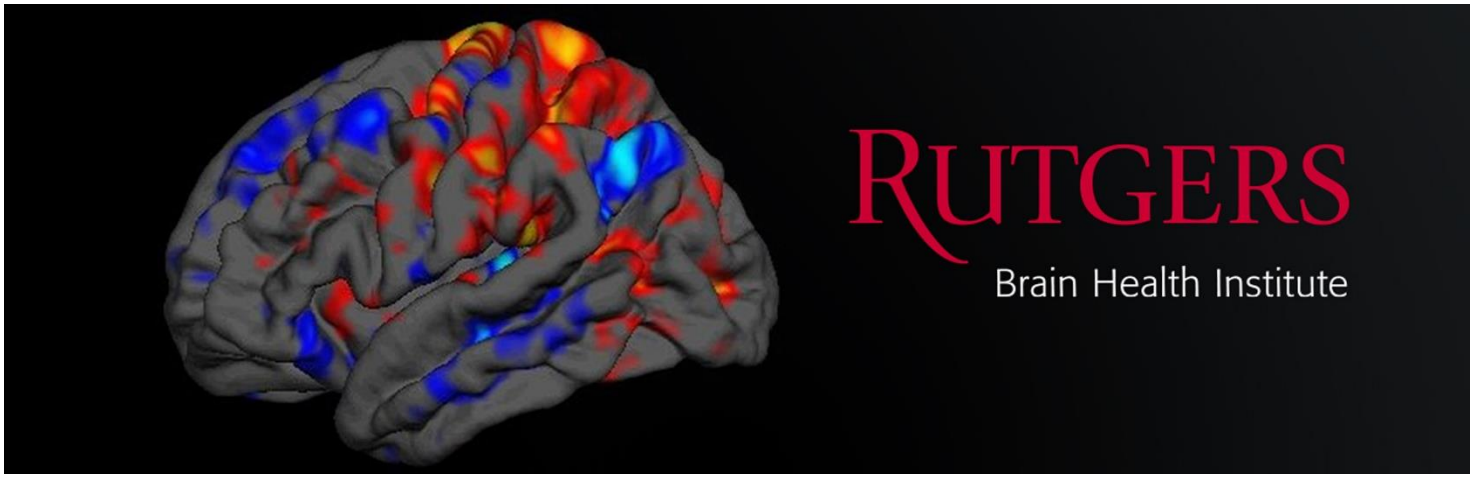
Ninth Annual Rutgers Brain Health Institute Symposium

Thursday, November 30th, 2023

Trayes Hall, Douglass Student Center
New Brunswick, NJ 08901

8.00 AM – 8.30 AM	Registration, Breakfast and Welcome
8.30 AM – 9.00 AM	***Dr. Gary Aston-Jones (Director, Brain Health Institute)*** *"BHI overview & updates"*
9.00 AM – 9.10 AM	***Dr. Avram Holmes (RH-RWJMS/BHI-Psychiatry)*** *"The cellular underpinnings of the human cortical connectome"*
9.15 AM –9.25 AM	***Dr. Nima Toosizadeh (RH-SHP/BHI-Rehab. & Movement Science)*** *"Screening cognitive decline: multiscale entropy analysis during dual tasking using functional near infrared spectroscopy"*
9.30 AM – 9.40 AM	***Dr. Noelle Stiles (RH-RWJMS/BHI-Neurology)*** *"Restoring sight to the blind: effects of plasticity and multimodality"*
9.45 AM – 9.55 AM	***Dr. Ying Xu (RH-NJMS/BHI-Anesthesiology)*** *"Mitochondrial phosphodiesterase 2A dysregulation in post-traumatic brain injury induced Alzheimer's disease"*
10.00 AM – 10.10 AM	***Dr. Tejbeer Kaur (RH-RWJMS/BHI-Otolaryngology)*** *"Macrophages as cobblers of the synapses: restoring lost cochlear ribbon synapses and hearing in noise-induced hidden hearing loss"*
10.15 AM – 10.25 AM	***Dr. Linden Parkes (RH-RWJMS/BHI-Psychiatry)*** *"Spatially embedded network models of the brain"*

10.30 AM – 10.45 AM	Refreshment Break
10.45 AM – 10.55 AM	***Dr. Soha Saleh (RH-SHP/BHI-Rehab. & Movement Science)*** *"Unlocking the potential of mobile neuroimaging: advantages and applications in motor function and brain connectivity studies"*
11.00 AM – 11.10 AM	***Dr. Andrew Westbrook (RH-RWJMS/BHI-Psychiatry)*** *"What criticality tells us about brain maturation, excitation-inhibition balance, and cognitive effort"*
11.15 AM – 12.15 PM	**Keynote:** ***Dr. Michael N Shadlen, Professor of Neuroscience at Columbia University Medical School.*** *"Neural signals underlying choice and response time on a single decision."*
12.30 PM – 2.00 PM	Buffet Lunch & *"Brainstorming for Brain Health"*
2.00 PM – 2.25 PM	***Dr. Michal Beeri (RH-RWJMS/BHI-Neurology)*** *"Site-specific glycoproteomic modifications are associated with cognitive decline in older adults with type 2 diabetes"*
2.30 PM – 3.10 PM	***Dr. Rey Panettieri & Nancy Reilly, RN, MS (RH-RWJMS/RTIMS-Medicine/Clinical Trials Office)*** *How can the New Jersey Alliance for Clinical and Translational Science (NJ ACTS) transform clinical research across our ecosystem?*
3.15 PM – 3.45 PM	***Dr. Maria Chiara Manzini & BHI Strategic Planning Committee*** *"Brainstorming for Brain Health: Outcomes & Next Steps"*
3.45 PM – 5.15 PM	Post-doc and Student Poster Session (*at the NJC Lounge in the Douglass Student Center*)
5.00 PM – 5.45 PM	Wine & Cheese Reception and Poster Awards (*back in Trayes Hall*)



Mission: The Rutgers Brain Health Institute (BHI) was established to become an internationally recognized center for basic, translational, and clinical research into the biological bases of human brain function and dysfunction. Its mission is to support and coordinate neuroscience across all campuses and unite Rutgers dynamic and diverse neuroscience community toward common goals:

- To create research programs focused on the biological underpinnings of the central nervous system's function and dysfunction.
- To develop treatments for these disorders using novel neuroscience tools.
- To establish a rich neuroscience resource in New Jersey that educates the public, clinicians, faculty, and students, as well as state, national, and international health officials.

Vision: BHI will develop neuroscience at Rutgers to become a highly translational and internationally preeminent research enterprise, to advance new treatments for debilitating nervous system disorders. This vision will be achieved by integrating cutting-edge basic and clinical research, recruiting new faculty with expertise in key focus areas, providing a state-of-the-art infrastructure, and enhancing scientific collaborations across Rutgers and neighboring institutions.

Current Overview and Focus Areas:

- ***Neurodevelopment*** (e.g., autism spectrum disorder, schizophrenia, Tourette's);
- ***Neurodegeneration and Injury*** (e.g., Alzheimer's disease, multiple sclerosis, Parkinson's disease, spinal cord and traumatic brain injury);
- ***Cognitive and Sensory Neuroscience*** (e.g., age-related dementias, pain, auditory disorders);
- ***Motivational and Affective Neuroscience*** (e.g., addiction, eating disorders, obesity, depression, anxiety).

BHI Centers:

The Rutgers University Center for Autism Research, Education and Services (RUCARES):

The new center was created by BHI in 2020 and is responsible for coordinating and fostering basic and clinical research at Rutgers focused on diagnosing, treating, and supporting patients with autism spectrum disorder (ASD). The goal is to develop a world-class autism research center engaged in cutting-edge basic research to identify mechanisms and biomarkers, developing novel interventional behavioral therapies, creating new technologies and services to support both pediatric and adult ASD patient population. BHI partnered with Children's Specialized Hospital (CSH) to form CSH-RUCARES focused on treating autistic children with severe behavior disorders. RUCARES and CSH-RUCARES are directed by Dr. Wayne Fisher, Henry Rutgers Endowed Professor of Pediatrics. RUCARES is the first autism center of its kind in New Jersey dedicated to innovative research, education, and services. The programs focus on diagnosing, treating, and supporting children and adults with ASD. This broad-ranging initiative provides the opportunity for multidisciplinary researchers to partner on care and research for those with ASD with significantly challenging behaviors throughout their lifespan.

Rutgers Alzheimer's Disease Research Center (RUADRC):

RUADRC was originally started by BHI in 2017 with the recruitment of Dr. Luciano D'Adamio, Krieger Klein Endowed Chair and Professor of Pharmacology, Physiology & Neuroscience at NJMS, spearheading basic and translational research into Alzheimer's disease. In 2023, Dr. Michal Beeri, was recruited by BHI as the Krieger Klein Endowed Chair and Professor of Neurology at RWJMS, and the Director of the Herbert and Jacqueline Krieger Klein Alzheimer's Research Center. The new center will conduct observational studies, host clinical trials with the intent of testing new medications and interventions to change the course of Alzheimer's disease and related disorders (ADRD). The center is committed to translational research and will foster collaborations to facilitate a bidirectional flow of research findings, from clinical observational studies in humans to basic science research in various disease models to unravel mechanisms underlying Alzheimer's. The center will serve as a hub for collaboration, innovation, and transformative research, with the mission of making meaningful strides in the prevention, diagnosis, and care of ADRD.

The Rutgers Addiction Research Center (RARC):

The RARC at BHI is a new center launched in 2022 developed to help build collaborations among scientists with the multidisciplinary expertise required to advance our understanding of the causes of opioid addiction and other addictive and substance use disorders. Housed within the BHI, RARC is directed by Dr. Danielle Dick, Greg Brown Endowed Chair and Professor of Psychiatry. The center is composed of faculty and trainees across all Rutgers schools and campuses with expertise in addiction prevention, research, treatment, education, and public policy. These include faculty and trainees from RWJMS, NJMS, School of Arts and Sciences, Center for Alcohol Studies, Center for Tobacco Studies, School of Public Health, School of Social Work, School of Nursing, University Behavioral Health Care, School of Pharmacy, and the Institute for Health, Health Care Policy, and Aging Research. RARC is the only comprehensive addiction center in NJ with the capacity to impact the addiction epidemic through the diverse strengths of its members.

The Rutgers-Princeton Computational Cognitive Neuropsychiatry Center (CCNP):

The CCNP was formed by BHI in 2016 to leverage the computational neuropsychiatry expertise in Princeton's Department of Psychology and Neuroscience Institute, and in Rutgers' Departments of Psychology, Psychiatry and Computer Science, Rutgers University Behavioral Health Care, Robert Wood Johnson Hospital, and the BHI, in a major collaborative initiative. The center with its human behavior testing facility is housed in the Research Tower on the Rutgers Busch campus in Piscataway, is co-directed by Dr. Anna Konova from Rutgers (RWJMS/Psychiatry/UBHC) and Dr. Yael Niv from Princeton University.

The Rutgers Center for Advanced Human Brain Imaging Research (CAHBIR):

To fill a critical infrastructure gap, BHI developed CAHBIR a new human brain imaging center located in the Staged Research Building on Busch campus in Piscataway. The center opened July 2021, and houses a state-of-the-art 3T Siemens Prisma MRI that is dedicated for human brain imaging research purposes. The core facility, which now includes equipment for EEG and TMS, is available for use to neuroscientists from across Rutgers and neighboring institutions. The center is directed by Dr. David Zald, Henry Rutgers Term Chair and Professor of Psychiatry in RWJMS. CAHBIR is fully staffed to support the human brain imaging needs of new and experienced users.

BHI is led by Director, Dr. Gary Aston-Jones, PhD, Distinguished Professor of Psychiatry and Strongwater Endowed Chair. BHI staff include- Dr. Eldo Kuzhikandathil, PhD, Executive Director of Administration, Andre Foster, Grant Administrator, Louise Petrone, Program Coordinator, Rose Smith, Business Liaison, Serena Claiborne, Business Liaison, Tongyue (Lily) Zhang, Program Coordinator of Marketing & Communications, and Andrea Dzioba, Secretary.

SPEAKER ABSTRACTS

Keynote Speaker

Michael N. Shadlen, MD, PhD
Professor
Department of Neuroscience
Zuckerman Mind Brain Behavior Institute
Kavli Institute of Brain Science
Howard Hughes Medical Institute
Columbia University

"Neural signals underlying choice and response time on a single decision"

A common framework, termed bounded evidence accumulation, or bounded drift-diffusion, accounts for the speed, accuracy, and confidence of many perceptual decisions. Up to now, however, the drift-diffusion signal has eluded direct observation. Recent advances in high density neural recording allow us to measure the stochastic drift-diffusion signal giving rise to a single decision. The technology also facilitates simultaneous recording from populations of functionally related neurons in the parietal cortex and the superior colliculus—two strongly connected nodes of the decision macro-circuit. I will contrast the drift-diffusion dynamics in LIP with single-trial dynamics of neurons in the superior colliculus (SC). The burst like dynamics of SC neurons suggest they do not participate in a distributed computation but instead play a distinct role in terminating the decision process. We confirm this hypothesis by focal inactivation of the SC while recording in area LIP. The findings highlight the promise of high-density neural recordings, but I will also share concerns about potential pitfalls, namely, the false allure of high dimensional neural representation.

Dr. Michael Shadlen is an Investigator of the Howard Hughes Medical Research Institute and Professor of Neuroscience at Columbia University Medical School. He is a member of the Mortimer B. Zuckerman Mind Brain Behavior Institute (ZI) and the Kavli Institute of Brain Science. Dr. Shadlen obtained his undergraduate and medical degrees at Brown University, his PhD at UC Berkeley with Ralph Freeman. Dr. Shadlen completed his residency at Stanford University School of Medicine where he was Chief Resident. He pursued neuroscience as a postdoctoral researcher at Stanford in the lab of William Newsome before joining the faculty of the Department of Physiology and Biophysics at the University of Washington. He became a Howard Hughes Medical Investigator in 2000 and joined Columbia University in 2012 as Professor of Neuroscience. His research focuses primarily on the neural mechanisms that underlie decision making.

Dr. Shadlen was elected a Member of the National Academy of Medicine in 2014, a Fellow of the American Association for the Advancement of Science in 2015 and a Member of the National Academy of Sciences in 2023. Other awards and honors include- McKnight Scholar Award, Swartz foundation Mind-Brain Lecture, Alden Spencer Prize, Golden Brain Award of the Minerva Foundation, Fellow of Association for Psychological Science, Karl Spencer Lashley Award from the American Philosophical Society. He is also a jazz guitarist and co-curates the Jazz Artist in Residence program at the Columbia Zuckerman Institute.

Avram Holmes, PhD

Associate Professor
Department of Psychiatry and BHI
Center for Advanced Human Brain Imaging Research
Robert Wood Johnson Medical School, Piscataway, NJ.

The Cellular Underpinnings of the Human Cortical Connectome

The functional properties of the human brain arise, in part, from the vast assortment of cell types that pattern the cortex. The cortical sheet can be broadly divided into distinct networks, which are further embedded into processing streams, or gradients, that extend from unimodal systems through higher-order association territories. Here, using transcriptional data from the Allen Human Brain Atlas, we demonstrate that imputed cell type distributions are spatially coupled to the functional organization of cortex, as estimated through fMRI. Cortical cellular profiles follow the macro-scale organization of the functional gradients as well as the associated large-scale networks. Distinct cellular fingerprints were evident across networks, and a classifier trained on post-mortem cell-type distributions was able to predict the functional network allegiance of cortical tissue samples. These data indicate that the in vivo organization of the cortical sheet is reflected in the spatial variability of its cellular composition.

