Eighth Annual Rutgers Brain Health Institute Symposium

Friday, December 2nd, 2022

Busch Student Center
Piscataway, NJ 08854

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. Carlos Pato (RBHS-RWJMS/NJMS-Psychiatry)*** ***"Cellular consequences and convergent biology of schizophrenia-associated rare variants in the diverse GPC cohort"***
9.15 AM –9.25 AM	***Dr. Jennifer Mulle (RBHS-RWJMS/CABM-Psychiatry)*** ***"The 3q29 deletion as a model system to study the neurodevelopmental hypothesis of schizophrenia"***
9.30 AM – 9.40 AM	***Dr. James Knowles (RU-NB-SAS-Genetics)*** ***"Mice with knock-outs of BTBD3 display features of human OCD and have altered cortico-thalamic tracts"***
9.45 AM – 9.55 AM	***Dr. Sabine Hilfiker (RBHS-NJMS-Anesthesiology)*** ***"The roles of cilia and centrosomes in LRRK2-related Parkinson´s disease"***
10.00 AM – 10.10 AM	***Dr. Marc Tambini (RBHS-NJMS/BHI-Pharm, Phys & Neuro)*** ***"LTP values, but not Aβ levels and amyloid pathology, correlate with behavioral performance in a rat model of Alzheimer disease"***
10.15 AM – 10.25 AM	***Dr. Pierre-Olivier Polack (RU-Newark-CMBN)*** ***"When the primary visual cortex does not code for orientations"***

10.30 AM – 10.45 AM	Refreshment Break
10.45 AM – 10.55 AM	***Dr. Justin Yao (RBHS-RWJMS/BHI-Otolaryngology)*** ***"Transformation of sensory information to decision variables in the parietal cortex"***
11.00 AM – 11.10 AM	***Dr. Kevin Monahan (RU-NB-SAS-Cell Biology & Neuroscience)*** ***"Tex15 shapes stochastic olfactory receptor gene choice"***
11.15 AM – 12.15 PM	Keynote: ***Dr. Connie Cepko, Bullard Professor of Genetics and Neuroscience at Harvard Medical School.*** ***"Gene Therapy to Prolong Vision"***
12.30 PM – 2.00 PM	Buffet Lunch
2.00 PM – 2.10 PM	***Dr. Wayne Fisher (RBHS-RWJMS/BHI-Pediatrics)*** *Chair- Neurodevelopment Focus Area Working Group*
2.15 PM – 2.25 PM	***Dr. Terri Wood (RBHS-NJMS- Pharm, Phys & Neuro)*** *Vice-Chair- Neurodegeneration and Injury Focus Area Working Group*
2.30 PM – 2.40 PM	***Dr. Danielle Dick (RBHS-RWJMS/BHI-Psychiatry)*** *Chair- Motivational & Affective Neuroscience Focus Area Working Group*
2.45 PM – 2.55 PM	***Dr. David Zald (RBHS-RWJMS/BHI-Psychiatry)*** *Chair- Cognitive & Sensory Neuroscience Focus Area Working Group*
3.00 PM – 3.10 PM	***Dr. Victoria Abraira (RU-NB-SAS-Cell Biology & Neuroscience)*** *Chair- Junior Faculty Working Group*
3.15 PM – 4.45 PM	Post-doc and Student Poster Session (*at the Fireside & International Lounge in the Busch Student Center*)
4.30 PM – 5.30 PM	Wine & Cheese Reception and Best Poster Awards

RUTGERS

Brain Health Institute

Mission: Rutgers Biomedical and Health Sciences (RBHS) has identified neuroscience as one of five signature areas for future focus and development. As part of this strategic plan, the 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. By supporting and coordinating neuroscience across all campuses, the BHI will unite Rutgers University's 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 established a partnership 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 BHI-recruited Director, Dr. Wayne Fisher, Henry Rutgers Endowed Professor in the Department of Pediatrics at RWJMS. BHI also recruited Dr. Brian Greer as a tenure track Assistant Professor in RUCARES, and also in the Department of Pediatrics at RWJMS. 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. (https://sites.rutgers.edu/rucares/).

Rutgers Alzheimer's Disease & Dementia Research Center (RUADRC):

BHI created RUADRC in 2017 to address these problems. The center includes Dr. Luciano D'Adamio, Krieger Klein Endowed Chair, and junior faculty, Dr. Hyung Jin Ahn and Dr. Marc Tambini, all recruited by BHI. Research at RUADRC focuses on identifying disease mechanisms using genetic, cellular, organismal and behavioral approaches in animal and human model systems. Understanding of disease mechanisms will help uncover pathways that need to be targeted by drugs to achieve therapeutic efficacy. Development of relevant *in vitro* and *in vivo* models will be important for pre-clinical evaluation of novel drugs. A dementia clinic for patient recruitment, assessment and treatment will also be developed for translating research to clinic. (https://brainhealthinstitute.rutgers.edu/centers-at-bhi/alzheimers-disease-and-dementia-research-center-ruaddrc/)

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 Rutgers Brain Health Institute, 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. (https://ccnp.princeton.edu/about-ccnp/)

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

To fill a critical infrastructure gap, BHI developed 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. This core facility 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 the Rutgers and wider community. (https://sites.rutgers.edu/cahbir/).

The Rutgers Addiction Research Center (RARC):

The RARC at BHI is a new center that is being 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. RUARC is the only comprehensive addiction center in NJ with the capacity to impact the addiction epidemic through the diverse strengths of its members. (https://addiction.rutgers.edu/)

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 and Andrea Dzioba, Secretary.

SPEAKER ABSTRACTS

Keynote Speaker

Constance Cepko, Ph.D.

