developmental etiology that leads to aberrant circuitry remains poorly understood. During development, different neuron subtypes come together to form precise synaptic connections to their respective partners. Subcellular specificity refers to the process of how a single neuron synapses to two distinct targets via different subcellular domains (i.e. dendrites and axon). Although subcellular specificity is widely seen throughout the nervous system, the developmental mechanism that guides this process is unclear. The mouse retina is an excellent system to study the molecular basis of subcellular specificity. Within the outer retina, horizontal cells synapse selectively to the different types of photoreceptors via distinct subcellular domains. The dendrites of horizontal cells synapse to cone photoreceptors, whereas the axon synapses to rod photoreceptors.



Hypothesis/Goals Our work will begin to elucidate the cellular and molecular mechanisms of subcellular specificity in the outer retina, with the overall goal of understanding how this process is achieved in other regions of the developing nervous system.

Methods To study this question, we developed an *in vitro* system coupled with live imaging to track the dynamic cellular interactions between horizontal cells and their corresponding photoreceptor partners.

Results Our preliminary data shows that horizontal cells extend long, complex processes when cultured with other cell types similar to what is seen *in vivo*. Moreover, horizontal cells that have been isolated via FACs and co-cultured with other cell types also display a similar complex morphology. Surprisingly, isolated horizontal cells that are cultured alone lacking the other cell types do not extend neuronal processes even after two days in culture.

Conclusions These initial findings lead us to propose that there must be signaling mechanisms between horizontal cells and other cell types that instruct the outgrowth and selective wiring of horizontal cells to their appropriate synaptic target during development. Future work will focus on identifying these cellular mechanisms by co-culturing horizontal cells with rod and cone photoreceptors using different transgenic mouse lines. In addition, we will perform a biased and unbiased molecular screen to identify novel signaling pathways involved in cell-cell interactions between horizontal cells and the different types of photoreceptors. Overall, our work will elucidate new mechanisms involved in subcellular specificity and neural circuit formation which may provide clues to explain the aberrant circuitry seen in patients with psychiatric disorders.

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Poster 30

C3ar1 Signaling in Anxiety-like Behavior

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Background
Behavior changes in anxiety disorders are linked with immune system activation. However, it is still unclear how the innate immune system affects anxiety. The complement system is a part of the innate immune system that has three defined pathways that culminate in complement component 3 (C3) being cleaved into C3a and C3b. C3a modulates immune signals via C3a receptor 1 (C3ar1). C3ar1 knockout (KO) mice exhibit increased anxiety-like behavior. However, the cellular mechanisms by which C3ar1 regulates anxiety-like behavior is not known.

Hypothesis/Goals
C3ar1 signaling through neurons promotes anxiety-like behavior in mice.

Methods
To address the cell-specific roles of C3ar1 in mediating anxiety-like behavior, we used C3ar1 conditional knock-out mice to restrict the C3ar1 function in microglia, macrophages, and neurons. Anxiety-like behavior was measured using validated tests, including, elevated plus maze, open field test, and light/dark test. These tests use the innate rodent tendency to explore new areas and fear of exposed areas. Flow cytometry analysis was performed to confirm C3ar1 expression on microglia, peripheral macrophages, and neurons.

Results
Flow cytometry analysis confirmed the expression of C3ar1 on neurons, microglia, and peripheral macrophages. In the open field test, mice lacking C3ar1 expression on microglia performed the same as wild-type mice. Similar results were seen in the elevated plus maze and light/dark test with mice lacking C3ar1 expression on peripheral macrophages.

Conclusions
Mice that lack C3ar1 in microglia and peripheral macrophages do not show anxiety-like behavior. A number of studies show that immune molecules can regulate neuronal activity by signaling through their receptors expressed in neurons. Our ongoing studies are exploring the role of neuronal C3ar1 in anxiety-like behavior.

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Poster 31

FGF13 Ligands Bidirectionally Modulate Nociceptive Behavior by Selectively Fine Tuning Nav1.7 Channels

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Background: The voltage-gated Na^+ (Nav) channel Nav1.7 is a molecular determinant of action potential firing of dorsal root ganglia (DRG) sensory neurons. Despite the canonical role of the pore-forming α subunit in conferring this function, protein:protein interactions (PPI) between the α subunit and its auxiliary proteins are necessary for the full physiological function of the Nav1.7 channel. Among such auxiliary proteins, fibroblast growth factor 13 (FGF13) is of particular prominence, and its PPI with the C-terminal domain of the Nav1.7 channel regulates conversion of noxious stimuli into persistent DRG firing and consequently pain sensation.

Hypothesis/Goals: We hypothesize that pharmacological targeting of FGF13 could either mitigate or enhance nociceptive behavior by bidirectionally regulating Nav1.7 channels.