Nima Toosizadeh, PhD

Associate Professor
Department of Rehabilitation & Movement Science and BHI
School of Health Professions, Newark, NJ.

Screening Cognitive Decline: Multiscale Entropy Analysis During Dual-Tasking Using Functional Near Infrared Spectroscopy Measurements

By 2060 the number of older adults with dementia will surpass 152 million globally, approximately a 200% increase compared to 2019. Over half of patients with dementia never receive an evaluation, indicating that a quick and objective routine test for screening cognitive decline is needed. Due to neural death and disconnections, Alzheimer's disease (AD) is associated with a low value of nonlinear complexity of the brain function, which can be quantified using entropy analysis. Our proposed solution was an upper extremity function (UEF) dual-task screening method combined with functional near infrared spectroscopy (fNIRS).

MoCA scores stratified older adult participants into cognitively normal (CN) (n=9, 69<age<90), mild cognitive impairment (MCI) (n=20, 65<age<97), and AD (n=8, 80<age<96). Healthy young (HY) participants were also included (n=15, 18<age<28). Participants performed a 3-minute dual-task with a 3-minute rest period before and after. The motor component of the dual-task was consistent elbow flexion while counting backwards by intervals of 3's. Measurements were taken over the frontal (right and left) and parietal (right and left) brain regions. Multiscale entropy (MSE) was chosen as the complexity measure with 1 representing more complexity and 0 representing less complex signal.

The cognitive status of participants was significantly associated with brain function entropy for all measured brain regions. The results of this study indicate potential for the use of fNIRS multiscale entropy analysis in combination with the UEF dual-task test as a screening tool for cognitive impairment

Noelle Stiles, PhD

Assistant Professor
Department of Neurology and BHI
Center for Advanced Human Brain Imaging Research
Robert Wood Johnson Medical School, Piscataway, NJ.

Restoring Sight to the Blind: Effects of Plasticity and Multimodality

Visual restoration after decades of blindness is now becoming possible by means of retinal and cortical prostheses, as well as emerging stem cell and gene therapeutic approaches. After restoring visual perception, however, a key question remains. Are there optimal means and methods for retraining the visual cortex to process visual inputs, and for learning or relearning to "see"? Up to this point, it has been largely assumed that if the sensory loss is visual, then the rehabilitation focus should also be primarily visual. However, the other senses play a key role in visual rehabilitation due to the plastic repurposing of visual cortex during blindness by audition and somatosensation, and also to the reintegration of restored vision with the other senses. I will present multisensory neuroimaging results as well as behavioral outcomes for patients with Retinitis Pigmentosa (RP), which causes blindness by destroying photoreceptors in the retina. These patients have had their vision partially restored by the implantation of a retinal prosthesis, which electrically stimulates still viable retinal ganglion cells in the eye. Our multisensory neuroimaging and behavioral results suggest a new, holistic concept of visual rehabilitation that leverages rather than neglects audition, somatosensation, and other sensory modalities.

Ying Xu, MD, PhD

Assistant Professor
Department of Anesthesiology and BHI
Rutgers - New Jersey Medical School, Newark, NJ.

Mitochondrial phosphodiesterase 2A dysregulation in post-traumatic brain injury induced Alzheimer's disease

Traumatic brain injury (TBI) exacerbates cognitive impairment in the progression of Alzheimer's disease (AD). Mitochondrial dysfunction and synaptic damage are early features of pathology in susceptible neurons of patients with TBI related AD, yet the complex molecular mechanisms remain elusive. Recent studies demonstrate that cAMP/cGMP signaling is involved in the regulation of mitochondrial homeostasis and expression/assembly of key enzymes in the electron transport chain (ETC) and mitochondrial respiration. Phosphodiesterase 2A (PDE2A) plays a crucial role in mediating cognition due to its key function in hydrolyzing cyclic AMP (cAMP) and cGMP and its broad expression in the hippocampus and frontal cortex, brain regions vulnerable to AD. PDE2A is encoded by three isoforms, PDE2A1, 2A2 and 2A3. The unique N-terminus of the PDE2A2 isoform contains a 17 amino acid sequence that leads to its mitochondrial localization, where it is the primary regulator of cyclic nucleotide signaling in mitochondria. To decipher the causal link between mitochondrial PDE2A2 and TBI-induced AD pathology, we generated a functional PDE2A2 conditional knockout (KO) mouse model where all PDE2A isoforms were knocked out but truncated PDE2A2 lacking the mitochondria-targeting domain was re-expressed (t2A2). A control line that re-expressed full length PDE2A2 was also generated (f2A2). These mice were crossed with APP/PS1 mice to determine whether PDE2A2 causally links TBI-induced mitochondrial dysfunction to cognitive impairment in AD mice. This study provides mechanistic insights into the molecular signaling underlying mitochondrial dysfunction in TBI associated with AD and deepen our understanding of PDE2A in the regulation of cognition in the brain.

Tejbeer Kaur, PhD

Assistant Professor
Department of Otolaryngology, Head & Neck Surgery and BHI
Rutgers-Robert Wood Johnson Medical School, Piscataway, NJ

Macrophages as Cobblers of the Synapses: Restoring Lost Cochlear Ribbon Synapses and Hearing in Noise-Induced Hidden Hearing Loss

Hearing relies on the sophisticated indefatigable glutamatergic ribbon-type synapses between the sensory structures i.e., hair cells and neurons in the cochlea of the inner ear that transduce auditory information from the outside world into the brain. These ribbon synapses are vulnerable to primary damage and/or loss due to noise overexposure (termed “synaptopathy”). This loss may represent the most common causes of sensorineural hearing loss also known as hidden hearing loss that results in degradation of auditory information, leading to difficulty in listening in noisy environments and other auditory perceptual disorders. Resident cochlear macrophages (type of innate-immune cell) rapidly migrate into the synaptic region and directly contact the damaged synaptic connections after noise overexposure. Eventually, such damaged synapses are spontaneously repaired, but the precise role of macrophages in synaptic degeneration and repair remains unknown. Our recent research has established that macrophages are necessary and sufficient to restore lost synapses and hearing following synaptopathic noise overexposure. Additionally, our data show that local delivery of an immune factor, fractalkine (CX3CL1) is robustly effective in restoring the lost ribbon synapses and hearing after noise-induced cochlear synaptopathy in a macrophage-dependent manner. Our work reveals a novel role for innate-immune cells, such as macrophages in synaptic repair that can be potentially harnessed via fractalkine to regenerate lost ribbon synapses and function in noise-induced hidden hearing loss and associated perceptual anomalies.

Linden Parkes, PhD

Department of Psychiatry and BHI
Center for Advanced Human Brain Imaging Research
Robert Wood Johnson Medical School, Piscataway, NJ.

Spatially Embedded Network Models of the Brain

The human brain is a complex system of structurally interconnected regions, and the elaborate topology of this macroscopic structural connectome enables a rich repertoire of dynamics. Typically, analysis of the human connectome involves extracting the brain’s connectivity to a graph adjacency matrix, which abstracts away lots of the spatially embedded biophysical details of regions’ connectivity. This abstraction of detail limits the insights we can draw about brain function and dysfunction from the connectome. In response to this limitation, recent developments in the field of network neuroscience have seen a push toward analyzing a biologically annotated connectome. This approach involves leveraging multi-scale information about regions’ gene expression profiles, cell type distribution, and function to embed the structural connectome for improved analysis. In this talk, I will present work from the lab that uses biologically informed connectome analysis to study the brain’s dynamics and development, as well as the relationship between the brain and behavior and mental health symptoms.

Soha Saleh, PhD

Assistant Professor
Department of Rehabilitation & Movement Science and BHI
School of Health Professions, Newark, NJ.

Unlocking the Potential of Mobile Neuroimaging: Advantages and Applications in Motor Function and Brain Connectivity Studies

Mobile neuroimaging technologies such as functional near infrared spectroscopy (fNIRS) and Electroencephalography (EEG) have several advantages including portability, non-invasiveness, safety, cost-effectiveness, and versatility. These devices also allow for the evaluation of motor function and brain activity in real-life situations. This means that activities like walking, dual-tasking, freezing of gait, and gross motor movements can be assessed in a more naturalistic way. I will address the various benefits of mobile neuroimaging as well its limitations that include susceptibility to movement artifacts, limited spatial resolution (particularly for EEG), and challenges associated with source localization. I will discuss how we used these technologies to study dual tasking in people with multiple sclerosis (MS). Participants with MS and healthy controls are subjected to cognitive and motor activities separately and concurrently while wearing mobile neuroimaging devices. The data, which included EEG event-related potentials and fNIRS hemoglobin concentration variations, provides insights into the cognitive-motor connections and neurological correlates of dual tasking in MS. In addition, I will discuss an ongoing work that uses mobile EEG to evaluate reorganization in cortical activation patterns and brain-to-muscle connectivity during walking in the subacute phase post stroke. Using mobile neuroimaging to gain a better understanding of cortical control of upper and lower extremity movement has clinical implications for tailoring rehabilitation programs, monitoring recovery, implementing neurofeedback training, and developing personalized interventions to improve motor rehabilitation outcomes.

Andrew Westbrook, PhD

Assistant Professor
Department of Psychiatry and BHI
Center for Advanced Human Brain Imaging Research
Robert Wood Johnson Medical School, Piscataway, NJ.

What Criticality Tells Us About Brain Maturation, Excitation-Inhibition Balance, and Cognitive Effort

The human brain is a complex dynamical system with emergent properties implying that it operates near a critical point – at the boundary between dramatically different dynamical regimes. A key control parameter determining proximity to criticality is the balance between excitatory and inhibitory neurotransmission (or “E-I balance”). While hyper-inhibited systems are non-responsive, hyper-excited systems have runaway dynamics. In contrast, operating near criticality, with excitation and inhibition in balance, affords desirable functionality, from the standpoint of cognition. Critical systems have maximal susceptibility and dynamic range. They also maximize entropy and exhibit long-range spatial and temporal correlations. Such properties are essential for demanding working-memory operations that require both flexibility for updating with new information and stability for maintenance over retention intervals. These properties also appear to diminish when people engage in working memory tasks suggesting a normative explanation for why we treat thinking as effortful. Brain development provides a tests of these hypotheses as prior work shows both more tightly regulated E-I balance and improved working memory performance with maturation through adulthood. Examining electroencephalography data through the lens of critical dynamics, we find evidence of increasing E-I balance and closer proximity to criticality in adulthood. We further find that working memory ability depends on proximity to criticality and, intriguingly, that people whose brains veer farther from criticality experience more subjective cognitive effort during demanding working memory tasks.

Michal Schneider Beeri, PhD,

Krieger-Klein Endowed Chair in Neurodegeneration Research
Director of the Herbert and Jacqueline Krieger Klein Alzheimer's Research Center
Professor
Department of Neurology and BHI
Robert Wood Johnson Medical School, New Brunswick, NJ

Site-specific glycoproteomic modifications are associated with cognitive decline in older adults with type 2 diabetes

Type 2 diabetes (T2D) is known to increase the risk of cognitive decline and dementia, yet the precise molecular mechanisms underlying or linking these conditions remain unclear. Posttranslational modifications of proteins with glycans, i.e., glycosylation, can modify protein function and is implicated in both T2D and dementia. We employed a novel glycoproteomics approach to investigate glycopeptiforms- peptides with a specific glycan composition at a specific site on a protein- in blood of older adults with T2D (N=23) and in postmortem human brain tissue (dorsolateral prefrontal cortex; N=366). In blood, we identified 4,913 glycopeptiforms. Of them, 9 glycopeptiforms showed significant alterations both at baseline and over time in participants who were initially cognitively normal, but developed cognitive impairment over time, compared to those who maintained normal cognition. In brain tissue, we identified 11,012 glycopeptiforms of whom 11 were significantly associated with longitudinal cognitive decline. These findings suggest that aberrant glycoproteomic modifications may contribute to the development of cognitive impairment in T2D and may serve as potential early biomarkers.

Reynold A. Panettieri, Jr, M.D.

Vice Chancellor for Translational Medicine and Science
Director, Rutgers Institute for Translational Medicine, and Science
Professor of Medicine,
Robert Wood Johnson Medical School.

Nancy Reilly, RN, MS

Executive Director
RBHS Clinical Trials Office

How can the New Jersey Alliance for Clinical and Translational Science (NJ ACTS) transform clinical research across our ecosystem?

Translational research transforms ideas and discoveries into clinical therapies, devices, and software that can sustain and improve health. In comparison, Translational science determines the best practices that disseminate and implement translational research discoveries into actionable outcomes. Both translational research and science require service platforms that are disease agonistic and that can address the needs of investigators whose backgrounds may be disparate. In 2019, NJ ACTS was founded as the only CTSA Hub in New Jersey based on an alliance among Rutgers, Princeton, and the New Jersey Institute of Technology (NJIT). Over the past 5 years, NJ ACTS has provided vibrant platforms across 14 Cores that include Informatics, Community Engagement, Pilot Award funding, Biostatistics, Epidemiology, and Research Design, among others. Additionally, the Clinical Trial Office has streamlined and harmonized clinical research in a manner that can facilitate the start-up, execution, and management of observational and interventional clinical trials. The development of a central Clinical Trials Office enables investigators to conduct feasibility assessments for building cohorts using state-of-the-art natural language processing and machine learning to query 7.2 million records in our Epic EHR through the RWJBHS; track and monitor trial execution using OnCore Enterprise, our clinical trial management system; and execute clinical research within five clinical research units that are strategically located across NJ. Collectively, NJ ACTS can meet the challenges of performing rigorous and impactful clinical research across NJ by building and sustaining extraordinary collaborations among our partners that include academic institutions, government and industry.

POSTER ABSTRACTS

Poster #1

The Role of C. elegans Metaxins in Mitochondrial Homeostasis

Authors

Jonathan V. Dietz, Eunchan Park, Nathaly Salazar-Vasquez, Nanci Kane, Carol Nowlen, and Christopher Rongo

PI Name: Christopher Rongo

Mitochondria are critical for neuronal function and health, as they are the primary supplier of energy and calcium storage for neurons. Mitochondrial dynamics – fusion, fission, and motility – facilitate energy production and calcium buffering by mitochondria at specific subcellular sites within neurons. Disturbances in mitochondrial function or dynamics contribute to various neurodegenerative disorders. Using a forward genetic screen in *C. elegans* searching for novel mutants defective in neuronal mitochondrial dynamics, we found that mutations in metaxin 1 (MTX-1), metaxin 2 (MTX-2), and VDAC-1 resulted in fewer mitochondria in *C. elegans* interneuron dendrites. Mammalian metaxin homologs interact with SAM50 to form the sorting and assembly machinery (SAM) complex, which mediates β-barrel protein assembly in the mitochondrial outer membrane (MOM). VDAC-1 is a highly conserved SAM complex substrate that acts as a channel for metabolites across the MOM. We hypothesize that the metaxins promote mitochondrial motility along *C. elegans* interneuron dendrites by mediating assembly of VDAC-1 in the MOM. Mutants for *mtx-1, mtx-2*, and *vdac-1* are viable but have reduced lifespans. We found that the mitochondrial unfolded protein response (UPRmt) was activated in *mtx-2* and *vdac-1* mutants, resulting in heat stress resistance and mitohormesis. We are currently investigating the role of *C. elegans* MTX-1 and MTX-2 in MOM β-barrel protein (VDAC-1) assembly and how that impacts neuron integrity.

NIH grant (R01GM101978 to C.R.) and the Charles and Joanna Busch Postdoctoral Fellowship (to J.V.D)

Poster #2

Perinatal exposure to organophosphate flame-retardants alters cognition in male and female adult offspring.