Bullard Professor of Genetics and Neuroscience
Harvard Medical School Departments of Genetics and Ophthalmology,
The Blavatnik Research Institute & Howard Hughes Medical Institute

"Gene therapy to prolong vision"

There are >200 human disease genes leading to blindness. Although gene therapy in which each disease gene is augmented or edited is possible, this approach would be extremely expensive and logistically challenging. To provide an alternative, more general approach, our laboratory has been analyzing mouse models of blindness, looking for problems that are common across genotypes. We were particularly interested in mouse models for retinitis pigmentosa (RP), as it is well modeled in mice, relative to humans. In RP, the disease starts with the expression of mutant genes in rod photoreceptors, the cell type that initiates dim light vision, leading to poor night vision. However, color vision, which originates with cone photoreceptors, is normal at birth. Over time, cones become affected due to bystander effects from rod loss. This causes color blindness and can lead to total blindness. Other cells also are affected by the loss of rods: the retinal pigmented epithelial cells (RPE), which provide various types of support to rods and cones. Studies of these mouse models led to the hypothesis that the bystander effects include: oxidative damage, metabolic shortcomings, and inflammation. To combat these problems, many different types of genes were delivered using adeno-associated viruses (AAV). Genes that fight inflammation, a transcription factor that regulates genes that fight oxidative damage, and genes that provide metabolic support were found to prolong cone and RPE survival as well as vision across 3 strains of RP mice.

Dr. Cepko's career at the bench began at a seventh-grade science fair in her hometown of Laurel, Maryland. Her project on yeast growth, based on an idea from a children's classroom science magazine, won first prize in her school's microbiology section, inspiring her to continue studying science. She attended the University of Maryland for her undergraduate degree, majoring in microbiology and biochemistry. Dr. Cepko received her doctoral degree from MIT in 1982 under the mentorship of virologist Phil Sharp. She stayed at MIT for her postdoctoral studies and constructed some of the first retroviral vectors to tag cells. After her postdoctoral studies, Dr. Cepko accepted a faculty position at Harvard Medical School and decided to use her expertise in virology and developing viral vectors to study neural development. Using novel viral vectors to genetically tag developing cells, her lab conducted groundbreaking lineage studies of cells during retinal development. Dr. Cepko's laboratory has moved from studying development at the cellular level to examining it at the genetic level. She and her colleagues have identified more than 300 photoreceptor genes majority of which have homologs in humans. Isolating these genes has narrowed the search for the genetic roots of retinal diseases such as macular degeneration and retinitus pigmentosa and could eventually lead to ways to replace dead or damaged cells.

Dr. Cepko's work has earned her honors ranging from induction in 1999 to the American Academy of Arts and Sciences to receiving a Leading Women Award in 2003. She was elected to the National Academy of Sciences in 2002. In 2011, she received the Bressler Prize in Vision Science. (*Biography adapted from PNAS 101(1), 14-15 (2004)*)

Carlos Pato, MD, PhD

Henry Rutgers Professor of Behavioral Health
Executive Chair, Psychiatry
Vice President - Research, Training and Academic Affairs in Behavioral Health and Addictions
Rutgers-New Jersey Medical School & Robert Wood Johnson Medical School, Newark/New Brunswick, NJ.

Cellular consequences and convergent biology of schizophrenia-associated rare variants in the diverse GPC cohort

Recent discoveries implicate specific genetic variants that confer extremely high risk for schizophrenia (SZ), a devastating psychiatric syndrome. Alongside these genetic discoveries there have been parallel advances in molecular neuroscience, including induced pluripotent stem (iPS) cell technology; high-throughput cellular technologies such as high content imaging and single cell genomics; and multiplex “cell village” approaches. These techniques allow for rigorous yet efficient interrogation of complex biological processes in previously inaccessible human neuronal cell types. We propose that high penetrance of rare SZ mutations derive from large effects at the molecular and cellular levels. We are studying the downstream targets and pathways impacted by; 1) five rare SZ-associated variants with large effect sizes: deletions at chromosomal locations 2p16 (localized to the NRXN1 gene), 3q29, 15q13.3, 22q11.2, and duplication at 16p11, and 2) a set of Loss of Function (LOF) mutations in a variety of genes. A key strength of this work is our Genomic Psychiatry Cohort (GPC) with over 65,000 participants that we began ascertaining nearly 30 years ago. Importantly, the GPC is a diverse cohort with significant representation of African, Latinx, Asian, and Euro-Caucasian ancestry. In these studies we use previously-banked cryopreserved lymphocytes from individuals with SZ and controls to generate iPS cell lines and test the hypothesis that these variants, or subsets of them, converge on downstream molecular targets and/or cellular pathways.

Jennifer G. Mulle, PhD

Associate Professor
Department of Psychiatry & CABM
Robert Wood Johnson Medical School, Piscataway, NJ.

The 3q29 deletion as a model system to study the neurodevelopmental hypothesis of schizophrenia

The 3q29 deletion is associated with neurodevelopmental and psychiatric phenotypes, including a staggering 40-fold increased risk for schizophrenia. We have conducted deep phenotyping, including neuroimaging, on individuals with the 3q29 deletion to understand nuances of the syndrome phenotypes and identify possible early markers of schizophrenia. 32 individuals with the canonical 1.6 Mb deletion (37% female) traveled to our study site and over the course of two days participated in transdiagnostic evaluations using gold-standard instruments. For eligible participants (n = 24), neuroimaging data were collected on a Siemens Magnetom Prisma 3T scanner. Average cognitive ability in this sample was 73 (range 40-99); 34% qualified for a diagnosis of intellectual disability. Other diagnoses included autism spectrum disorder (38%), anxiety disorders (40%), executive function deficits (47%), and ADHD (63%). 20% of participants were diagnosed with a psychotic disorder, and another 15% had features of schizophrenia prodrome. Individuals without psychosis had elevated subthreshold psychosis symptoms across all symptom domains (positive, negative, disorganized, and general), with a profile similar to 22q11.2 deletion syndrome. Neuroimaging data revealed abnormalities of the posterior fossa in 71% of participants. Smaller cerebellar volume was significant associated with reduced cognitive ability and greater positive symptoms of psychosis, suggesting the cerebellum may be a site of vulnerability of 3q29 deletion pathology. Deep phenotyping of the schizophrenia-associated 3q29 deletion has inspired new hypotheses about the molecular and cellular pathology of the syndrome

James Knowles, MD, PhD

Distinguished Professor of Genetics
Director of the Human Genetics Institute of New Jersey (HGINJ)
Rutgers-New Brunswick, NJ.