Results: We employ a peptidomimetic derived from the PLEV motif of the β12 sheet of FGF13 (PW164) and show that the ligand inhibits FGF13:Nav1.7 complex assembly. Functionally, PW164 prevents FGF13-mediated potentiation of Nav1.7 currents, reduces channel availability in heterologous cells and human DRG neurons, and suppresses firing in donor-derived DRG neurons. In preclinical pain models associated with hyperactivity of Nav1.7 channels, intradermal injection of PW164 prevents capsaicin-induced mechanical and thermal hypersensitivity at the level of nociceptive behavior without affecting normal mechano- and thermal sensitivity. Genetic silencing of FGF13 in human DRG neurons or through intrathecal injection of AAV-shRNA-FGF13 selectively blocks hyperactivity of Nav1.7 channels and nociceptive behavior in mouse pain models, respectively. Furthermore, silencing FGF13 prevents any further inhibitory activity of PW164 in both human DRG neurons and mouse pain models. Conversely, an FGF13 ligand shown to stabilize FGF13:Nav1.7 complex assembly (ZL192) induces hyperactivity of Nav1.7 channels in human DRG neurons and nociceptive behavior in mice in the absence of noxious stimuli. Genetic silencing of FGF13 prevents ZL192 activity in both human DRG neurons and mice.

Conclusions: These studies demonstrate that FGF13 is a tunable target that confers protection against nociceptive behavior through direct binding to Nav1.7 channels. Thus, FGF13 ligands provide novel tools to probe for molecular events triggering pain sensation and to guide future drug discovery efforts for pain management.

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Poster 32

Restoring the Gut Microbiota of Alzheimer's Disease Mice May Facilitate Recovery from Brain Injury

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Background: Traumatic brain injury (TBI) is one of the largest risk factors for the later development of neurodegenerative diseases such as Alzheimer's disease (AD). Gut microbiota dysbiosis has been linked to numerous neurological disorders, including both TBI and AD. In a recent publication, we found that gut microbiota from AD mice aggravated the neuroinflammatory response and neurological outcomes after TBI in young wild-type (WT) controls. Specifically, WT mice exhibited larger lesion, increased activated microglia/macrophages, and reduced motor recovery after receiving a fecal microbiota transplantation (FMT) from aged AD mice compared to the recipients of an FMT from young controls.

Hypothesis/Goals: Given the detrimental effect of AD gut microbiota following TBI, we hypothesize that restoration of the AD microbiome to a healthy state could improve the neuropathological consequences of brain injury. Therefore, the aim of this study was to characterize the effect of an FMT from WT mice administered to aged AD mice after TBI.

Methods: Eight- to nine-month-old 5XFAD transgenic males and females, and their WT littermates, underwent a controlled cortical injury (CCI) as model of TBI. Prior to the surgeries, all mice received a gut microbiota depletion treatment consisting of an antibiotic cocktail delivered by oral gavage for three days. We prepared FMTs from the cecum of 2- to 3-month-old C57BL/6 wild-type mice that were administered orally 24 hours after injury. We characterized the microbiota composition of fecal samples collected at baseline, after the antibiotic regimen, and at 1-, 3- and 11-days post-injury.

Results: 16S rRNA gene sequencing analysis revealed changes in the gut bacteria community induced by the microbiome depletion and the FMT treatment. As expected, the 5XFAD mouse model showed a significant increase in inflammatory brain response at 3 days post injury. However, there was no major effect of the FMT treatment on lesion volume or neuroinflammatory markers after CCI in the 5XFAD mice. Similarly, the 5XFAD mice that received FMTs showed no differences in the motor recovery following TBI, or in the memory and anxiety-like behaviors.

Conclusions: In summary, microbiota depletion followed by a single FMT at 24h post-TBI could not limit the neuropathology associated to brain injury in 5XFAD mice, and future studies will focus on testing alternative approaches of microbiota restoration.