Authors

Kimberly Wiersielis, RidhaFatima Mukadam, Jarrett Early, Ali Yasrebi, Nadja Knox, Thomas Degroat, Troy Roepke

PI Name: Troy Roepke

Endocrine disrupting compounds (EDCs) are compounds found in our environment that interrupt typical endocrine function. A particular group of EDCs are flame-retardants that interact with steroid and nuclear receptors. A commonly used class of flame-retardants are the organophosphate flame-retardants (OPFRs), which have been shown to alter adult behavior in rodent species after developmental exposures. We have previously identified that females perinatally exposed to OPFRs had a significant increase in locomotion and males had a trending reduction in the open field task. In addition, we detected OPFR-exposed males exhibited anxiolytic-like behavior in the elevated plus maze. However, the effects of perinatal OPFR exposure on cognition in the adult offspring are underexplored. Here we evaluate cognitive behavior using the Y maze, spatial object recognition (SOR), novel object recognition (NOR), and the Barnes maze (BM) in male and female adult offspring that were perinatally exposed to a mixture of OPFRs (tris(1,3-dichloro-2-propyl)phosphate, triphenyl phosphate, tricresyl phosphate) or vehicle. Our results demonstrate sex- and exposure-dependent effects of perinatal OPFR exposure on cognition in male and female adult mice, suggesting developmental neurotoxicity. Future studies will examine the influence of perinatal OPFR exposure on the long-term potentiation of pyramidal cells in hippocampal CA1 and acetylcholine excitatory synaptic transmission.

Supported by R01MH123544, 1K99ES033256-01A1, and USDA-NIFA NJ06195.

Poster#3

Targeting alternatively spliced variants of the mu opioid receptor gene, oprm1, in specific brain regions to alleviate opioid-induced respiratory depression

Authors

Ayma F. Malik, Raymond Chien, Jin Xu, Ying-Xian Pan

PI Name: Ying-Xian Pan

Opioid overdose deaths have skyrocketed by 3.5x in the last decade, mainly due to “opioid-induced respiratory depression (OIRD).” Understanding the mechanisms underpinning this is essential towards prevention and the development of new effective interventions. Mu opioid-induced actions are primarily mediated through mu opioid receptors. The single-copy mu opioid receptor gene, Oprm1, undergoes extensive alternative splicing to generate two classes of splice variants: Exon 1- (E1) and Exon 11- (E11) associated variants. The functional relevance of these splice variants has been demonstrated in mediating actions of various mu opioids, including analgesia, tolerance, dependence, and reward. However, it remains unknown how the two sets of Oprm1 splice variants influence OIRD. To address this question, I used two Oprm1 gene-targeted rat models, in which E1- or E11-associated variants are floxed with loxPs and can be conditionally disrupted by Cre-loxP recombination, and measured OIRD using Whole-Body Plethysmography (WBP) technology that can define specific changes in respiration from opioids. The results demonstrated that E1- and E11- associated variants differentially influence OIRD, with varied responses from three opioids (fentanyl, morphine and buprenorphine), as well as between male and female rats. We have also demonstrated the role of E1- and E11-associated variants in specific brain regions that modulate OIRD through site-specific microinjections of AAV-Cre in our transgenic rat models using stereotaxic surgeries. Together, this study not only provides a better understanding of the unique role of E1- and E11-associated variants on OIRD, but also enables the development of potential therapeutic strategies to reduce unnecessary opioid-related deaths

Supported in part by grants from NIH (DA059061 and DA042888)

Poster#4

Blockade of the cyclooxygenase-2 prevents chemotherapy-induced cognitive impairments

Authors

Mohammad Abdur Rashid, Jason, J. Tang, Ki-Hyun Yoo, Ana Corujo-Ramirez, Sang Hoon Kim, Alfredo Oliveros, Peter Cole, John R. Hawse, Mi-Hyeon Jang

PI Name: Mi-Hyeon Jang

Chemotherapy-induced cognitive impairment (CICI, also termed “chemobrain”) is a major neurotoxic side effect exhibited by a wide range of chemotherapeutic agents. CICI persists well after cessation of therapy, severely interfering with quality of life. Utilizing cisplatin, a platinum-based chemotherapy, to model chemobrain mice in vivo, we have established that cisplatin accelerates the brain aging process thus leading to long-term memory impairment in mice similar to what is clinically reported. We further show that cisplatin causes oxidative DNA damage, mitochondrial defects, impaired neurogenesis, synaptic defects, and increased gliosis in the adult hippocampus, a brain region critical for learning and memory. Mechanistically, we show that cisplatin dramatically increases COX-2 (Ptgs2) expression and its major product, prostaglandin E2 (PGE2) in adult mouse brain and human cortical neurons derived from induced pluripotent stem cells (iPSCs). Similar as cisplatin treatment, the levels of COX-2 expression began to increase at 0.1 µM methotrexate treatment, which significantly increased at 1 µM in human cortical neurons, indicating that COX-2 induction is a common pathogenic mechanism mediating cognitive impairment associated with cisplatin and methotrexate in spite of the fact that these compounds have different mechanisms of action for cancer eradication. Most importantly, NS-398, a selective COX-2 inhibitor, effectively prevents cognitive deficits in mice and reduction in cell viability of human neurons associated with these chemotherapies, without promoting tumor growth or interfering with cisplatin’s anti-tumor activity. Taken together, our findings strongly suggest that COX-2 induction is a main cause of CICI, making COX-2 inhibition a therapeutic target for CICI.

Supported by NIH (R01CA242158, R01AG058560), Eagles 5th District Cancer Telethon Funds, CINJ survivorship award, and AACR.

Poster #5

Asymptomatic maternal ZIKV Infection impacts fetal brain development

Authors

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PI Name: Brian Daniels

Since its emergence in the Western hemisphere, Zika virus (ZIKV) infection during pregnancy and subsequent vertical transmission have been linked to a constellation of severe developmental abnormalities referred to as congenital Zika syndrome (CZS). However, the impacts of maternal ZIKV infection during late gestation, when CZS is rare, have not been well studied. To better understand the potential outcomes of late-term maternal ZIKV infection, we have developed an immunocompetent mouse model of maternal ZIKV infection during late gestation. In this model, murine *Stat2* is replaced with human *STAT2*, rendering mice susceptible to ZIKV infection while leaving innate immune signaling intact. Subcutaneous infection of pregnant mice expressing human STAT2 (hSTAT2) on E12.5 resulted in viremia and dissemination of virus to the placenta and vertical transmission to fetuses, without significant effects on morphology or number of fetuses. Infected dams mounted a robust anti-ZIKV immune response, as indicated by elevated concentrations of inflammatory cytokines in maternal serum and placental tissues. Transcriptomic profiling revealed downregulation of key genes controlling neural developmental in the brains of 3-week-old offspring from infected dams compared to those from uninfected dams. Thus, we propose that ZIKV infection during late gestation may impact fetal brain development and function, even in the absence of severe congenital abnormalities and microcephaly. Future work will characterize anatomical and molecular changes to offspring brains in our model, as well as profile behavioral correlates of neuropsychiatric disorders in offspring as they age into adulthood.

Supported by NIH R21MH125034.

Poster# 6

Inhibitory pedunculopontine input to the dopaminergic midbrain mediates goal-directed action selection

Authors

Sirin Zhang, Duygu Yilmaz, Nadine Gut, Juan Mena-Segovia

PI Name: Juan Mena-Segovia

The pedunculopontine nucleus (PPN) is a midbrain structure that has traditionally been defined as part of the mesencephalic locomotor region. However, emerging data suggest the multifaceted involvement of PPN in goal-directed decision-making that might be attributed to its dense, monosynaptic projections to the dopamine neurons of the substantia nigra. We have recently reported that PPN_{GABA} neurons inhibit dopamine neurons and modulate goal-directed responses to unsigned valence, affecting the completion of tasks that entail both appetitive and aversive outcomes, without interfering with the overall motor output. Here, we explored the dynamics of PPN_{GABA} neurons during different stages of goal-directed behaviors. Using fiber photometry techniques, we recorded the population activity of PPN_{GABA} neurons by injecting a calcium indicator (GCamp) into the PPN of VGat-Cre mice. Additional intersectional strategies were used to target subpopulations of PPN_{GABA} neurons, and to record dopamine release in select striatal regions. Mice were tested in the progressive ratio task and the novel object interaction task. Our initial observations suggest that PPN_{GABA} neurons exhibit transient excitation during the execution of learned actions, the magnitude of which decreases with the length of the action sequence and negatively correlates with the possibility of behavioral abortion. We also found that PPN_{GABA} activity decreased for the duration of reward consumption. Ongoing experiments attempt to further elucidate the role of PPN_{GABA} in goal- directed action selection, especially during the sustainment of action sequences and interactions with novel stimuli, while exploring its potential projection-specific targets in the dopaminergic midbrain and select regions of the striatum.

Supported by Rutgers BHI travel award; Rutgers GSN travel fund; Sigma Xi Grant in Aid of Research

Poster#7

A rodent model for prescription opioid-associated opioid use disorder: Role of the orexin system

Authors

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PI Name: Gary Aston-Jones

Abuse of prescription opioids may lead to development of opioid use disorder (OUD). Important facets of OUD are increased drug demand and physical and affective withdrawal. Following OUD development, negative affect in withdrawal may drive increased opioid demand via negative reinforcement mechanisms. Orexin, a hypothalamic neuropeptide, promotes opioid seeking and withdrawal states, representing a promising pharmacological target for OUD. We sought to establish a rodent model of prescription opioid-associated OUD development and determine whether orexin system antagonism could attenuate OUD phenotypes. Male rats were given 21d of saline or oxycodone and tested for negative affect during acute abstinence. Compared to saline-treated controls, oxycodone-treated rats displayed behaviors indicative of increased negative affect, including decreased body weight gain, anhedonia, and hyperalgesia. Rats were then trained to self-administer fentanyl and on a within-session behavioral economics procedure to assess demand for fentanyl. In the initial days of acquisition, rats pretreated with oxycodone had higher cumulative fentanyl intake than saline-pretreated controls. Further, oxycodone-pretreated “high takers” self-administered more fentanyl than saline-pretreated “high takers”. Controlling for high consumption, we found that oxycodone-pretreated rats were more motivated for fentanyl. Finally, an orexin receptor-1 antagonist administered prior to BE testing most effectively reduced motivation for fentanyl in highly motivated oxycodone-pretreated rats. These results indicate that prescription opioid-associated OUD development can be modeled in rodents and may be due to opioid exposure and individual differences. Finally, the orexin system may be upregulated following chronic opioid exposure to drive increased opioid demand, representing a promising pharmacological target for OUD.

This work was supported by NIH award R01DA006214.

Poster#8

The time course of distorted representations in the primary visual cortex

Authors

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PI Name: Pierre-Olivier Polack

Learning is a vital process that fine-tunes how the brain processes information to help animals adapt to new situations. Recently, we demonstrated that when mice learn a visual task, it leads to certain modifications in how neurons in the primary visual cortex (V1) respond. Our findings indicated that trained mice show more precise and stable representations of rewarded and non-rewarded orientations across trials. This improvement was a result of a change in how orientations are represented, causing stimuli close to the task-relevant orientations to be perceived as the task stimuli themselves. This implied that orientation representation becomes distorted in trained mice, generalizing the flanking orientations as task cues. To explore the timeline of this distortion in trained mice, we conducted a new set of experiments. We disengaged the animals from the task and imaged L2/3 of V1 to observe how distortions decay over time. We discovered that the distortion of orientation representation persisted for a few days after the mice were disengaged from the task but gradually decayed over time. Importantly, the disappearance of these distortions did not impact the mice's performance when they were later asked to complete the orientation discrimination task. Our findings suggest that once expertise is achieved, the neural activity in V1 returns to a baseline state, and this return does not affect the animals' behavioral performance.

Supported by NIH NEI (R01 030860), NIH BRAIN (R01 NS120289), Rutgers BHI Trainee Travel Award 2022-2023

Poster #9

Behavioral phenotypes and comorbidity in 3q29 deletion syndrome: Results from the 3q29 registry

Authors

Rebecca M Pollak, Michael Mortillo, Melissa M Murphy, Jennifer G Mulle

PI Name: Jennifer Mulle

3q29 deletion syndrome (3q29del) is associated with a significantly increased risk for neurodevelopmental and neuropsychiatric disorders. However, the full spectrum of behavioral phenotypes associated with 3q29del is still evolving. Individuals with 3q29del (n=96, 60.42% male) or their guardian completed the Achenbach Child or Adult Behavior Checklist (CBCL/ABCL) via the online 3q29 registry (3q29deletion.org). Typically developing controls (n=57, 49.12% male) were ascertained as a comparison group. We analyzed mean performance on the CBCL/ABCL for individuals with 3q29del and controls across composite, DSM-keyed, and developmental scales; and the relationship between CBCL/ABCL performance and clinical and developmental phenotypes for individuals with 3q29del. Individuals with 3q29del showed significant behavioral impairment relative to controls across CBCL/ABCL domains. We found that the DSM-keyed CBCL/ABCL scales are potential screening tools for autism spectrum disorder (ASD), anxiety disorder, and attention-deficit/hyperactivity disorder (ADHD) for individuals with 3q29del. We identified a high degree of psychiatric comorbidity in individuals with 3q29del, with 60.42% (n=58) of individuals with 3q29del scoring in the Borderline or Clinical range on two or more DSM-keyed CBCL/ABCL scales. Finally, we found that the degree of developmental delay in participants with 3q29del does not explain the increased behavioral problems observed on the CBCL/ABCL. The CBCL/ABCL can be used as screening tools in populations such as 3q29del, even in the presence of substantial psychiatric comorbidity. These results expand our understanding of the phenotypic spectrum of 3q29del and demonstrate an effective method for recruiting and phenotyping a large sample of individuals with a rare genetic disorder.

Supported by NIMH R01 MH110701 (PI Mulle)

Poster #10

The Behavior Biomarker Scale (BBS): A machine-vision approach for automated locomotor recovery evaluation at millisecond timescales

Authors

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PI Name: Victoria Abraira

Complex motor behaviors, like those affected by SCI, are composed of specific sequences of simpler motor modules. Traditionally identified individually through human observation (i.e., BBB and BMS scales) or by isolated kinematic analysis, recent advances in computer vision and machine learning offer a fast, comprehensive, and unbiased approach to characterize movement and movement impairment. Published work combining infrared depth imaging with machine learning (Motion Sequencing: MoSeq) demonstrate that mouse motor behavior can be characterized as stereotyped sub-second movement modules that are reused with defined transition probabilities depending on context. Since recovery from injury can be conceptualized as a process of regaining movement modules, we believe that this technology can be applied to both scale the recovery process and uncover underlying neuropathology. Our study included multiple spinal cord injury models (mild and moderate contusion injuries, transections) and control cohorts of C57/Bl6 mice. Our data reveals that SCI induces profound changes in module usage, with over 70 unique movement modules showing distinct recovery trajectories. Correlation with traditional BMS scores showed distinct modules associated with either low or high BMS scores, providing evidence that module usage can be a sensitive measure of the recovery process. MoSeq represents an innovative, unbiased, and highly sensitive approach to characterize and quantify rodent behavioral biomarkers of recover. We will use MoSeq to establish a robust, generalizable, and user-friendly platform to define functional recovery in rodents, which we call the Behavioral Biomarker Scale (BBS).

Supported by Craig H. Neilsen Foundation, NJ Commission on Spinal Cord Research, K01NS116224, R01NS119268 (all to VEA) and F32NS131535, T32NS115700 (to JTE)

Poster #11

An antioxidative gene therapy for the prevention of Cisplatin-induced hearing loss.