Mice with knock-outs of BTBD3 display features of human OCD and have altered cortico-thalamic tracts

Human genetics has made historic progress over the past 2 decades using the Genome-Wide Association Study (GWAS) experimental design. At the present time, tens of thousands of loci are genome-wide significant (GWS) for thousands of diseases and traits, most of which are thought to cause relatively small changes in gene expression (a percent or two). Much less is known about these variations in the DNA sequence (genome space) alter these phenotypes. For the neuropsychiatric phenotypes, it is very likely that the variation at the causative genetic loci are altering brain structure or function (brain space). To discover these changes in the brain, we have piloted a strategy of determining the target genes of GWS loci (transcriptome space), acquiring or making a highly penetrant gene disruption in the target gene in a model organism, phenotyping the resultant animals for behaviors that resemble the human phenotype, and if they are observed, we have a new animal model of the phenotype. For the brain disorders, we then have a very valuable reagent for study, brains from genetically identical animals with, and without the gene disruption. Human brains from individuals with varying levels of predicted expression of the target gene can then be examined for the differences observed in the model organism brains, reducing the multiple testing penalty of brain-wide analyses. I will illustrate this strategy using preliminary data from the study of BTBD3, nominated by a GWAS of OCD, knocked-out in mice and studied using DTI.

Sabine Hilfiker, PhD

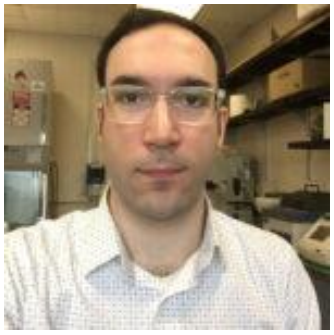
Associate Professor
Department of Anesthesiology
Rutgers - New Jersey Medical School, Newark, NJ.

The roles of cilia and centrosomes in LRRK2-related Parkinson´s disease

Point mutations in leucine-rich repeat kinase 2 (LRRK2) which increase its kinase activity are the most frequent cause of familial Parkinson´s disease (PD), and LRRK2 variants increase risk for sporadic PD. LRRK2 phosphorylates a subset of Rab proteins, small GTPases which are master regulators of intracellular membrane trafficking events. We find that when phosphorylated, phospho-Rab8 and phospho-Rab10 interact with RILPL1, a centrosome-localized protein. The phospho-Rab/RILPL1 interaction blocks ciliogenesis and interferes with the cohesion of duplicated centrosomes, and we identify the underlying molecular mechanism. We detect kinase-mediated centrosomal alterations in lymphoblastoid cell lines from patients with LRRK2 mutations as compared to healthy controls. Such alterations are also observed in a subset of sporadic PD patients. Our data suggest that determination of centrosomal deficits may assist in the stratification of sporadic PD patients who will benefit from LRRK2-related therapeutics.

Marc Tambini, MD, PhD

Assistant Professor
Department of Pharmacology, Physiology & Neuroscience and BHI
Rutgers-New Jersey Medical School, Newark, NJ



LTP values, but not Aβ levels and amyloid pathology, correlate with behavioral performance in a rat knock-in model of AD

Amyloid precursor protein (APP), whose mutation causes familial Alzheimer's disease (FAD), undergoes cleavage by β- and γ-secretases to produce Aβ, a putative toxic fragment of APP that aggregates into plaques. We generated FAD-associated App-Swedish (Apps) knock-in rats which display increased β-secretase processing of APP and Aβ production. This increased β -secretase processing also facilitates glutamate release in Apps rats, via a mechanism defined as β-secretase and APP-dependent glutamate release (BAD-Glu). Here, we examined 11–14-month-old male and female Apps rats for behavioral deficits using the IntelliCage platform, an automated behavioral testing system. Surprisingly, a spatial discrimination and flexibility task that can reveal deficits in higher order brain function showed that Apps female, but not Apps male rats, performed significantly worse than same sex controls. Moreover, female control rats performed significantly better than control and Apps male rats. Despite a significant increase in Aβ, male and female Apps rats showed no plaque pathology. Given the APP Swedish mutation-related alterations in glutamate release, we analyzed long term potentiation (LTP), a long-lasting form of synaptic plasticity and cellular basis for learning/memory. Strikingly, LTP was significantly impaired in Apps female rats, compared to control females. In addition, female control rats' LTP was significantly increased, compared to both Apps and control males. Thus, behavioral performances are sex and App-genotype dependent, correlating more closely with LTP values and not Aβ or AD-related pathology. These data, and the clinical failure of anti-Aβ therapies, suggest that alternative pathways, such as those leading to LTP dysfunction, should be targeted in AD..

Pierre-Olivier Polack, PhD

Assistant Professor
Center for Molecular and Behavioral Neuroscience
Rutgers-Newark, NJ.

When the primary visual cortex does not code for orientations

A puzzling discrepancy exists between the orientation discrimination ability of mice, and what it could be. Indeed, algorithms using the neuronal population activity of the mouse primary visual cortex (V1) can decode the orientation of a drifting grating with a precision up to 0.5°. Yet, mice poorly perform at orientation discrimination tasks when the angle between task cues is smaller than 20°. So, why encoding information with such a high precision if the animal does not use it? In our quest to determine the links between visual representations in V1 and visual perception, we found a paradigm-shifting, yet very simple answer to that issue: in a discrimination task context, V1 main function is not encoding orientation, but assigning the stimulus to a task-relevant categories. Indeed, when mice learn a discrimination task, V1 allows for generalization by representing any stimuli with an orientation close to that of the task stimulus as the task stimulus itself. Moreover, when the angle between the orientations of the two drifting grating is close to the perceptual limits of the animal (around 20°), V1 uses a categorization strategy and encodes the probability that the stimulus belongs to the Go or NoGo category. Altogether, our results provide a new framework for understanding how visual information is encoded by the cerebral cortex as well as the cellular and network mechanisms underpinning visual perception.