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Poster 33

Role of Mitochondrial DNA in CD4+ T Cell-Mediated Neuroinflammation and Behavioral Deficits Under Chronic Stress Conditions

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Background: Chronic stress is a major risk factor for many neuropsychiatric conditions and is known to induce inflammation and behavior deficits. Prior studies have focused on the role innate immune system in chronic stress-induced behavioral abnormalities, however, the mechanisms that link adaptive immunity to behavioral changes are not well understood. T cells (also called T lymphocytes) are major components of the adaptive immune system and have been shown to regulate social behavior. Mitochondria are the powerhouse of the cell, when compromised release cell-free mitochondrial DNA (cf-mtDNA) in circulation, which trigger inflammation. In the present study we sought to determine the role of mtDNA in chronic stress-induced neuroinflammation and behavior deficits. **Hypothesis:** We hypothesize that cf-mtDNA released from T cells mediate chronic stress-induced neuroinflammation and social behavior deficits. **Method:** To test our hypothesis, we conducted experiments using ICR mice, mitochondrial antiviral signaling protein (MAVS) knock out (KO), and stimulator of interferon genes (STING) KO mice. We used the chronic restraint stress (RS) mouse model to examine the effects of chronic stress on neurobehavior. Deoxyribonuclease (DNase) I was injected intraperitoneally (i.p.) for systemic reduction of cf-mtDNA in mice. To investigate subpopulation of T lymphocytes, we depleted CD4+ or CD8+ T cells by i.p. injection with neutralizing antibodies. Three-chamber and reciprocal interaction tests were performed to study social behavior. Flow cytometry for monocyte infiltration and qRT-PCR for cytokine measurements were conducted in our experiments. Data were analyzed using two-tailed Student's t-tests (for two-group comparisons) or Analysis of Variance (ANOVA; for multiple-group comparisons). $p < 0.05$ was considered significant. Bonferroni's posthoc test was performed within the comparison. **Results:** Our findings show that RS significantly increased serum cf-mtDNA levels and social behavior deficits. Peripheral reduction of cf-mtDNA attenuated the RS-induced inflammation and behavioral deficits. Antibody-mediated depletion of CD4 + T cells significantly attenuated RS-induced increases in cf-mtDNA and social behavior deficits in mice. MAVS and STING deletion attenuated chronic stress-induced social behavior deficits in mice. **Conclusion:** Our findings show the role of CD4+ T cells in stress-induced increases in cf-mtDNA levels and social behavior deficits. Also, our results found a role of STING in mediating these effects. These results suggest that STING pathway represents a promising therapeutic option especially for patients with an elevated immune profile as seen in many depressed subjects. **Acknowledgements:** The authors acknowledge the funding support from US National Institute of Health/ National Institute of Mental Health (NIMH) grants (MH120876 and MH121959), and the Merit Review Award (BX004758) from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development to AP. The contents do not represent the views of the Department of Veterans Affairs or the United States Government. AP acknowledges the funding support from Louis A Faillace Endowed Chair in Psychiatry.

Poster 34

Prelimbic Cortex Neurons Encode Changes in Cued Food-seeking Behavior Under Distinct Internal States

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Background: Flexibly adjusting foraging behavior based on internal metabolic needs and environmental threats is crucial for animal survival. However, the neural mechanisms underlying the transition in cued food-seeking behaviors under distinct metabolic and threat states remain unclear.
Hypothesis/Goals: Neurons in the prelimbic (PL) subregion of the medial prefrontal cortex change their activity in response to food-associated cues. We therefore hypothesize that PL neurons adjust their responses to food cues according to animals' metabolic states (hungry vs. satiated) or threat states (safe vs. threatened).
Methods: We used a miniature fluorescent microscope to record calcium transients in freely behaving rats (n = 548 neurons, 6 rats). Adult male Long-Evans rats were initially trained to press a lever for sucrose upon the presentation of an audiovisual cue. During the metabolic state test, rats were presented with 12 food cues followed by a 50 min sucrose *ad libitum* period to induce satiation, and subsequently exposed to 12 additional food cues. During the threat state test, rats were presented with12 food cues in a safe arena followed by a 10 min period of predator odor (cat saliva) exposure to induce fear, and subsequently presented with 12 additional food cues.
Results: Rats showed a reduction in food seeking from hungry to satiated states, as well as from safe to threatened states. After aligning the calcium transients of all PL neurons to the onset of the food cues, we observed no differences in the averaged PL activity under hungry vs. satiated states but a significant increase from safe to threatened states, suggesting that PL neurons are preferentially recruited during more salient internal states. In contrast, the number of food-cue responsive neurons and the magnitude of their responses remained the same across the distinct states. Interestingly, tracking the activity of the same cells across the session revealed that different PL neurons respond to food cues during distinct internal states. PL neurons showing excitatory or inhibitory responses to food cues when rats were in the hungry or safe states exhibited an overall reduction in their responses during the satiated or threatened states. In parallel, when rats transitioned to satiated or threatened states, separate groups of non-responsive cells emerged to display either excitatory or inhibitory responses to food cues.
Conclusions: Taken together, our results suggest that the recruitment of distinct PL neuron subpopulations when animals transition between metabolic or threat states may serve to adjust behavioral responses to environmental food cues. Our findings may help to understand maladaptive food-seeking behavior in patients with eating- and anxiety-related disorders.
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