Authors

Sean Hong, Damian Murphy, Nikhil Suresh, Mina Beshy, Todd Mowery

PI Name: Todd Mowery

According to WHO nearly half a billion people suffer from some form of hearing loss. For many individuals, this hearing loss is cumulative and stems from oxidative damage through ototoxic agents and noise exposure. Cancer treatments involve the use of drugs with ototoxic properties that result in many patients acquiring permanent hearing loss. These drugs make the inner hair cells very sensitive to levels of noise that are generally considered safe and experienced by the population on a daily basis. There is also direct oxidative damage that over time leads to hair cell death. In this project we used an animal model of Cisplatin-induced hearing loss that produces permanent moderate to severe hearing loss to test the neuroprotective effects of our proprietary gene therapy. Hearing status at baseline was collected followed by cisterna magna injections of AAV or Saline. After three weeks of transfection animals received 4 cycles of Cisplatin (24 mg/kg) over 4 weeks. Hearing status was assessed by ABR recordings weekly to assess auditory thresholds. Group comparisons were made at each timepoint using Tukey's T-tests and linear regression analysis was used to determine main effects over time. We found that the gene therapy provided robust protection from Cisplatin induced hearing loss. We will use the same experimental approach to test higher doses of cisplatin on gene therapy neuroprotection.

Poster #12

Preserved neural encoding of subjective valuation under uncertainty in human opioid addiction.

Authors

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PI Name: Anna Konova

Opioid use disorder (OUD) is associated with increased risk-taking and an increased tolerance for uncertainty. People's idiosyncratic tolerances for uncertainty modulate their computation of a reward's subjective value (SV). Researchers have posited that continued use of opioids could be the result of a 'broken' internal mapping of objective value to SV. Using fMRI, we examined whether subjective valuation in OUD reflects normative differences due to idiosyncratic tolerances or a breakdown of SV computations. Treatment-engaged OUD patients (n=32; 6 females; mean [SE] age=44.7 [2.19] years) and matched controls (n=27; 11 females; age=45.0 [2.87] years) completed a decision-making fMRI task targeting uncertainty. A modified utility model parameterizing uncertainty was used to compute trial-by-trial SV. Model-based fMRI analyses were used to identify regions encoding SV and assess for a brain-behavior match. Multivariate analyses were also used to ascertain that specific patterns of activation were decodable based on individual uncertainty tolerances. Behaviorally, most subjects were averse to uncertainty (76%; consistent with previous research) with no group differences; this ensures that any observed neural differences cannot be explained by idiosyncratic uncertainty tolerances. Neurally, we found that canonical value areas encode SV similarly across the OUD and control groups ($p<0.001$; ventromedial prefrontal cortex, $t=4.42$; ventral striatum, $t=3.95$; posterior cingulate cortex, $t=4.50$). Multivariate analyses indicated that SV could be significantly decoded above chance levels (permutation test) in all three regions, and in both groups separately, further demonstrating shared SV signal patterns. These results imply that the encoding and computation of SV is preserved in people with OUD.

Supported by grants from Busch Biomedical Research Program and the National Institute on Drug Abuse (R01DA053282 to ABK).

Poster #13

A novel mouse model to study potassium ion channel related early-onset epileptic encephalopathies

Authors

Alessandro Bortolami, David P. Crockett, Federico Sesti

PI Name: Federico Sesti

Potassium channels play a role in controlling the excitability of neurons and can trigger a cascade of signals within the central nervous system. One specific potassium channel, called voltage-gated potassium channel subfamily B member 1 (KCNB1), is associated with integrins (IKCs) and is important for converting its electrical properties into signals that promote cell proliferation and migration. Mutations in the KCNB1 gene are linked to brain disorders. In particular, a substitution mutation at position 312 in the KCNB1 gene, where arginine is replaced by histidine (Kcnb1R312H), has been found in children with developmental and epileptic encephalopathies (DEEs). Children affected by this disorder experience severe developmental delay and in the majority of cases recurrent seizures. To study this neurological condition, we created a mouse model harboring the Kcnb1R312H gene variant using CRISPR knock-in (KI) technology. In this study, we verified aberrant neurodevelopment and synaptic connectivity. We assessed the behavior of the Kcnb1R312H mouse, focusing on anxiety, motor functions, and complex tasks, in order to establish a reliable model for studying DEEs. Our results indicate that the Kcnb1R312H mouse model offers a valuable tool for gaining a deeper understanding of human potassium ion channels related DEEs.

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Poster #14

Loss of the polarity protein Par3 promotes dendritic spine neoteny and enhances learning and memory

Authors:

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PI Name: Huaye Zhang

Partitioning defective 3 (Par3) is critical for subcellular compartmentalization in different developmental processes. In addition, several single nucleotide polymorphisms (SNPs) and copy number variation (CNV) of Pard3, which encodes Par3, are associated with intelligence, schizophrenia, and autism spectrum disorder (ASD). However, the role of Par3 in glutamatergic synapse formation and cognitive functions in vivo remains completely unknown. Here we show that postnatal forebrain conditional knockout of Par3 leads to an increase in the density of dendritic spines, which are the main sites of glutamatergic synapse formation, in hippocampal CA1 pyramidal neurons in vivo. Specifically, loss of Par3 leads to an increase in long, thin dendritic spines without significantly impacting mushroom spine formation. Consistent with the morphological changes, we observed a decrease in the amplitude of miniature excitatory postsynaptic currents (mEPSC). Surprisingly, we found loss of Par3 in vivo enhances hippocampal-dependent spatial learning. Phosphoproteomic analysis revealed that proteins regulating cytoskeletal dynamics are significantly dysregulated downstream of Par3. Mechanistically, we found loss of Par3 causes increased activation of the Rac1 GTPase pathway, which is a key regulator of actin and microtubule dynamics. Together, our data reveal an unexpected role for Par3 in vivo by limiting the pool of dendritic spine with immature morphology and also negatively regulating learning and memory.

This study was supported by NIH F31NS122477 and Fall 2023- BHI Trainee Travel Award to Mikayla Voglewede and NIH R01NS089578 to Huaye Zhang.

Poster #15

Neural mechanisms of economic decisions are reflected in orbitofrontal high-gamma.

Authors

Dixit Sharma, Shira Lupkin, Vincent McGinty

PI Name: Vincent McGinty

The orbitofrontal cortex (OFC) has an important role in value-based decisions, and much of what we know about its function comes from studying the spiking activity of single neurons. However, not much is known about how local field potentials represent decision-specific computations in primate OFC. We recorded OFC spiking and high-gamma activity using multi-channel linear probes in monkeys performing a two-option value-based decision task, and then compared spikes and high-gamma signals recorded concurrently from the same electrodes. We report four key results. First, both spikes and high-gamma represent the values of the decision offers, with each signal explaining a unique portion of variance in value, when measured on a channel-by-channel basis. Second, on average high-gamma signals increased monotonically as a function of value, whereas spikes showed neutral value encoding on average. Third, high-gamma signals, but not spikes, reflected a comparison between the offer values. Fourth, at a single-channel level high-gamma was generally a better predictor of decision outcomes; however, when using a multi-channel, population-based decoder, spikes furnished more accurate predictions than high-gamma. Overall, our findings suggest that OFC high-gamma reflects critical decision-related computations that are not always detectable from OFC spikes. High-gamma may therefore provide novel insights into the neural mechanisms of economic decision-making. Furthermore, because high-gamma is known to be tightly related to non-invasive imaging signals, our findings have potential implications for cross-species translational work.

This study was supported by NIH Grant K01-DA-036659-01, Busch Biomedical Foundation fellowship, Whitehall Foundation fellowship, and BNS Graduate program

Poster #16

Genetic preclinical mouse models for Tourette Syndrome (TS) display enhanced habit formation, behavioral inflexibility, and elevated intrinsic motivation

Authors

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PI Name: Max Tischfield

Tourette Syndrome (TS) is a highly prevalent neurodevelopmental disorder, characterized by urges to perform tics - stereotyped, repetitive, and uncontrollable movements or sounds. Despite the negative impact that TS can have on an individual's emotional and physical wellbeing, the underlying neuropathology of TS is still under researched and not well understood. It is hypothesized that TS arises from neurodevelopmental changes to cortical-striatal-thalamic-cortical (CSTC) circuits. More specifically, it is proposed that tics may stem from dysfunction within circuits controlling compulsive/habitual behaviors and dopamine dysregulation. Interestingly, a clinical study recently demonstrated that people with TS develop habits faster and engage in habitual strategies more often than control subjects. Thus, the Tischfield lab hypothesizes that tics may be maladaptive habits, reinforced by changes to habitual circuitry and dopamine signaling. To investigate the proposed changes to habit formation in TS, our lab has engineered novel genetic preclinical TS mouse models. Each model expresses one orthologous de novo human mutation discovered in high confidence risk genes for TS. Using these models, we employed operant conditioning paradigms designed to induce either habitual or goal-directed motor responding in mice. In accordance with clinical studies, we found that our TS mouse models demonstrate enhanced habit formation compared to control littermates. Additionally, our models show enhanced motor responding, increased intrinsic motivation, and behavioral inflexibility. Importantly, these results both compliment human data as well as establish our genetic TS models as a novel tool with which to further study tic etiology and the underlying neuronal mechanisms of this disorder.

This work is supported by New Jersey Center for Tourette Syndrome (NJCTS), Tourette Association of America (TAA), Brain and Behavior Research Foundation (BBRF), TIC Genetics.

Poster #17

Single-nuclei paired multiomic analysis of young, aged, and Parkinson's disease human midbrain reveals age- and disease-associated glial changes and their contribution to Parkinson's disease

Authors

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PI Name: Yoon-Seong Kim

Age is the primary risk factor for Parkinson's disease (PD), but how aging changes the expression and regulatory landscape of the brain remains unclear. Here, we present a single-nuclei multiomic study profiling shared gene expression and chromatin accessibility of young, aged, and PD post-mortem midbrain samples. We profiled 69,289 high-quality nuclei from 31 individuals (9 young donors, 8 aged donors, 14 PD patients). To investigate how the aging process affects PD pathogenesis, we combined the snRNA and snATAC sequencing datasets and established a combined pseudopathogenesis (cPP) trajectory. cPP trajectory reveals all glial cell types are affected by age, but microglia and oligodendrocytes are further altered in PD. Using this analytical strategy, we identified three distinct subsets of oligodendrocytes in the human substantia nigra. Most cells exhibited a low cPP score and had a transcriptome signature characteristic of healthy, canonical oligodendrocyte function. All donors, regardless of age or disease status, had a large population of healthy cells. We present evidence for a novel disease-associated oligodendrocyte subtype characterized by a high cPP score and identify genes lost over the aging and disease process, including CARNS1 and RBFOX1, which may predispose healthy cells to develop a disease-associated phenotype. We also identified genes such as QDPR and SELENOP altered during PD. We confirmed our bioinformatics findings with RNA-FISH on FFPE human substantia nigra sections. Peak-gene association analysis from paired data identifies 89 PD-associated SNP loci, including five in MAPT, that show differential association with gene expression in disease-associated oligodendrocytes. Our study suggests a previously undescribed role for oligodendrocytes in aging and PD pathogenesis.

Poster #18

Selection of small molecules that reduce the intrinsically disordered protein α-synuclein using iPSC-derived dopamine neurons from Parkinson's disease patients.

Authors

Jun Liu, Yuquan Tong, Jessica L. Childs-Disney, Santhosh Maddila, Kambiz Hassanzadeh, Matthew D. Disney, and M. Maral Mouradian

PI Name: M. Maral Mouradian

Alpha-synuclein (α-syn) is a key protein in the pathogenesis of Parkinson's disease (PD). A strong driver of pathological α-syn aggregation is its concentration in the brain, as individuals with multiplication of the SNCA gene locus develop early onset PD. Thus, reducing α-syn protein expression is a plausible disease modifying strategy. We previously discovered small molecules that directly target a structured iron-responsive element in the 5' untranslated region of the SNCA mRNA, which controls its translation. To improve drug-like properties, the lead compound Synucleozid was used as a prototype for further optimization. Here, by using a successive series of innovative cell-based approaches, we identified additional analogues and diverse scaffolds that reduce α-synuclein protein levels in Hela cells. We then explored the potential of combining two screen hits. We found that the activity of certain compound-combinations (combos) was concentration dependent, with substantial reductions in α-syn levels occurring at considerably lower concentrations for certain compound pairs. To maximize the predictability of the activity of these compounds in clinical trials, we then tested top performers in human iPSCs-derived dopaminergic (DA) neurons to evaluate therapeutic candidates for PD. Notably, the amount of high-molecular-weight insoluble species of α-syn and phosphorylated α-syn aggregates were significantly reduced in α-syn pre-formed fibrils-challenged neurons when incubated with combos. Cell toxicity studies further demonstrated that potent combos provide a significant cytoprotective effect in PD iPSC-derived neurons. Altogether, our studies provide a promising compound selection strategy for PD and establish a path towards identifying effective disease-modifying small molecules for α-synucleinopathies.

Supported by NINDS UH3NS116921; MJFF-001006.

Poster #19

All-optical approach for the study of synaptic plasticity between neuronal ensembles in vivo.

Authors

Barbara Gruszka

PI Name: Ian Oldenburg

Hebbian plasticity describes strengthening of synaptic connections when neurons are co-active, which is thought to be involved in learning, memory, and development. Whether a connection is strengthened or weakened has been shown in vitro to depend on the relative timing of pre- and post-synaptic spikes. However, the timing dependence of synaptic plasticity has been challenging to study in vivo. The Oldenburg lab uses a variant of multiphoton optogenetics known as 3D-SHOT to selectively activate individual neurons in vivo with unprecedented temporal resolution. With this technique, we can “write” patterns of activity into neurons with holographic stimulation while simultaneously performing calcium imaging in a large volume of tissue. We leverage this temporal resolution to explore synaptic plasticity rules, as well as to better understand the role of neural activity and plasticity on behavior. Here, we outline a framework for the development of an all-optical protocol to determine the spike-timing dependence of synaptic plasticity in vivo. This represents the first-ever all-optical STDP approach to unravel the mechanisms of learning, and more specifically, how plasticity influences motor behavior. Further developing these methods has applications beyond learning and memory, as the brain is heavily reliant on temporally sensitive neuronal activity for sensory processing, decision-making, motor control, and more.

Supported by R00EY029758 and Whitehall Award No: 2023-05-40

Poster #20

Insights into the mechanisms of respiratory and electrocerebral suppression by alcohol.

Authors

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PI Name: Detlev Boison

Excessive alcohol use is a significant public health issue and contributes to over 5% of global mortality. Acutely, alcohol poisoning can cause decreased electrocerebral activity and life-threatening suppression of breathing. Unfortunately, the mechanistic underpinnings of alcohol-induced respiratory and electrocerebral suppression are poorly understood. The goal of this investigation was to: (1) evaluate the differential mechanisms of alcohol-induced respiratory and electrocerebral suppression; (2) determine whether alcohol-induced respiratory and electrocerebral suppression are tractable to adenosine-based therapeutics; (3) differentiate between the direct effects of alcohol and the effect of acetaldehyde, its downstream metabolite, on respiration; and (4) characterize the effect of alcohol on respiratory sensitivity to CO2. Our approach was to utilize a mouse model of acute alcohol poisoning with a range of pharmacological and transgenic manipulations while monitoring breathing and EEG. The effects of alcohol on breathing and electrocerebral activity were distinct both in their timescale and their response to adenosinergic interventions. Peak electrocerebral suppression occurred within 30 minutes whereas respiratory suppression peaked at approximately 3 hours. Alcohol-induced respiratory suppression, but not electrocerebral suppression, was improved by adenosine receptor antagonism. Alcohol-induced respiratory suppression was exacerbated by inhibition of acetaldehyde metabolism, but not by inhibition of alcohol metabolism. Neither increasing serotonergic activity via reuptake inhibition nor decreasing GABAergic and opioidergic signaling with receptor antagonists counteracted the respiratory effects of alcohol. These results indicate that the effects of alcohol on breathing and electrocerebral activity are mechanistically distinct. Better understanding of these disparate mechanisms may improve therapeutic strategies for individuals undergoing alcohol poisoning.