Justin D. Yao, PhD

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

Transformation of sensory information to decision variables in the parietal cortex

The process by which sensory evidence contributes to perceptual choices requires an understanding of its transformation into decision variables. Here, I address this issue by evaluating the neural representation of acoustic information in auditory cortex-recipient parietal cortex while gerbils either performed a two-alternative forced-choice auditory discrimination task or while they passively listened to identical acoustic stimuli. During task engagement, stimulus identity decoding performance from simultaneously recorded parietal neurons significantly correlated with psychometric sensitivity. In contrast, the decoding performance during passive listening was significantly reduced. Principal component and geometric analyses revealed the emergence of linearly separable manifolds with respect to stimulus identity and decision, but only during task engagement. Finally, using a clustering analysis, we found subpopulations of neurons that may reflect the encoding of separate temporal segments throughout a trial during task performance. Taken together, our findings demonstrate that sound-driven decisions are supported by the accumulation of auditory information and its transformation into decision variables within parietal cortex.

Kevin Monahan, PhD

Assistant Professor
Department of Molecular Biology & Biochemistry
Rutgers-New Brunswick, Piscataway, NJ.

Tex15 shapes stochastic olfactory receptor gene choice

In mammals, smells are detected at the back of the nose in the olfactory epithelium, where olfactory sensory neurons (OSNs) use olfactory receptor proteins to detect inhaled chemical odorants. Mice express over 1200 different types of olfactory receptor proteins, but each OSN chooses only one type of receptor for expression. This choice is controlled at the level of transcription; each OSN stochastically selects only one allele of one olfactory receptor gene for expression. Once a receptor gene has been chosen, its ongoing expression is coordinated by the formation of 3D chromatin hubs composed of olfactory receptor gene clusters and specialized enhancer elements. However, it remains unknown how the initial stochastic gene choice is controlled. We have found that a gene expressed in OSN progenitors, Testis expressed 15 (Tex15), is required for the expression of hundreds of olfactory receptor genes by OSNs. In Tex15 knockout mice, stochastic olfactory receptor choice is severely skewed, leading to the very frequent choice of a handful of olfactory receptors. Our preliminary data suggest that this results from changes in the chromatin structure of OSN progenitors, which lead to severe biases in the process of stochastic receptor choice.

Wayne W. Fisher, PhD, BCBA-D

Henry Rutgers Endowed Professor of Pediatrics, RWJMS,
Director of Rutgers Center for Autism Research, Education and Services (RUCARES),
Director of CSH-RUCARES and the Severely Affected Behavior Disorders in Children Program at CSH.

Chair- Neurodevelopment FAWG

Terri Wood, PhD,

Professor, Rena Warshow Endowed Chair in Multiple Sclerosis,
RBHS-NJMS- Department of Pharmacology, Physiology and Neuroscience.

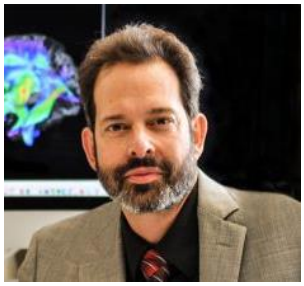
Vice-Chair- Neurodegeneration & Injury FAWG

Danielle Dick, PhD,

Greg Brown Endowed Chair,
Professor of Psychiatry, RWJMS,
Director of Rutgers Addiction Research Center (RARC).

Chair- Motivational & Affective Neuroscience FAWG

David Zald, PhD,



Henry Rutgers Term Chair,
Professor of Psychiatry, RWJMS,
Director of Center for Advance Human Brain Imaging Research (CAHBIR).

Chair- - Cognitive & Sensory Neuroscience FAWG

Victoria Abraira, PhD,

Assistant Professor, Cell Biology & Neuroscience, RU-NB.

Chair- Junior Faculty Working Group (JFWG)

POSTER ABSTRACTS

Poster #1

Multimodal sensory control of motor output by inhibitory neurons within the deep dorsal horn

Authors

N Ozeri-Engelhard, MA Gradwell, OD Laflamme, A Upadhyay, M Gonzalez, G Abbas-Zadeh, JT Eisdorfer, Y Hernandez, T Akay, VA Abraira

PI Name: Victoria Abraira

Locomotion is generated by intrinsic spinal networks that set the pattern and rhythm of muscle activity. These parameters must also be adaptable in respect to changes in the environment such as when walking on slippery, rough or hot terrains; as well as changes in kinematics requirements, such as when walking uphill, downhill or at different speeds. Thus, effective gait cannot solely rely on intrinsic networks and must be amenable to multiple modalities of sensory input. However, our understanding of the role of multimodal sensory information in locomotion is still lacking. However, our understanding of the role of multimodal sensory information in locomotion is still lacking. What are the circuits connecting multimodal sensory information to motor pathways? Do sensory modalities remain segregated, or do they converge to modulate motor output? What are the properties of sensorimotor circuits that allow for flexible modulation of pre-set locomotion programs defined by intrinsic spinal networks? Here, we characterize the medial deep dorsal horn as the spinal region that integrates proprioceptive and cutaneous sensory input and identify inhibitory interneurons within this region as key players in sensorimotor processing. Our simplified model, using dPVs, demonstrates that cutaneous and proprioceptive inputs converge on inhibitory interneurons within the medial deep dorsal horn to regulate the gain and timing of motor output. We propose that early sensory convergence and divergent inhibition increases the diversity of mechanisms by which sensory information can influence network activity to ensure contextually relevant motor output.