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Poster #21

Maternal overnutrition causes hyperphagia and decreases excitability of lateral hypothalamic glutamate neurons

Authors

Vikshar Athreya, Kuldeep Shrivastava, Mark A. Rossi

PI Name: Mark Rossi

The obesity epidemic is a growing public health concern, and while much research has been conducted on the effects of high-fat diets on the brain, relatively little is known about the intergenerational effects of high-fat diets in obesity. Using a mouse-model of maternal obesity, we find that maternal overnutrition leads offspring with no prior exposure to a high-fat diet to overeat the high fat diet compared to the offspring of mothers fed a low-fat diet. Patch-clamp electrophysiology experiments reveal that maternal overnutrition leads to a decrease in the excitability of lateral hypothalamus (LH) glutamate cells, which have previously been shown to inhibit feeding behavior. While no differences were observed in the activity and anxiety-like behavior between offspring of obese and non-obese mothers, the offspring of obese mothers exhibit a decreased lick rate and lick bout length when provided a sucrose reward, something that occurs in the offspring of non-obese mothers only after 3 weeks of high-fat diet. Thus, while decreased LH glutamatergic excitability potentially underlies the hyperphagia phenotype in the offspring of obese mothers, further research is required to understand mechanisms behind the decreased effort exerted by the offspring of obese mothers to obtain a sucrose reward.

Supported by R00-DK121883 and NJHF Grant 156-23

Poster #22

CX_3CR1 fate mapping reveals heterogeneity in cochlear macrophages and blood circulating CCR2 expressing recruited macrophages promote neuron survival after acoustic trauma.

Authors

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PI Name: Tejbeer Kaur

Cochlear trauma activates resident macrophages (RM) and allows infiltration of blood circulating monocytes and monocyte-derived macrophages (Mo-M). The chemokine fractalkine receptor (CX_3CR1), expressed on both RM and Mo-M, influences macrophage density and promotes neuron survival in the injured cochlea (Kaur et al., 2015). However, it is unknown if CX_3CR1-RM and CX_3CR1-Mo-M differentially promote neuron survival after cochlear injury. We used tamoxifen inducible *$CX_3CR1^{YFP-CreER/YFP-CreER}$* mouse crossed with Rosa-lsl-tdTomato reporter line wherein CX_3CR1-RM and CX_3CR1-Mo-M are differentially fluorescent labeled to define their origin, spatiotemporal distribution, morphology, fate, states, and function. Also, to determine the precise role of CX_3CR1-Mo-M in neuron survival, CCR2 knockout mice were used. Mice were exposed for 2 hours at 112 dB SPL noise level at 8-16 kHz and subjected to hearing function assessment followed by euthanasia and tissue collection. After acoustic trauma, the distinctly labeled but morphologically similar RM (YFP+RFP+) and Mo-M (YFP+RFP-) were observed in the spiral ganglion neurons, lateral wall, and organ of Corti, whereas sham exposed mice showed only RM. Both RM and Mo-M were Ki67 positive, suggesting both subtypes contributed to the increased macrophage numbers in the noise-damaged cochlea. CX_3CR1-Mo-M expressed CCR2 receptor, absence of which was associated with increased loss of sensory hair cells and neurons after acoustic trauma. The data suggest that macrophages are heterogeneous, and CX_3CR1-Mo-M may contribute to the survival of neurons in the noise-injured cochlea.

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Poster #23

Regional differences in oligodendroglial cholesterol acquisition and myelin lipid composition

Authors

Marie L. Mather, Luipa Khandker, Angelina V. Evangelou, Teresa L. Wood

PI Name: Teresa Wood

Cholesterol comprises over 40% of myelin lipids and is often dysregulated in neurodegenerative diseases affecting myelin integrity. Despite the prominence of promyelinating drugs targeting sterol synthesis and our increasing knowledge of oligodendrocyte heterogeneity, few studies have explored lipid metabolism in both the brain and spinal cord. Therefore, understanding how cholesterol metabolism is regulated in different oligodendrocyte populations is essential to developing effective promyelinating therapies. Our previous study revealed that spinal cord oligodendrocyte precursor cells (OPCs) have higher rates of cholesterol synthesis compared to brain OPCs. Further analyses show higher expression of lipoprotein receptors in brain oligodendroglia compared to spinal cord oligodendroglia throughout rapid myelin development (P10-P18). Subsequently, treatment of primary OPCs with lipoproteins resulted in increased myelin gene expression in brain OPCs while spinal cord OPCs showed no response. These data suggest that brain OPCs have a greater capacity cholesterol uptake rather than cholesterol synthesis. We also explored whether lower rates of cholesterol synthesis in brain oligodendrocytes could be due to lower lipid requirements to produce myelin. Analysis of myelin composition from spinal cord and several regions of the CNS revealed that brain myelin has a lower lipid concentration compared to spinal cord myelin. Further regional comparisons suggest that myelin lipid content is correlated to average axon diameter within each region. The results of this study further highlight the regional specificity of both myelin and oligodendroglial populations, providing significant functional differences that should be considered when targeting components of lipid metabolic pathways.

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Poster #24

Prevention of epilepsy through the small molecule adenosine kinase inhibitor MRS4203

Authors

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PI Name: Detlev Boison

Epilepsy is one of the most frequent neurological conditions affecting 80 million people worldwide, yet existing antiseizure medications fail to be effective in over one third of patients and do not affect the pathogenic process that leads to epilepsy and its progression. Epileptogenesis, the process through which a brain becomes epileptic, is characterized in part by an increase in adenosine kinase (ADK) and resulting changes in DNA methylation. ADK metabolizes adenosine (ADO), the mammalian brain's endogenous anti-convulsant and a key metabolic component of the transmethylation pathway which drives DNA methylation. Prior studies have shown that maladaptive overexpression of ADK drives the epileptogenic process through increased DNA methylation. Therefore, ADK is a target for epilepsy prevention. Non-selective ADK inhibitors have been considered in the past as therapeutics for seizure suppression but have mostly been abandoned due to systemic side effects associated with long-term use. Our group is looking at novel, more selective ADK inhibitors as potential drug candidates to interrupt epileptogenesis and prevent epilepsy. One of these is MRS4203. Using mouse models of intrahippocampal kainic acid and controlled cortical impact induced epilepsy, we demonstrate that a transient dose of MRS4203 given for only 5 days after the brain injury robustly interrupted the epileptogenic process in both models. We further show that MRS4203, in contrast to s first generation ADK inhibitor, did not cause any sedation or motor function defects. We conclude that MRS4203 is a novel inhibitor capable of preventing epilepsy without sedative side effects.

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Poster #25

Audiovisual decision-making deficits after hearing loss

Authors

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PI Name: Justin Yao

Sensory impairments, such as hearing loss, can lead to cognitive processing deficits. For example, hearing-impaired individuals exhibit reduced temporal integration when performing an auditory task and diminished audiovisual integration compared to age-matched individuals with normal hearing. Here, we examined how hearing loss impairs the decision-making variables of temporal integration and multisensory enhancement. We trained adult gerbils to perform a single-interval alternative forced-choice audiovisual decision-making task. Gerbils initiated trials by placing their nose in a nose port and were required to discriminate between slow (<6-Hz) versus fast (>6-Hz) presentation rates of amplitude-modulated (AM) noise (“auditory-only” condition), light-emitting diode (LED) flashes (“visual-only” condition), or simultaneous AM and LED flashes (“audiovisual” condition) by approaching the left or right food tray. Temporal integration was quantified as the duration from trial onset to when animals departed the nose port area and approached one of the two food trays (i.e., “integration time”). Discrimination performance for audiovisual trials were the most accurate, and displayed the fastest integration times, compared to the single-modality trials. We induced hearing loss by exposing animals to loud noise (~115-120 dB SPL) during a single 2-hour session. Noise exposure significantly reduced hearing sensitivity as auditory brainstem response thresholds increased ~30-50 dB SPL for clicks and tones. Hearing loss severely impaired discrimination performance for auditory-only trials and modestly altered performance for visual-only and audiovisual trials. Hearing loss significantly extended integration times for all sensory conditions. These findings suggest that hearing loss impairs sensory processing outside of the auditory domain

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Poster #26

Selective disruption of target value and target location signals in primate orbitofrontal cortex: effects on binary choice

Authors

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PI Name: Vincent McGinty

During economic decision-making, the primate orbitofrontal cortex (OFC) encodes multiple decision-related variables, including the target value and location. While the role of value signals is well-characterized, the role of location signals remains unclear. We investigated the role of these signals by selectively disrupting them with the electrical micro-stimulation of the OFC. One monkey performed a two-alternative value-based decision-making task while stimulation was delivered unilaterally to the OFC. The aim was to disrupt neural activity concurrent with encoding the target values or locations in separate sessions. To disrupt value signals, stimulation was delivered in a 200ms epoch after the monkey fixated upon either the first or second target in each trial. Likewise, we also stimulated during an earlier epoch following the moment the first target was initially shown. Stimulation was delivered through linear recording/stimulation arrays (Plexon V-Probes) as 20-25µA biphasic current pulses, delivered to five channels simultaneously with 200 Hz frequency. Consistent with previous studies, stimulation following fixation onto the first target (when its value was encoded) decreased the monkey's probability of choosing the first target (Ballesta et al., 2020). Interestingly, stimulation after the first target was initially displayed increased the probability of choosing the first target - showing the opposite effect as stimulation during the first target value-encoding epoch. This was unexpected, given that value signals were not yet evident in OFC in this epoch. Though preliminary, these results suggest the possibility of a causal role for non-value-related OFC activity in economic choice

Whitehall Foundation Fellowship, Busch Biomedical Foundation, BNS Graduate Program.

Poster #27

Role of NMDARs in balancing excitation and inhibition in a model of hippocampal place cells.

Authors

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PI Name: Aaron Milstein

Place cells in hippocampal area CA1 exhibit spatially selective firing during spatial navigation. Underlying the increase in firing is a ~10 mV subthreshold membrane potential depolarization that in large part reflects an increase in the strength of excitatory synapses active within a cell's place field. Evidence suggests this increase in excitation arises during learning via long-term potentiation of AMPAR-mediated synaptic currents. However, as a place cell depolarizes, AMPARs lose ionic driving force as they approach their equilibrium potential (0 mV), while inhibitory GABARs increase driving force with increasing distance from their equilibrium potential (-70 mV). This predicts that even if AMPAR conductance increases in-field, and GABAR conductance stays equal at positions out-of-field and in-field, GABAR currents will increase in-field, while AMPAR currents will be blunted. However, recent in vivo experiments showed that optogenetic depolarization of place cells does not change the ratio of excitation to inhibition within a place field. In that study, a simple model indicated that in order to explain the experimental data, synaptic inhibitory conductance would have to decrease dramatically from out-of-field positions to in-field. However, this model did not account for the presence of voltage-dependent NMDAR-type glutamate receptors at excitatory synapses in CA1 place cells. Here we examine the effects of NMDARs on the ratio of excitation to inhibition in hippocampal place cells and discuss its implications for the role of spatially biased synaptic inhibition in place field expression.

Poster #28

Dysregulated neuroimmune interactions and sustained type I interferon signaling after human immunodeficiency virus type 1 infection of human iPSC derived microglia and cerebral organoids.

Authors

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PI Name: Arnold Rabson

Human immunodeficiency virus type-1 (HIV-1) associated neurocognitive disorder (HAND) affects up to half of HIV-1 positive patients with long term neurological consequences, including dementia. There are no effective therapeutics for HAND because the pathophysiology of HIV-1 induced glial and neuronal functional deficits in humans remains enigmatic. To bridge this knowledge gap, we established a model simulating HIV-1 infection in the central nervous system using human induced pluripotent stem cell (iPSC) derived microglia combined with sliced neocortical organoids. Upon incubation with two replication-competent macrophage-tropic HIV-1 strains (JRFL and YU2), we observed that microglia not only became productively infected but also exhibited inflammatory activation. RNA sequencing revealed a significant and sustained activation of type I interferon signaling pathways. Incorporating microglia into sliced neocortical organoids extended the effects of aberrant type I interferon signaling in a human neural context. Collectively, our results illuminate the role of persistent type I interferon signaling in HIV-1 infected microglial in a human neural model, suggesting its potential significance in the pathogenesis of HAND.

Support part by grants from the NIH (R21NS120806), a Rutgers Busch Biomedical Grant, a Rutgers Brain Health Institute Pilot Grant, and the Robert Wood Johnson Foundation (Grant #74260). AJB was supported by NIH NIGMS T32GM8339 and NIH NCATS TL1TR003019.

Poster #29

Endothelin-converting enzyme-2 (ece-2) regulates endogenous synaptosomal and secreted β-amyloid in distinct brain regions.

Authors

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PI Name: Elizabeth Eckman

Levels of the Alzheimer's disease (AD) associated β-amyloid (Aβ) peptide are tightly regulated by proteases responsible for its production and degradation. Endothelin-converting enzymes (ECEs) cleave Aβ within acidic vesicles and pharmacological inhibition of ECEs causes rapid accumulation of both intravesicular and secreted Aβ. Compared to ECE-1, ECE-2 expression in the brain is both spatially and neuronal cell-type restricted, with the highest expression in GABAergic interneurons, and impaired ECE-2 activity has been implicated as a risk factor for late-onset AD. Understanding the spatial relationship between ECE-2 activity and endogenous Aβ metabolism will provide insight into regional and cell-type-specific Aβ regulation. Whole brain or microdissected regions from ECE-2 knockout (KO) and wild-type mice were homogenized to prepare crude synaptosomes and separate them from the extracellular (ISF-enriched) fraction. ECE-2 protein expression was confirmed by western blot and Aβ was measured by ELISA. ECE-2 localizes to synapses and, globally, ECE-2 KO mice had significantly increased synaptosomal and secreted Aβ. Subcortical structures and cerebellum had the highest ECE-2 protein expression and, in ECE-2 KO mice, the largest increases in synaptosomal Aβ. Secreted Aβ was significantly increased in all brain regions except cortex, with hippocampus showing the largest change and overall Aβ levels. Our results demonstrate that ECE-2 regulates endogenous synaptosomal and secreted Aβ within brain regions known to be important for cognition and impacted early in AD pathogenesis. Future research will determine how ECE-2 regulation may relate to the physiological function of Aβ and whether changes in endogenous ECE-2 activity can alter AD pathogenesis.

Poster #30

Using causally informed functional connectivity methods to identify prefrontal-cingulate TMS target for reward positivity modulation

Authors

Nicole D Lalta, Malte Gueth, Ravi D Mill, Michael W Cole, and Travis E Baker

PI Name: Travis E Baker

Anterior midcingulate cortex (MCC) dysfunction has been implicated in several psychiatric disorders, including addiction and depression. However, MCC's deep location from the skull makes it infeasible to develop treatments using transcranial magnetic stimulation (TMS). Recent attempts to indirectly modulate cingulate activity with TMS have used connectivity "hotspots" in prefrontal cortex (PFC). However, functional connectivity (FC) targets estimated with Pearson correlations pose theoretical limitations (e.g., spurious connections) and may in fact produce incorrect functional connections between two regions. We propose that FC methods grounded in stronger causal principles allow for effective control over spurious connections than standard correlation approaches and produce FC targets that better represent the direct functional connections between two regions. To test this idea, we used EEG-fMRI data from 18 healthy participants and created PFC-MCC targets using the field-standard Pearson correlation and combined-FC. Next, in our proof of target engagement study, we will present the TMS efficacy results of the standard correlation approach (PFC-MCC) in modulating the reward function of the MCC, as evaluated using the Reward Positivity. Combining TMS with resting-state FC methods and EEG provides a great opportunity for systematic investigations of the potential role of TMS in modulating deeper cortical activity, thereby opening an exciting new era of investigative possibilities in basic and clinical research in the domain of MCC function and beyond.

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Poster #31

Age-dependent, region-specific and cell type-specific ciliary defects and cell loss in the brains of a LRRK2 mouse model of Parkinson´s disease

Authors

Besma Brahmia, Yahaira Naaldijk, Pallabi Sarkar and Sabine Hilfiker

PI Name: Sabine Hilfiker

Pathogenic point mutations in the LRRK2 kinase cause Parkinson´s disease (PD), and previous studies have shown that cholinergic interneurons of the dorsal striatum lose their cilia in distinct mutant LRRK2 mouse models. Cholinergic alterations have been observed in sporadic PD patients and may arise due to altered cholinergic tone in the striatum and/or due to degeneration of specific cholinergic nuclei in the basal forebrain and brainstem. Cholinergic alterations have also been reported in manifesting and in prodromal LRRK2 G2019S mutation carriers, suggesting that pathogenic LRRK2 may impact upon cholinergic neurons in various susceptible brain areas before the onset of motor symptoms. Here, we probed for age-dependent ciliary deficits in different cell types and brain regions in a mouse strain carrying the most common human G2019S LRRK2 mutation. We show that cilia loss is cell type-specific and already evident in cholinergic neurons in the basal forebrain and brainstem in young G2019S LRRK2 mutant mice. In aged mice, cilia loss is also observed in striatal cholinergic interneurons and in dopaminergic neurons of the substantia nigra. In addition, ciliary loss in basal forebrain and brainstem cholinergic neurons in aged G2019S LRRK2 mutant mice correlates with cell death. Our data support a model in which pathogenic LRRK2 causes region-specific and cell type-specific cilia loss followed by age-dependent cell death of cholinergic neurons in vulnerable brain areas which is directly relevant to our understanding of early-stage changes in PD.

Supported by Busch Biomedical Research Grant.

Poster #32

Transcriptional changes within the adult auditory system contribute to lasting experience-dependent neuroplasticity of auditory temporal processing.

Authors

Aysegul Gungor Aydin, Faiza Ramadan, Alex Lemenze, Kasia M Bieszczad

PI Name: Kasia M Bieszczad

The ability to appreciate spectrotemporally rich speech sounds relies on learning-dependent processes in the cortex. Auditory cortical (AC) neuroplasticity can establish memories for the language-relevant acoustic cues that help the auditory system to “tune in” to salient timing cues in the auditory soundscape by enhancing sound-evoked temporal processing for learned salient cues. Recent work has demonstrated that blocking an epigenetic regulator of neuroplasticity, histone deacetylase 3 (HDAC3), promotes long-term memory formation for highly specific temporal features of acoustic cues in animals learning a temporal discrimination task. The mechanism of HDAC3 action is on de novo gene expression events that are required for memory. Thus, we capitalized on an opportunity to determine genes and biological pathways that may be important for efficient and high-fidelity temporal cue learning and processing in the auditory cortex. We performed bulk RNA-seq on adult AC samples in trained rats treated with an HDAC3 inhibitor learning the same established temporal discrimination task and utilized snRNA-seq to determine cell-type-specific patterns of experience-induced transcription with a particular focus to uncover transcriptional contributions in non-neuronal cell types. This work demonstrates that auditory associative learning results in changes to the adult auditory transcriptome. There are 28 unique genes, including *Homer1* and *Shank2*, which regulate excitatory synapse morphogenesis and play a critical role in synaptic plasticity, that were differentially expressed. Bioinformatic analysis was used to determine gene network analysis and protein-protein interactions and revealed three functional clusters in learning-induced AC genes. Revealing gene targets for temporal processing informs mechanisms of developmental language disorders.

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Poster #33

Regulation of dopamine function by the gastrin-releasing peptide in stress-enhanced fear

Authors

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PI Name: Gleb P. Shumyatsky

The role of dopamine in fear learning and extinction is poorly understood compared to its role in reward-related behavior. A core symptom observed in post-traumatic stress disorder and phobias are deficits in fear extinction. Thus, identification of molecules that regulate dopamine function in stress-related memories would help our understanding of the mechanisms behind post-traumatic stress disorder and phobias. A prior history of stress can enhance subsequent learning of conditioned fear, making it more resistant to extinction. Stress-Enhanced Fear Learning (SEFL) is a behavioral assay used in mice to assess the effect of an acute stressor over fear acquisition and extinction. We generated the *gastrin-releasing peptide* gene knockout (*Grp*-/-) mice and found that they exhibit delayed fear extinction and enhanced long-term memory recall after SEFL. When examining candidate genes in the basolateral nucleus of the amygdala (BLA) following long-term memory recall of SEFL, we found that transcription of dopamine-related genes was decreased in *Grp*-/- mice. Using fiber photometry approach to record dopamine signals, we also found enhanced signal of the dLight sensor in the BLA of *Grp*-/- mice during training and extinction. Altogether, our data suggest that the Grp may regulate dopamine function during stress-enhanced fear learning and extinction.

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Poster #34

Resurgence of destructive behavior following decreases in alternative reinforcement: a prospective analysis

Authors

Brian D. Greer, Timothy A. Shahan, Casey Irwin Helvey, Wayne W. Fisher, Daniel R. Mitteer, and Ashley M. Fuhrman

PI Name: Brian D. Greer

Basic and retrospective translational research has shown that the magnitude of resurgence is determined by the size of the decrease in alternative reinforcement, with larger decreases producing more resurgence. However, this finding has not been evaluated prospectively in a clinical population. In Experiment 1, five participants experienced a fixed progression of reinforcement schedule-thinning steps during treatment of their destructive behavior. Resurgence magnitude was uniformly low across steps and participants. In Experiment 2, five other participants experienced these same schedule-thinning steps but in a counterbalanced order. Size of the decrease in alternative reinforcer availability and order of the schedule-thinning steps jointly appeared to determine resurgence magnitude, with larger transitions occurring earlier producing the most resurgence. Analysis of the first transition experienced across participants in Experiment 2 resembled a positively accelerating exponential function relating resurgence magnitude to size of the decrease in alternative reinforcer availability. Implications of these findings will be discussed.
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Poster #35

Studying transmissive properties of mutant huntingtin using multimodal bioimaging

Authors

Nora Jaber, Yun-Kyung Lee, Jennifer Jiang, Bruna Favetta, Benjamin Schuster, Wei Dai

PI Name: Wei Dai

Many proteins associated with neurodegenerative diseases are intrinsically disordered proteins (IDPs) that exhibit “prion-like” behaviors, in which they are transmitted from cell-to-cell, spreading pathological proteins that act as nucleation sites for aggregates. The goal of this project is to seek answers on the how neurodegenerative IDPs spread, using mutant huntingtin protein (HTT), associated with Huntington’s Disease (HD), as a model. Evidence shows that when mutant HTT poly-glutamine (polyQ) track is expanded, the protein has a higher propensity to aggregate and is more transmissive in nature. Since membranes modulate the formation of IDP inclusions, protein-membrane interactions may be promoting transmission. We take an interdisciplinary approach by combining cryo-electron tomography (cryoET) with biochemical and biophysical assays to elucidate the molecular mechanisms of HTT transmission and to understand how interactions with membranes affect mutant HTT aggregation and potential spread. We hope to shed light on fundamental characteristics that influence neurodegeneration, opening new avenues for more precise and effective therapeutic approaches.

Supported by NSF grant MCB-2046180

Poster #36

Effects of manipulation of various reinforcement parameters on responding during extinction .

Authors

Catherine Kishel, Wayne Fisher, Brian Greer, Daniel Mitteer, and Casey Helvey

PI Name: Wayne Fisher

Children who engage in problem behavior (e.g., aggression) often so do because that behavior works to gain access to reinforcement (e.g., toys, attention). Treatment involves providing reinforcement for an appropriate response instead of for problem behavior. However, in real-world contexts, reinforcement for appropriate requests cannot always be delivered precisely how or when the child wishes (i.e., sometimes the child might have to wait for attention or play with a less preferred toy). Periods of time during which the child cannot access reinforcement are known as extinction, and contacting extinction sometimes results in the resurgence of problem behavior. The current research seeks to evaluate the effects of manipulating several parameters of reinforcement (e.g., rate, magnitude) on responding during an extinction context (i.e., when no reinforcement is delivered). The purpose is to identify how changes in reinforcement delivery during treatment (e.g., such as when reinforcement is delivered less often for an appropriate request) affects problem behavior during extinction (again, when reinforcement is not delivered at all) such that those variables can be controlled and the resurgence of problem behavior mitigated. Preliminary results indicate that manipulating parameters of reinforcement in treatment might not result in an increase in problem behavior during extinction; the clinical significance of this finding is discussed.

This study was supported by R01HD079113, R01HD093734, R01HD108617 and R01HD109266

Poster #37

Influence of interleukins in the lateral habenula on alcohol use disorders

Authors

Wanhong Zuo and Jiang-Hong Ye

PI Name: Jiang-Hong Ye

Prolonged alcohol consumption has been shown to influence proinflammatory cytokines and microglia in the brain. In the context of the brain's lateral habenula (LHb), which is associated with aversive processing, the high expression of interleukin-6 (IL-6) and interleukin-18 (IL-18) receptors raises questions about their involvement in alcohol use disorder. Our study reveals reduced IL-6 levels in rats experiencing withdrawal from chronic ethanol exposure. Furthermore, it appears that IL-6 and IL-18 inhibit the activity and excitatory synaptic transmission within LHb neurons. Interestingly, when IL-6 and IL-18 are administered through microinjections directly into the LHb, they produce anxiolytic effects and help alleviate depressive-like behaviors in rats undergoing withdrawal from chronic alcohol exposure. Importantly, either IL-6 or IL-18 significantly reduced ethanol consumption. Notably, this effect is more pronounced in female rats. Our findings suggest that IL-6 and IL-18 in the LHb play a significant role in alcohol use disorder.

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Poster #38

Elevated perinatal interleukin-6 modifies hippocampal physiology to produce ASD-like behaviors

Authors

Rouba Houbeika, Sidra Ali, Naia Marcelino, Simon Szotak, Corina Brito, Tazneem Alayoubi, Fernando Janczur Velloso, Ozlem Gunal and Steven W. Levison

PI Name: Steven W. Levison; Ozlem Gunal)

Autism (ASD) spectrum disorder is a neurodevelopmental disorder characterized by difficulties in communicating and interacting with other people. Successful social interaction requires acquiring information and reconstructing those memories to behave accordingly, highlighting the importance of the hippocampus. Epidemiologic studies have demonstrated that maternal infections stimulate the production of interleukin-6 (IL-6), which can cross the placenta and fetal blood brain barrier to alter brain development. To model the effects of increased levels of IL-6 at the end of the second trimester of human development we have injected male and female mice with PBS as controls or IL-6 twice daily, from post-natal day 3 until post-natal day 6. Our published studies have shown that IL-6 treatment altered patterns of ultrasonic vocalizations, reduced social interactions and increased self-grooming in male mice. Here we show that contrary to our expectations, when tested at 5 weeks of age, the IL-6 treated males performed better on the object location task of spatial memory while the IL-6 treated females performed worse than controls. Correspondingly, using hippocampal slices, the males exhibited a trend towards increased long-term potentiation (LTP) and showed increased long-term depression (LTD) in the CA1 of the dorsal hippocampus. IL-6 treated males also showed a decrease in total apical dendritic spines in the CA1 region of the hippocampus vs. controls (but an increase in thin spines). Taken altogether, these data show that a short increase in circulating IL-6 is sufficient to causing lasting changes in synaptic plasticity that are sex dependent.

Supported by a grant awarded to FJV from the Governor's Council for Medical Research and Treatment of Autism (CAUT22AFP009) and by NS116828-04 awarded to SWL

Poster #39

A potential patient stratification biomarker for Parkinson´s disease based on LRRK2 kinase-mediated centrosomal alterations in peripheral blood-derived cells

Authors

Yahaira Naaldijk., Fasiczka, R., and Hilfiker, S.

PI Name: Sabine Hilfiker

Parkinson´s disease (PD) is a common neurodegenerative movement disorder and leucine-rich repeat kinase 2 (LRRK2) is a promising therapeutic target for disease intervention. However, the ability to stratify patients who will benefit from such treatment modalities based on shared etiology is critical for the success of disease-modifying therapies. Ciliary and centrosomal alterations are commonly associated with pathogenic LRRK2 kinase activity and can be detected in many cell types. We previously found centrosomal deficits in immortalized lymphocytes from G2019S-LRRK2 PD patients. Here, to investigate whether such deficits may serve as a potential blood biomarker for PD which is susceptible to LRKK2 inhibitor treatment, we characterized patient-derived cells from distinct PD cohorts. We report centrosomal alterations in peripheral cells from a subset of early-stage idiopathic PD patients which is mitigated by LRRK2 kinase inhibition, supporting a role for aberrant LRRK2 activity in idiopathic PD. Centrosomal defects are detected in R1441G-LRRK2 and G2019S-LRRK2 PD patients and in non-manifesting LRRK2 mutation carriers, indicating that they acumulate prior to a clinical PD diagnosis. They are present in immortalized cells as well as in primary lymphocytes from peripheral blood. These findings indicate that analysis of centrosomal defects as a blood-based patient stratification biomarker may help nominate idiopathic PD patients who will benefit from LRRK2-related therapeutics.

Supported by MJFF-019358, MJFF-020338

Poster #40

Effects of a neuroprotective serotonin receptor peptide on behavioral pattern separation following mild traumatic brain injury in the rat

Authors

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PI Name: Mark B. Zimering

Accelerated cognitive decline frequently complicates traumatic brain injury (TBI). Human TBI patients and several rat species harbored G-protein coupled receptor agonist IgG autoantibodies whose *in vitro* neurotoxicity was prevented by a novel synthetic peptide fragment of the second extracellular loop of the serotonin 2A receptor (SN.8). Intraperitoneal (IP) delivery of SN.8 strengthened recall of spatial learning (one-week) after sham injury in Zucker rats. In this study, we tested whether SN.8 (2mg/kg) administered IP at 1-,3- and 5-days after mTBI altered behavioral pattern separation performance vs. 2 mg/kg scrambled peptide. Male Sprague-Dawley (SD) rats were trained (pre-injury) to differentiate between stable and unstable swim platforms (located 1.5, 3.0 or 4.5 feet apart) in a modified Morris water maze protocol, behavioral pattern separation (BPS), to assess deficits in pattern separation at 2- and 5-weeks after mTBI injury. Five weeks' post injury, mTBI rats displayed an increase in the number of errors compared to pre-injury performance at 1.5 feet, while sham injured rats significantly improved performance (5-weeks post injury) compared to pre-injury, perhaps consistent with a 'practice effect.' SN.8 peptide was associated with significantly improved BPS performance in mTBI rats tested at 4.5- and 3.0-feet separation, two weeks post-injury. There was no significant difference in BPS performance in TBI rats treated with SN.8 vs scrambled peptide at baseline or five weeks post-injury. These results suggest that SN.8 may modulate behavioral pattern separation at an early time point after mTBI in the adult SD rat.