This research was supported by NIH, NJCSCR, Neilson Foundation

Poster #2

Modeling cell-cell communicational mechanisms in the suprachiasmatic nucleus and the implication of circadian regulation

Authors

Yannuo Li, Ioannis P. Androulakis

PI Name: Ioannis P. Androulakis

To promote survival and optimize energy resource allocation, the circadian time-keeping mechanism evolved to maintain homeostasis by synchronizing internal physiology with predictable environmental variations. Nearly every cell in our body has a self-sustained rhythm rooted in the translational-transcriptional feedback loop involving numerous circadian clock genes. Through various coupling mechanisms, these cells consist of oscillators at the cellular, tissue, organ, and system levels, resulting in a highly tuned network of the endogenous circadian timing system. The hypothalamic suprachiasmatic nuclei (SCN) in our brain have been widely identified as the central pacemaker that transduces photic information to the periphery. The SCN consists of ~20,000 oscillatory neurons. These neurons are organized as a coupled network through neural projections and humoral signals, as cells communicate with each other and convey the temporal information to the downstream compartments. However, due to experimental limitations, the inter-neuronal communication mechanisms are currently poorly understood. Building upon the limited amount of information, deciphering systemic clock-to-clock communication within the SCN remains one of the most challenging and critical investigations in chronobiology, as a misaligned circadian system is commonly associated with adverse health outcomes. The current presentation suggests a mechanisms-based mathematical modeling approach to investigate the detailed cell-cell coupling mechanisms in the complex SCN organization. By simulating different potential SCN organizations based on experimental findings, our model provides insights into the realistic SCN topology as well as its plasticity changes as a mechanism to adapt to disrupted light/dark schedules such as jetlag, shiftwork, and seasonal variations.

This research was supported by NIH GM131800.

Poster#3

Regulation of locus coeruleus: a chemogenetic approach to treat neurodegenerative disorders

Authors

G Crozier, S.I. Delcourte, H.E. Bowrey, Y.Rakholia, G.Aston-Jones

PI Name: Gary Aston-Jones

Abnormal accumulation of tau protein in the locus coeruleus (LC) may play an early role in Alzheimer's Disease (AD) progression. Using an animal model of AD with this early LC tau pathology, the TG-F344 AD rat, Rorabaugh et al. (2017) showed that specific chemogenetic activation of LC rescued impaired reversal learning observed in this model. Given its deep location in the brainstem, LC is difficult to access in humans, limiting this approach for clinical application. Suprachiasmatic nucleus (SCN) provides an indirect input to LC via a relay in dorsomedial hypothalamus (DMH). SCN is therefore in a key position to integrate retinal information with LC, via a circuit we denote as the Photic Regulation of Arousal and Mood (PRAM) pathway: retina→SCN→DMH→LC. Tg-F344 or WT rats received intravitreal injections of an AAV encoding a Gq DREADD or control virus. 6 months later, we assessed the effects of retinal DREADD stimulation on learning and memory using the Morris Swim Maze (MWM). Injections of the DREADD agonist clozapine-N-oxide (CNO; 2mg/kg, ip) were given 30min before the Referral and each Reversal session. Tg-F344-AD rats showed poor initial as well as reversal learning. Retinal DREADD stimulation decreased reversal deficits in the Tg-F344 rats without affecting WT performance. Dysregulation of the noradrenergic LC, which is associated with behavioral deficits in Alzheimer disease, can be attenuated by PRAM-induced activation of LC. The PRAM pathway is a novel circuit for a non-invasive approach to treating multiple neuropsychiatric disorders linked to LC.

Supported by PHS grant R21-MH121723-S1

Poster#4

Electrophysiological recording during real-world goal-directed navigation using augmented reality

Authors

Jaleesa Stringfellow-James, Mei-Heng Lin, Omer Liran, Travis E. Baker

PI Name: Travis Baker

The ability to make adaptive decisions during goal-directed navigation is a fundamental and highly evolved behavior that requires continual coordination of perceptions, learning and memory processes, and the planning of behaviors. Although these mechanisms have been well studied in animal experiments, whether similar mechanisms exist in freely moving humans remains elusive. One key issue raised is the limitation inherent to traditional human neuroimaging—whilst rats and other nonhumans can be examined during free movement, human studies rarely achieve equivalent realism. To overcome this limitation, we developed a novel mobile EEG and Augmented Reality (AR) technique aimed to record brain activity and manipulate real-world environments in real-time during spatial navigation. AR is an interactive experience where the objects that reside in the real-world are "augmented" by computer-generated perceptual information across multiple sensory modalities using a special kind of optic glasses (Hololens2, Microsoft). In the present study, we recorded EEG in 20 subjects as they freely navigated an operant chamber with left and right goal locations (west vs east trajectories). In the time domain, reward feedback evoked both the reward positivity (RewP; valence effect) and the topographical N170 (spatial effect). Overall, this study provides the first evidence that combining mobile EEG with AR technology is possible during real-world navigation and provides a unique opportunity to move toward increasing ecological validity in human EEG studies of goal-directed navigation.

This work was supported by NIGMS of the National Institutes of Health under award number 5T32GM140951 (JS).

Poster #5

The role of the lateral habenula in individual susceptibility to opioid abuse

Authors

Chris O'Brien, Dhruvi Desai, Roshni Vemireddy, David J. Barker

PI Name: David J. Barker

Opioids are widely prescribed and highly effective for treating acute pain. Although opioids have high abuse liability, some individuals transition to abuse while others remain resilient. The ability to predict individual susceptibility to opioid use disorder (OUD) is limited, partially because OUD is comorbid with other psychological illnesses including depression or anxiety. One common risk factor for these disorders is a history of stressful experiences. Thus, stress may trigger key physiological or neurological changes in certain individuals that determine the risk for developing OUD. To better understand how stress can lead to emergent individual differences for OUD susceptibility we developed a comprehensive behavioral paradigm examining how a history of stress impacts negative valence behaviors and nociception and then use these measures to identify individuals predisposed to opioid seeking following oral opioid self-administration. We discovered that mice with and without a history of stress exhibit different profiles of negative valence and pain-related behaviors that predict opioid abuse susceptibility. Specifically, we discovered that heightened mechanical pain sensitivity and heightened sucrose preference following stress, predicts individuals with increased fentanyl seeking. Conversely, control mice who show low sucrose consumption, a sign of anhedonia, also exhibit increased risk for fentanyl seeking. To determine the neural substrates supporting these changes, we first turned to the lateral habenula (LHb). The LHb processes aversive stimuli, modulates reward response, and has roles in pain and depression. Our preliminary results show that inhibition of the LHb via hM4D(Gi)-DREADDS during stress can block the induction of mechanical hypersensitivity following stress.

Supported by NIDA R00DA043572.

Poster# 6

Endothelin-converting enzyme-2 regulates secreted β-amyloid in the brain

Authors

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PI Name: Elizabeth A. Eckman (Biomedical Research Institute of NJ)

Alzheimer's disease is characterized by abnormal aggregation and accumulation of the β-amyloid (Aβ) peptide in the brain. Aβ is generated by a series of proteolytic cleavages of the amyloid precursor protein (APP) within endocytic vesicles and is then trafficked either to the degradative lysosomal pathway or released extracellularly through secretory pathways. Endothelin-converting enzyme-2 (ECE-2), a GABAergic interneuron-expressed zinc-metallopeptidase, localizes within intracellular vesicles including late endosomes and autophagosomes and has been shown to degrade Aβ. We sought to determine, using both in vitro and in vivo models, which pools of Aβ ECE-2 activity modulates. Neuro-2A (N2a) cells were transfected with ECE-2 and Aβ was measured in cell lysate and medium. For in vivo studies, brains from ECE-2 knockout (KO) mice and ECE-2 KO mice crossed with transgenic APP mice (CRND8) were processed using a stepwise brain homogenization method that separates cellular vesicles from interstitial fluid. Then intravesicular and extracellular Aβ were measured using ELISAs. Overexpression of ECE-2 in N2a cells decreased secreted Aβ. In vivo, lack of ECE-2 enzymatic activity resulted in a significant increase in endogenous extracellular Aβ. This effect was more pronounced when examined in CRND8 mice, where reduced ECE-2 enzyme activity in heterozygous KO mice resulted in a 20% increase, and complete enzyme KO resulted in a 60% increase in extracellular Aβ. ECE-2 activity in interneurons tightly regulates a pool of secreted Aβ. Future experiments will evaluate whether reduced ECE-2 activity can accelerate disease pathology.

Poster#7

Assessing impulsivity through the lens of negative urgency: effects of mtbi on avoidance, serotonin, & inflammation

Authors

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PI Name: Kevin D. Beck

Mild traumatic brain injuries (mTBIs) disproportionately affect military personnel and can cause alterations in cognition. Impulsivity and suicidality are two behavioral changes included in the psychological sequelae of mTBI. One facet of impulsivity is negative urgency. Defined as a tendency to experience impulses under conditions of stress, previous studies have shown negative urgency is predictive of maladaptive behaviors such as problematic drinking and risky sexual behavior. Importantly, serotonin has been implicated as a key regulator of impulsivity. Given this, it is possible that impulsivity resulting from mTBI is exacerbated by stressful life events and dysfunction of the serotonergic system, ultimately aiding in the increasing rate of suicide among veterans. To elucidate the relationship between mTBI and impulsivity, we used an operant avoidance paradigm to model negative urgency. Rats underwent a single mTBI using the lateral fluid percussion model. Their performance on the avoidance task was assessed immediately after injury following a short recovery period. Additionally, a separate cohort of rats was given an mTBI and sacrificed at 1-month, 3-months, and 6-months following injury. Tissue punches of the brainstem were collected for qRT-PCR analysis. Our data indicate there is no difference in expression of serotonergic-related genes between injured and sham animals of either sex. However, expression of inflammatory markers CD68, IL-1β, and IL-1α were found to be elevated in the locus coeruleus of females at 3-months post-injury. Results for negative urgency will be discussed. This study serves to enrich our understanding of TBI-induced changes of impulsivity and associated molecular changes.

Supported by the VA Office of Research & Development, Biomedical Laboratory R&D Service I01BX004561-01A2.

Poster#8

Chronic pain provokes epigenetic modifications and changes in cytokine levels in key limbic structures

Authors

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PI Name: David Barker

Chronic pain involves both central and peripheral neuronal plasticity that encompasses changes in the brain, spinal cord, and peripheral nociceptors. Within the forebrain, mesocorticolimbic regions associated with emotional regulation have recently been shown to exhibit lasting gene expression changes in models of chronic pain. To better understand how such enduring transcriptional changes might be regulated within brain structures associated with processing of pain or affect, we examined epigenetic modifications involved with active or permissive transcriptional states (histone H3 lysine 4 mono and trimethylation, and histone H3 lysine 27 acetylation) in periaqueductal gray (PAG), lateral hypothalamus (LH), nucleus accumbens (NAc), and ventral tegmental area (VTA) 5 weeks after sciatic nerve injury (SNI) in mice to model chronic pain. For both male and female mice in chronic pain, we observed an overall trend for a reduction of these epigenetic markers in periaqueductal gray, LH, and NAc, but not VTA. Moreover, we discovered that some epigenetic modifications exhibited changes associated with pain history, while others were associated with individual differences in pain sensitivity. When taken together, these results suggest that nerve injury leads to chronic chromatin-mediated suppression of transcription in key limbic brain structures and circuits, which may underlie enduring changes in pain processing and sensitivity within these systems. Additionally, we have found an elevation of pro-inflammatory cytokine Interleukin-1β (IL-1β) in the VTA and LH of female SNI subjects. Our ongoing study focuses on changes in cytokine expression associated with chronic pain.