This work was supported by CBIR 22 PIL022 from New Jersey Commission Brain Injury Research to MZ

Poster #41

Neural mechanisms of scaled value under craving: relationship to drug and food-related addictive symptomatology

Authors

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PI Name: Anna Konova

Craving is commonly experienced by both healthy individuals and those with addictive disorders. We previously showed that craving scales subjective value in a multiplicative-gain manner along a similarity dimension: people value disproportionately more craved items and similar ones, but craving is not reflected in changes in the value of dissimilar options. To understand how these scaling and similarity effects are generated, here we investigated BOLD activity within the putative craving circuit in an incentivized decision task. Additionally, we examined if addictive-like symptomatology potentiated these effects. Participants (N=32) repeatedly reported on their willingness-to-pay (WTP, indexing current subjective value) and desire for various palatable snack foods both before and after a multisensory craving induction designed to elicit craving for one of the snacks. Behaviorally, all participants demonstrated a significant increase in desire and WTP for the 'craved snack', especially when offered in higher quantities. Neurally, we found canonical value regions (ventromedial prefrontal cortex and ventral striatum) tracked these changes in value and psychological state; however, there were no differences by addiction symptomatology. Low symptomatology individuals only increased WTP for the target 'craved snack', whereas individuals with more problematic and addictive-like eating displayed greater WTP across all snacks offered post-induction, suggesting overgeneralization of craving. Moreover, the amygdala tracked similarity contingent on symptomatology, with higher symptomatology individuals displaying increased activation post-induction. These results tie in the putative craving circuit to value-based decision making and implicate the amygdala in differentially tracking similarity effect, which is integrated into computed subjective value.

Supported by NIDA (R01DA054201) & NJACTS (1TL1TR003019)

Poster #42

Investigating genetic susceptibility for chemotherapy-induced cognitive impairment in a juvenile ApoE4 rat model

Authors

Chadni Patel, Frank Diglio, Jeremy Willekens, Derek Adler, Yongkyu Park, Peter D. Cole

PI Name: Peter D. Cole

While cure rates are rising for pediatric cancer patients, many survivors experience chemotherapy-induced cognitive impairment (CICI) (or "chemobrain"), which negatively impacts the quality of life. Despite extensive research into the multifactorial causes of CICI, the interpatient variability in susceptibility to CICI is not well understood. The E4 allele of Apolipoprotein E (ApoE) in pediatric cancer survivors is associated with increased vulnerability to cognitive dysfunction after treatment with identical chemotherapy doses than those with the more prevalent ApoE3 allele. In our experimental model, juvenile rats homozygous for either the human ApoE3 or ApoE4 allele were exposed to doxorubicin (DOXO) at a clinically relevant dose (2 mg/kg of DOXO once weekly for 4 weeks) or saline. ApoE4 rats were more likely than ApoE3 rats to exhibit DOXO-induced impairments in visual memory. However, there was no difference between ApoE3 and ApoE4 rats in sensitivity to DOXO-induced spatial memory impairments. Analysis of MRI scans focused on specific brain regions showed no significant alterations in the blood-brain barrier (BBB) integrity within the hippocampus, corpus callosum, and cortex. In summary, ApoE genotype contributes to differential susceptibility to CICI. To delve deeper into the neuropathological basis of DOXO-induced cognitive impairment, ongoing investigations involve immunohistochemical analyses targeting changes in neuronal and glial cell populations in the brain.

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Poster #43

Supt6 deletion in parvalbumin-expressing interneurons induces seizure development and behavioral abnormalities in mice

Authors

Bruno Carabelli, Tho Lai, Madhuvika Murugan, Detlev Boison, Yong Kim

PI Name: Yong Kim

Supt6 is a histone chaperone, a binding partner of RNA polymerase II, and an interactor of S100a10 (also called p11), alterations of which have been implicated in the etiology of major depressive disorder and antidepressant actions. Because dysfunction of parvalbumin (PV)-expressing interneurons are implicated in epilepsy and neuropsychiatric disorders, we examined the effects of Supt6 deletion in PV neurons on seizure development and behavioral alterations. We generated PV neuron-specific Supt6 homozygous and heterozygous KO mice. Measurement of behavioral seizures, EEG analyses, immunofluorescence for PV expression, and Timm staining for mossy fibers sprouting were performed. Animals were subjected to Open Field Test, Sucrose Splash Test (SST), Nest Building and Forced Swim Test (FST). PV-Supt6 homozygous KO mice displayed a convulsive seizure phenotype and died around 5 weeks of age. These mice also presented mossy fibers sprouting in the hippocampus. PV-Supt6 heterozygous KO mice displayed subclinical electrographic seizures and deficits in grooming behavior in the SST, faster passive coping in the FST, and lower nesting scores. Immunoreactivity for PV was significantly decreased in the hippocampus and cortex of PV-Supt6 heterozygous and homozygous KO mice compared to WT controls. Supt6 deletion in PV neurons causes seizure development and behavioral abnormalities related to apathy-like behavior, faster passive coping to stress and impaired welfare. This animal model may serve as a useful tool for the studies of PV neuronal development and the mechanisms relevant to epilepsy and psychiatric disorders.

Supported by BHI Trainee Travel Award, 2023 (BC), AES seed grant and R21 NS130250 (YK)

Poster #44

Identification of cell-specific differential gene expression profiles by snRNA-seq following repetitive weaponry-type blast-induced traumatic brain injury

Authors

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PI Name: Bruce A. Citron

Mild traumatic brain injuries (mTBIs) among military and law enforcement personnel are frequently caused by low-level blast exposures from use of heavy weaponry during training and active service. Service personnel who sustain repetitive weaponry-type blast-induced TBI (rwbTBI) develop mild symptoms including cognitive impairments, attention deficits, mood changes, irritability, and sleep disturbances. We are interested in neuronal health and understanding mechanisms to improve cognitive outcomes for Veterans and others. We investigated whether modulation of neuroprotective transcription factors can help combat neuroinflammatory responses and neuronal loss following rwbTBI by influencing gene expression profiles of cell populations within the hippocampus. Male C57Bl/6J mice received five 70 kPa blast exposures at 1-min intervals in a well-established shock tube system to model occupational use of heavy weaponry. Mice were treated with tert-butylhydroquinone (tBHQ), a Nrf2 activator, and pioglitazone, a Pparγ agonist, at 30 minutes post-injury. Single nucleus RNA sequencing (snRNA-seq) was performed using nuclei isolated from mouse hippocampal tissue at 24 hours post-injury. Preliminary analysis identified differential expression of genes of interest including a 3-fold upregulation of *Nfe2l2*, the gene that encodes Nrf2, in dentate granule cells due to injury. We also conducted gene ontology and pathway analysis to identify functional profiles in various cell types after injury and/or treatment. This study provides a deeper understanding of the mechanisms that underlie neuropathological changes following repetitive weaponry-type blast exposure and provides a foundation for the identification of therapeutic targets that could be modulated to improve the health of Veterans and others with histories of blast exposures.

Supported by VA grants I01BX005015 & IK6BX006188 (BAC), I01BX004561 (KDB), I01RX001520 (BAC), IK2RX003253 (VD)

Poster #45

Biallelic ABCC9 loss-of-function variants are associated with AIMS - an emerging neurodevelopmental disorder with myopathic features.

Authors

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PI Name: Conor McClenaghan

Loss-of-function (LoF) mutation of *ABCC9*, the gene encoding the SUR2 subunit of ATP sensitive-potassium (K_{ATP}) channels, was recently associated with autosomal recessive *ABCC9*-related intellectual disability and myopathy syndrome (AIMS). The affected individuals exhibited mild cerebral white matter hyperintensities, intellectual disability, similar facies, myopathy, and cardiac systolic dysfunction in the two oldest patients. In this study, we identified nine additional subjects, from seven unrelated families, harboring different homozygous LoF variants in *ABCC9* and presented with a conserved range of clinical features, which were observed in the original AIMS subjects. All variants are predicted to result in severe truncations or in-frame deletions within SUR2, leading to the generation of non-functional K_{ATP} channels in heterologous expression studies. These patients show psychomotor delay and intellectual disability of variable severity associated with microcephaly, corpus callosum and white matter abnormalities, seizures, spasticity, short stature, muscle fatigability, and weakness. Interestingly, the heterozygous parents were unaffected but report multiple incidences of intrauterine fetal death. Zebrafish carrying a 13-base frame-shift deletion in the *abcc9* resulting in a loss of SUR2-dependent K_{ATP} channel expression were used as *in vivo* model of AIMS. The zebrafish larvae also exhibited a distinct AIMS phenotype. *In vivo* studies of *ABCC9* LoF in zebrafish revealed an exacerbated motor response to pentylenetetrazole, a pro-convulsive drug. These findings are consistent with impaired neurodevelopment associated with an increased seizure susceptibility. Our findings define a distinct *ABCC9*-related phenotype, expanding the clinical spectrum of AIMS.

Supported by K99/R00 HL150277

Poster #46

Characterizing the Impact of Developmental *Cc2d1a* Reduction as a Novel mouse model of ASD/ID

Authors

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PI Name: M. Chiara Manzini

Intellectual disability (ID) and Autism Spectrum Disorder (ASD) are highly heterogeneous neurodevelopmental disorders, making driving neuronal mechanisms difficult to isolate and study. Research has linked CC2D1A loss of function (LOF) to fully penetrant ID and highly penetrant ASD. Existing mouse models for CC2D1A LOF rely on conditional knockouts (cKOs) due to early postnatal lethality in global knockouts (KOs). However, cKO models have limited translatability to CC2D1A LOF patients due to their cell-specific and postnatal gene removal. Our lab created a mouse line homozygously tagged with V5 and HA epitope tags to enhance endogenous CC2D1A signal detection, but this led to protein degradation. These V5-HA homozygous mice survived with an approximately 86% developmental reduction in CC2D1A but did not exhibit ASD/ID-like behavioral deficits. To explore the phenotypic expression threshold, we bred Cc2d1a heterozygous and V5-HA tagged alleles to generate Cc2d1a-/V5-HA compound heterozygous (compHET) mice, which displayed viability but tended to be smaller, particularly among females. Current data from these mice suggests a male-specific memory acquisition deficit during Morris Water Maze, similar to male CaMKII-Cre cKOs. Additionally, compHET male mice showed slight memory retention deficits and cognitive flexibility deficits not observed in cKOs. However, they did not replicate the social and affective deficits seen in cKOs. We are exploring CREB activation through PKA, ERK, PDK1, and CaMKII pathway dysregulation. This *Cc2d1a* developmental haploinsufficiency mouse model suggests a very narrow CC2D1A expression threshold for phenotypic penetrance and neuronal dysregulation.

Supported by Eagles Autism Foundation, RWJ Foundation (grant #74260), and NIH R01NS105000

Poster #47

Knockdown of VMH nNOS reduces spontaneous physical activity, leading to hyperglycemia and increased adiposity

Authors

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PI Name: Vanessa H. Routh

The ventromedial hypothalamus (VMH) and lateral hypothalamus (LH) play an established role in weight maintenance. The effects of LH orexin neurons on energy balance are dependent on inhibition of VMH AMP-activated protein kinase (AMPK). The VMH possesses AMPK-dependent glucose inhibited (GI) neurons that we have previously shown to regulate blood glucose. We hypothesize that VMH GI neurons, which also depend on neuronal nitric oxide synthase (nNOS) for glucose sensing, project to the LH and regulate energy and glucose homeostasis. To test this hypothesis, we used retrograde tracing and optogenetics paired with electrophysiological recordings, as well as viral knockdown with shRNA. We found that ~40% of VMH neurons projecting to the LH are GI, and that VMH neurons form glutamatergic synapses on ~10% of LH orexin neurons. shRNA knockdown of VMH nNOS (putative GI neurons) significantly increases body weight (mean ±SEM, nNOS: 32.04 ± 2.45% vs. control: 7.35 ± 1.51%, $p<0.0001$) and inguinal fat weight (nNOS: 0.226± 0.021% vs. control: 0.102± 0.0102, $p<0.0001$). This was associated with increased blood glucose (nNOS: 289 ± 15 mg/dl vs. control: 246± 8 mg/dl, $p=0.026$) and decreased dark (nNOS: 94.28 ± 19.05” vs. control: 336.6± 59.88” $p=.0084$) and light period (nNOS: 102.9± 28.10” vs. control: 438.4± 108.10”, $p=0.0239$) physical activity. We conclude that VMH nNOS neurons exert a tonic suppression of blood glucose level by increasing spontaneous physical activity. This may be mediated by LH orexin neurons. Inhibition of VMH nNOS neurons reduces spontaneous physical activity, leading to hyperglycemia and increased adiposity.

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Poster #48

Striatal dopamine in a high-risk schizophrenia mouse model.

Authors

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PI Name: Miriam Bocarsly

Schizophrenia is a mental disorder affecting behavior, cognition, and emotion. While schizophrenia is characterized by the dysregulation of dopamine in the brain, specifically the striatum, its physiology is undetermined. Olanzapine, an atypical antipsychotic, is commonly prescribed to patients with schizophrenia. Notoriously, the chronic treatment of Olanzapine presents with a slew of side effects, most notably weight gain, depression, and anxiety. The 3q29 microdeletion presents a 40>fold increased risk of schizophrenia in humans with symptoms including executive function deficits and psychosis. This deletion has been recapitulated in a CRISPR mouse model. Mice with this deletion have reduced brain volume and several behavioral impediments including social interaction, cognition, and increased sensitivity to amphetamines. Utilizing fast scan cyclic voltammetry, 3q29 deletion mice were compared to littermate controls for electrically evoked dopamine in the striatum. Dopamine release in both strains were significantly different at baseline without any treatment. Another group of mice were surgically implanted with osmotic pumps that delivered either Olanzapine (8mg over 24 hours) or vehicle for 9 weeks. We observed electrically evoked dopamine release in the striatum, weight changes, and depressive-like and anxiety-like behaviors that may arise due to chronic Olanzapine treatment. Together, these data will help determine the mechanisms of Olanzapine treatment, and help inform the development of better, targeted drugs in the future.

Poster #49

Secreted semaphorin signaling regulates aging-associated dendritic modifications and cognitive function

Authors

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PI Name: Tracy S. Tran

There is a significant loss of dendritic complexity with age, which may account for age-associated synaptic loss and cognitive decline in mammals, including humans. However, molecular mechanisms underlying these changes are unclear. Some molecular players in dendritic morphogenesis are class 3 semaphorins. In development, in layer V cortical neurons, semaphorin 3A (Sema3A) signals through receptors Neuropilin-1/Plexin-A4 to induce basal dendritic arborization, while Sema3F signals through Neuropilin-2/Plexin-A3 to induce spine pruning on apical dendrites. Interestingly, both ligands are expressed in adulthood, but their role in age-associated dendritic remodeling is unknown. To address this, we established an *in vitro* model of aging mouse primary cortical neurons and examined effects of Sema3A and Sema3F on dendritic branching in aged vs. young neurons. We confirmed that significantly more neurons 15-30 days *in vitro* (DIV) express aging-associated senescence-associated-β–gal than 5DIV. Treating with either ligand increases branching from 5-15DIV, but not 30DIV, suggesting changes in the cellular response to Sema3A/3F with time in culture and possibly with aging. Furthermore, Plexin-A4 expression in wildtype cortices decreases in 18- vs. 6-month-old mice. When we assessed cognition in aged wildtype and adult *Plexin-A4*$^{-/-}$ mice with reversal learning, adult *Plexin-A4*$^{-/-}$ and aged wildtype mice performed significantly worse than adult wildtypes, suggesting that age-associated loss of Plexin-A4 may be responsible for impaired cognition. Collectively, our study provides novel insights into the involvement of semaphorin-plexin signaling in age-associated dendritic loss and cognitive decline. This work serves as a platform for future experiments to investigate the role of semaphorin signaling in neurodegenerative diseases.

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Poster #50

Post-ictal oscillations are associated with tissue integrity in the hippocampus of epileptic mice

Authors

Daniel J. Valdivia, Fabio C. Tescarollo, Koray Ecran, Betsy Vasquez, Spencer Chen, Hai Sun

PI Name: Hai Sun

The electrophysiological characteristics of the immediate post-ictal state remain unexplored. We identified characteristic post-ictal oscillations (PIOs) that may shed light on neural substrate integrity, providing clinicians with useful diagnostic information. Sixteen mice were microinjected with kainic acid (KA) in the dorsal (dKA) or ventral (vKA) hippocampus, and electrodes were implanted in bilateral CA1 and DG of the dorsal hippocampus to record LFPs of spontaneously occurring seizures. All animals underwent 24-hour video-EEG recordings. In animals from the vKA group, there was a higher proportion of animals that showed PIOs (87.5%) and higher PIO occurrence (51.0%) compared to the dKA group (37.5% and 32.5% respectively). 191 of 416 seizures recorded exhibited PIOs in one or more LFP channels. PIOs had a median duration of 12.3s (IQR 8.3-23.3s), with the majority showing the strongest power in the gamma band (30-80Hz). We also observed a correlation between the hippocampal sclerosis in the recording site and PIO rate, whereas recording areas that displayed pyramidal cell loss and granule cell dispersion had the lowest PIO rates recorded (1.2%) compared to recording areas with relatively undisturbed tissue (74%). A strong positive correlation was observed between PIO incidence and CA1 thickness, and a negative correlation with DG thickness. We detected PIOs in tissue immediately adjacent to epileptogenic hippocampal tissue, whereas at the focus of epileptogenesis, the pathological disruptions likely blocked the emergence of PIOs. Our results may help clinicians in determining the location of the seizure focus for surgical resection.

Poster #51

Peripubertal bisphenol-a exposure is associated with early puberty onset, dysregulated feeding, and anhedonia-like outcomes in adulthood: a role for the orexin (hypocretin) system.

Authors

Michelle M. Bilotti, Verena Isskandar, Shabree Anthony, Nick T. Bello, Troy A. Roepke, Morgan H. James

PI Name: Morgan H. James

Early pubertal onset is the strongest predictor of depression in girls. Puberty onset is determined by an interaction of several endogenous factors but can be altered by exposure to endocrine-disrupting compounds, including bisphenol-A (BPA, which been shown to accelerate puberty onset and alter feeding and mood outcomes in early adulthood. Studies have linked these outcomes to the hypothalamic orexin system, yet no study has investigated how BPA exposure may affect orexin functioning. Female rats were exposed to BPA (0, 25, 250µg/kg/day) via their drinking water on post-natal days 29-56. Rats were monitored for vaginal opening (VO) and estrus cycling. After BPA exposure, motivation for palatable food was assessed with different assays: 1) binge-like eating of sweetened fat (10% sucrose and 90% vegetable shortening, 2x/week for 30 mins); 2) economic demand for sucrose; and 3) saccharine preference. Brains were collected for immunohistochemistry and qPCR analyses. BPA exposure was associated with earlier VO (advanced puberty) and irregular estrous cycling. BPA (250µg/kg) reduced binge-like eating, demand for sucrose, and saccharine preference, indicating amotivation for palatable food. Additionally, BPA decreased orexin gene and protein expression in hypothalamus, and reduced reactivity of orexin neurons to reward-associated stimuli. Together, these data indicate that peripubertal BPA predisposes to early puberty onset and reduced motivation in early adulthood – a phenotype reminiscent of anhedonia in depression. These outcomes are associated with a downregulation of orexin functioning, indicating that normalization of this system might be a potential strategy for improving mental health outcomes in women that experience early pubertal onset.

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Poster #52

Loss of PAR3 affects pTua accumulation by increasing lysosomal pH

Authors

Ruizhe Tang, Sun Miao, Anisha Patel. Huaye Zhang

PI Name: Huaye Zhang

Par3 is a conserved partitioning-defective polarity protein found in various organisms. It forms a complex with Par6, PKC, and Cdc42, participating in the regulation of animal cell development. In the process of structural remodeling of axons and dendrites, the regulation of actin filament cytoskeletal assembly and contractile forces contributes to the morphogenesis, polarization, and migration of neurons during brain development. Synaptic failure is the direct reason for cognitive decline and memory dysfunction in Alzheimer's disease, and the loss of dendritic spines directly correlates with the loss of synaptic function. By using Par3 conditional knockout mice, in recent experiments we further found that mice lacking Par3 protein significantly increased pTau accumulation with age compared with wild-type mice. Simultaneously, lysosomes in neuronal cells PH increased significantly. Lysosomal enzymes function optimally within a narrow acidic pH range, and their functions include the degradation of large amounts of proteins in lysosomes and aiding in the initiation of the apoptotic process within the cytoplasm. The increase in pH value in Par3 KO neurons further indicates that the loss of Par3 accelerates the reduction of the efficiency of the intracellular clearance system. The study of how Par3 affects lysosomal pH can help us further understand the new ways in which polarizing proteins are involved in mediating synaptic failure.

Supported by the National Institutes of Health grant to HZ

Poster #53

Astrocyte calcium activity improves motor function in Parkinson's disease.

Authors

Wesley R. Evans, Sindhuja Baskar, Ana Raquel Castro E Costa, Abimbola Arigbe, Rafiq Huda

PI Name: Rafiq Huda

The dorsal striatum is an integrative nucleus innervated by sensorimotor projections from the cortex and thalamus and is reliant on dopaminergic (DA) neuromodulation for proper functioning. Loss of DA projections into the striatum is the major cause of motor dysfunction in Parkinson's disease (PD). In lieu of electrical excitability, astrocytes have spatiotemporally rich and robust calcium dynamics that are modulated under multiple forms of local neuronal activity. These transient increases in astrocyte calcium levels are implicated in local circuit dynamics. Here, we studied the role of astrocyte calcium signaling in the dorsal striatum. We characterized the role of astrocytes in the dorsal striatal circuit by recording fiber photometry signals from mice virally expressing the membrane-tagged calcium indicator GCaMP6f-lck under the astrocyte specific gfaABC$_1$D promoter. We recorded voluntary and forced locomotion conditions in head-fixed animals. Astrocytes in the dorsal striatum exhibit robust increases in calcium during locomotion across behavioral paradigms. Acute dopamine receptor antagonism and chronic dopamine projection lesioning with 6-OHDA reduced movement-related astrocyte calcium activity. To understand the behavioral effects of direct astrocyte activation, we unilaterally injected an astrocyte specific viral vector expressing either Gi-DREADD or mCherry control into the dorsal striatum and infused 6-OHDA (or vehicle) into the medial forebrain bundle (MFB). Chemogenetic activation of astrocytes in 6-OHDA lesioned animals increased contralateral paw usage in cylinder task compared to control conditions. Our data suggests that astrocytes are important endogenous neuromodulators of movement-related dorsal striatal circuits, and represent a potential therapeutic target for the motor symptoms of PD.

Supported by Brain Research Foundation, American Parkinson Disease Association, Parkinson Foundation, NIAAA 5T32AA028254 – MNADRT Fellowship

Poster #54

Administration of the dual orexin receptor antagonist suvorexant during the active vs. inactive period: Implications for cocaine behaviors.

Authors

Shayna L O'Connor, U Gyawali, MS. Paladino, N Krishnakumar, MM. Bilotti, DJ. Barker, MH. James

PI Name: Morgan James

Cocaine self-administration in rats is associated with an increase in the number and activity of orexin (hypocretin) neurons. Orexin neurons are involved in reward and sleep, both of which are perturbed in cocaine use disorder. Here, we tested if the FDA-approved dual orexin receptor antagonist suvorexant, which is currently indicated to promote sleep in insomnia, can be used i) at low, non-sedating doses during the active period to reduce drug seeking, and ii) at higher doses to normalize sleep and subsequent drug seeking during cocaine abstinence. Male and female Long Evans rats were assessed for baseline economic cocaine demand using a within-session threshold procedure. Rats were then given daily intermittent access (IntA) to cocaine (5min access every 30min for 6h) for 2w. One group of rats (n=24) was treated with suvorexant (0, 3, 10, 30mg/kg; p.o., within-subjects) prior to being reassessed for demand during the active period. To test for soporific effects of suvorexant, these rats were also tested on the rodent psychomotor vigilance task (rPVT), which requires rats to maintain attention for 30min to earn sucrose rewards; rats received suvorexant prior to testing, as above. A second group of rats (n=14) underwent extinction training for 7d; during this time, rats received suvorexant (0, 30mg/kg, p.o.) 30min prior to the onset of the inactive period. Males and females both exhibited increased cocaine demand following IntA; this was reversed by suvorexant (10, 30mg/kg). Suvorexant did not impair performance on the rPVT. Repeated dosing with suvorexant during the inactive period facilitated extinction. Suvorexant efficacy in females was not affected by estrus stage. Suvorexant can be used acutely during the active period to reduce drug motivation and during the inactive period to accelerate extinction of drug seeking.

Supported by R00 DA045765; Busch Biomedical Research Grant FP00027458

Poster #55

Advanced Fluorescence Microscopy Techniques Facility: Waksman Institute Shared Imaging Facility, a Rutgers Core Facility.

Authors

Nanci Kane

PI Name: Arvin Lagda, PhD, Director of Waksman Institute Core Facilities

The Waksman Institute Shared Imaging Facility is located on Busch Campus of Rutgers, The State University of New Jersey. Our Facility provides training and access to cutting edge optical imaging capabilities on five fluorescent microscopes and two image analysis workstations and provides researchers the ability to image a variety of sample types. Our Facility has the following microscopes: two Leica SP8 Confocals, Leica Stellaris8 Confocal, Andor Dragonfly Spinning Disk Confocal, and Zeiss Elyra7 Structured Illumination. Some of our microscope features include deconvolution, quantification, co-localization, FLIM (Fluorescence Lifetime Imaging Microscopy), FRET (Förster Resonance Energy Transfer), FRAP (Fluorescence Recovery After Photobleaching), time-lapse, Super Resolution Radial Fluctuations (SRRF-Stream), photo-ablation, optogenetics, Structured Illumination super resolution (SIM), Single Molecule Localization (SMLM), Total Internal Reflection (TIRF) and widefield (WF), as well as software tools for image analysis. We are a Rutgers Core Facility and are open to researchers from Rutgers University as well as from other institutions and companies in the area. Our services include consultation for instrument selection, training, technical support, individual use by trained and approved researchers, and consultation on image analysis. We do not provide sample prep services.

Poster #56

Preclinical brain imaging at the Rutgers University Molecular Imaging Core and the Advance Preclinical Imaging Lab.

Authors

Patricia Buckendahl (SR Research Scientist), Sushil Tripathi (Manager), Derek Adler (Assistant Director), Edward Yurkow (Director)

PI Name: Edward Yurkow

The Rutgers University Molecular Imaging Core (RUMIC), located on the Busch Campus, and the Advance Preclinical Imaging Lab (APIL) located on the Newark Campus, provide a noninvasive approach to study various biological and disease models in living systems and ex vivo organs. Our comprehensive imaging modalities for the basic sciences include MRI, SPECT/PET/CT, Micro-CT, Optical/X-ray Imaging and High-Resolution Ultrasound Technologies. The facilities allow researchers to generate multiple, spatially-resolved anatomical, functional, and molecular-level readouts from a single study. Image reconstruction, 3D displays, and quantitative image analysis are also available. The Cores are adjacent to animal holding facilities for serial imaging, anesthesia, surgery, and veterinary care. In addition to consultation and experimental services, the Cores offer periodic training and conducts research to improve existing imaging technologies. Our mission is to empower Rutgers users by promoting independent utilization of the facility and to provide imaging resources to external organizations. Example images generated in 2022-2023 at our Cores for various projects associated with brain structure and function are highlighted.

RUMIC is supported by the National Institutes of Health through an S10 instrumentation grant (Award#: 1S10OD030291-01) and by the National Science Foundation through a Major Research Instrumentation (MRI) grant (Award#: 1828332).

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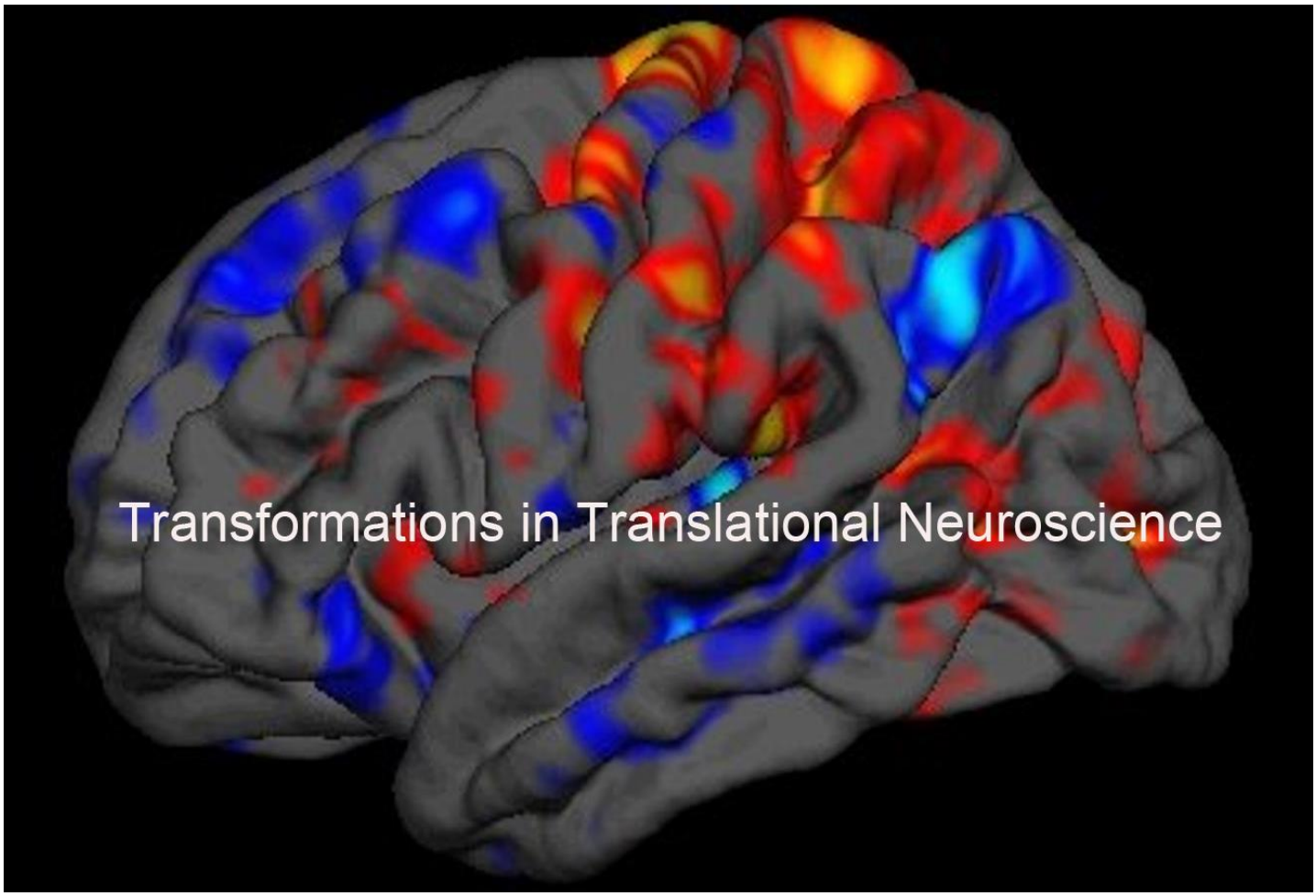
*Above attendees pre-registered for the symposium. Attendees who registered on-site are not listed.



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