Supported by NIH grants UL1TR003017, MH115096, and DA043572

Poster #9

Developmental exposure to the Parkinson's disease-associated organochlorine pesticide dieldrin exacerbates synucleinopathy-induced deficits in dopamine uptake in the striatum in the α-synuclein PFF mouse model

Authors

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PI Name: Alison I. Bernstein

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and one of the fastest growing neurological diseases worldwide. This rise in incidence outpaces the rate of aging and is increasing most rapidly in newly industrialized areas, suggesting that environmental factors, such as decreased smoking and specific environmental toxicants, may contribute to these increases. Epidemiological studies have shown that exposure to the organochlorine pesticide dieldrin is associated with increased risk of PD. In addition, animal studies in our lab and others have identified a link between developmental dieldrin exposure and increased neuronal susceptibility to synucleinopathy in the α-synuclein preformed fibril (PFF) model and MPTP toxicity in adult male C57BL/6 mice. However, the mechanisms mediating this effect remain incompletely defined. Our previous results show that developmental dieldrin exposure induces a male-specific exacerbation of PFF-induced increases in dopamine (DA) turnover as indicated by an increased ratio of the DA metabolite, homovanillic acid, to DA and motor deficits on the challenging beam at 6 months post-PFF injection. To expand on these results, we measured vesicular monoamine transporter 2 (VMAT2) uptake velocity by vesicular 3H-DA uptake assays and striatal DA release by fast scan cyclic voltammetry (FSCV) in the dieldrin-PFF paradigm. There was no dieldrin-induced change in VMAT2 uptake velocity ipsilateral to the PFF injection site. We found a dieldrin-induced change in peak height (DA release), but no dieldrin-induced change in tau (DAT uptake) in PFF-injected animals ipsilateral to the injection site.

Supported by R01ES031237

Poster #10

Characterization of ADK expression in a mouse model of traumatic brain injury

Authors

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PI Name: Detlev Boison

Epilepsy is characterized by recurrent seizures and affects ~70 million people worldwide. 10-20% of symptomatic epilepsy occurs due to a traumatic brain injury (TBI), which can lead to the appearance of seizures immediately, months, or years after injury. This period is known as the "latent phase" of epileptogenesis, during which molecular and epigenetic changes accumulate in brain tissue, functionally altering it and lowering the excitability threshold for repeated seizures. Despite the range of anti-seizures drugs, the percentage of patients not responding to treatment remains at 30%, demonstrating an urgent need for new therapies that prevent or halt the initial development of epilepsy (epileptogenesis) instead of seizure suppression. One proposed mechanism of intervention is targeting adenosine kinase (ADK), an enzyme that is responsible for metabolizing adenosine. Extracellular adenosine is a well-characterized endogenous anticonvulsant. The present study was designed to comprehensively characterize ADK expression in the hippocampus of mice after TBI. To this effect, and to better understand ADK dynamics following TBI, we performed controlled cortical impact (CCI) surgeries on mice who were sacrificed at various time points to illustrate the transient and chronic increases in ADK following brain injury. We then utilized immunohistochemistry and Western blot assays to assess changes in the expression of ADK. Our preliminary results showed an increase in ADK expression following CCI. Future work will explore the cell-type expression of ADK following CCI, as well as the impact of ADK expression on seizure thresholds in the context of PTE.

Supported by DOD grant.

Poster #11

Learning a continuous attentional template in the fronto-parietal network

Authors

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PI Name: Timothy J. Buschman (Princeton)

Attention filters the flood of sensory inputs, allowing us to focus on goal-relevant information. Importantly, attention is not static. As the environment, or our goals, change, attention adapts to what is currently relevant. To study how the brain adapts its attention to the current situation, we trained monkeys to perform a novel attention-learning task. On each trial, monkeys searched a visual array for a color that best matched a 'template' color. Monkeys were never instructed as to the template color, they had to learn it through trial and error by choosing a color, getting feedback (amount of reward), and updating their internal attentional template. After they learned a template, it would unexpectedly change, requiring monkeys to repeatedly relearn new attentional templates. Monkeys responses were well explained by a reward-learning model. Neurons in frontal and parietal cortex represented the attentional template. Using multi-class classifiers, we found template representations were updated after each trial – templates moved towards rewarded colors and away from unrewarded colors. In addition, we found the template was used to directly transform the color of each stimulus into its expected value. Location-specific value signals facilitated decisions, while global value signals facilitated updating the template. Together, these results suggest that learning of new attentional templates leads to re-mapping of stimulus representations in prefrontal and parietal cortex but does not change decision representations.

Funded by NSF CAREER BCS-2143391

Poster #12

The role of Top2b in the motility of transplantable retinal progenitor cells

Authors

Brianna Rodriguez, Alexandra Dabrowski, Li Cai, and Maribel Vazquez

PI Name: Li Cai

Progressive vision loss will impair an unprecedented 25M Americans by 2050. Promising cell replacement therapies have transplanted retinal progenitor cells (RPCs) into degenerated tissue to restore vision. In an idealized model, cells must migrate to sites of injury, differentiate appropriately into specialized neurons, and synapse within native cellular networks to restore vision. While numerous projects have independently illustrated that replacement cells can survive and differentiate when transplanted, the integration needed to restore vision has yet to be achieved. A primary challenge is the inability of replacement cells to migrate appropriately within retinal tissue to achieve desired cellular positioning. Our project has linked RPC migration with Top2b, an enzyme critical to post-mitotic differentiation, cell migration, and synapse formation in terminally-differentiated, retinal neurons. Our data is the first to examine the molecular mechanism(s) underlying Top2b regulation needed for RPC migration within damaged retina to guide future transplantation strategies. The ability to influence the motility of transplanted RPCs into adult retina has transformative potential for restoring vision. Linking molecular mechanisms of Top2b expression with chemotactic fields will enable a highly tunable, tissue engineering approach to facilitate functional integration within damaged adult retina.

Poster #13

Neural mechanisms for sickness induced changes in social behavior

Authors

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PI Name: Ioana Carcea

In mammals, inflammatory responses to infections trigger adaptive behavioral changes collectively known as 'sickness behavior'. Among these, lethargy protects the sick individual by conserving energy, increased anxiety is believed to prevent exposure to threats, and changes in social behavior are thought to reduce the spread of contagion. However, the characterization of lethargy and anxiety in sickness could be an artifact of behavioral assessment, particularly in rodents. We adjusted existing behavioral testing and designed a new paradigm to disambiguate between increased lethargy versus increased anxiety. Our data indicate that in mice sickness induces a significant increase in lethargy but not in anxiety. When investigating social behavioral changes, we find that sick mice prefer to interact with familiar social partners and that this might depend on social rank or 'hierarchy'. Further supporting our behavioral results, at the neuronal level we found evidence that sickness activates anxiolytic rather than anxiogenic regions of the amygdala, including oxytocin receptor expressing neurons (CeA-OTR+). Putative mechanisms by which sickness could activate CeA-OTR+ neurons were investigated.

Supported by a R00 and R01 grant from NIMH and BHI Pilot award

Poster #14

Sex-dependent fear memory impairment in cocaine-sired rat offspring

Authors:

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PI Name: R. Christopher Pierce

Cocaine taking induces epigenetic modifications in sperm resulting in neuronal and behavioral alterations in offspring. Given the high degree of overlap between the brain systems resulting in pathological responses to cocaine and stress, we examined whether sire cocaine taking would influence fear-associated behavioral and physiological effects in drug-naïve male and female progeny. Adult male Sprague-Dawley rats self-administered cocaine for 60 days while a second group of male rats received yoked saline infusions. Rats then mated with drug-naïve female rats to create an F1 generation of saline- or cocaine-sired offspring. F1 rats were then subjected to amygdala-dependent auditory fear conditioning and cue extinction. Separate groups of rats underwent electrophysiological analyses of amygdala synaptic activity. Experiments revealed a sex-dependent effect of sire, whereby cocaine-sired males generated stronger fear-associated memories. During cue extinction, cocaine-sired males spent a significantly higher percentage of time freezing relative to saline-sired rats. Similarly, we observed a sex dependent difference in synaptic activity, whereby cocaine-sired male rats showed no increase in EPSC amplitude at amygdala synapses following standard LTP induction protocols. This LTP blockade was not observed in saline-sired male rats or in female rats of either sire. In summary, male, but not female, cocaine-sired rats exhibit resistance to extinction of cue-conditioned fear memories and this resilience may be related to deficits associated with amygdala synaptic LTP. Ongoing experiments are working to further delineate the molecular and physiological mechanisms responsible for the deficits in fear extinction and LTP in cocaine-sired male rats.

This study was supported by R01DA033641, T32DA028874, F32DA052993.

Poster #15

Effects of genotype on gene regulation in response to mild blast-induced traumatic brain injury in mice

Authors

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PI Name: Bruce A. Citron

Approximately 400,000 traumatic brain injuries (TBIs), most of them mild, have been sustained among the 2 million service personnel deployed from 2000 to 2020. In training and combat zones, TBIs are typically caused by exposure to blast waves from a variety of sources, and long-term neurodegenerative deficits can develop without an effective treatment. Additional attention is needed to better understand genetic predispositions for susceptibility vs. resilience and repair. Our injury model utilizes a well-established blast tube system designed to mimic pressure waves experienced during a field explosive detonation. Using a variety of genetically distinct mouse strains, we assessed the effects of sex and genotype on sub-acute gene regulation using whole transcriptome sequencing (RNA-Seq) at 30 days post-injury following a single mild/moderate (180 kPa) blast exposure. We evaluated changes in gene ontology categories for cellular components, molecular functions, and biological processes and conducted pathway analysis to determine significantly affected canonical biochemical pathways (i.e., neuroinflammation signaling). This research represents a multi-level examination of how certain genes may influence blast-induced TBI and recovery and provides a foundation for understanding how these genes play roles in the post-injury outcomes in order to advance the identification of therapeutic targets that could be modulated to improve the health of Veterans and others with histories of blast exposures.

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Poster #16

A multivariate approach to understanding the genetic overlap between externalizing phenotypes and substance use disorders

Authors

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PI Name: Danielle M. Dick

Substance use disorders (SUDs) are phenotypically and genetically correlated with each other and with other psychological traits characterized by behavioral undercontrol, termed externalizing phenotypes. In this study, we used Genomic Structural Equation Modeling to explore the shared genetic architecture among six externalizing phenotypes and four SUDs used in two previous multivariate GWAS of an externalizing and an addiction risk factor, respectively. Using a preregistered set of criteria, we first evaluated the performance of five confirmatory factor analytic models, including a common factor model, alternative parameterizations of two-factor structures, and a bifactor model. We used a combination of model fit, factor reliability, and model characteristics to adjudicate among the models. We next explored the genetic correlations between factors identified in these models and other relevant psychological traits. We found that a common factor model, in which all externalizing phenotypes and SUDs were influenced by a single dimension of genetic risk best characterized the relationships among our phenotypes. Although two two-factor models also performed well, we found that the factors in those models were very highly correlated with each other (rgS > .87) and similarly genetically correlated with external criteria, suggesting they did not represent meaningfully distinct dimensions. Results from this study can be used to inform future efforts to characterize genetic liability for broad externalizing as well as specific externalizing phenotypes.

This work is supported by NIAAA 5T32AA028254-04 and NIDA R01DA050721.

Poster #17

Investigating the role of NOS1AP isoforms in human neuron dendritogenesis and schizophrenia

Authors

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PI Name: Bonnie L. Firestein

Schizophrenia (SCZ) is a heterogenous and polygenic psychiatric illness characterized by the presence of positive, negative, and cognitive symptoms. Since little is known about the molecular and genetic etiology of the disease, current therapeutics are often inadequate for treating all associated symptoms, resulting in high rates of lifelong disability. The N-methyl-D-aspartate receptor (NMDAR) hypofunctioning hypothesis suggests that positive, negative, and cognitive symptoms of the disease are caused by a reduction in NMDAR signaling. Nitric oxide synthase 1 adaptor protein (NOS1AP) is encoded by a SCZ susceptibility gene, disrupts nitric oxide (NO) signaling, and negatively regulates NMDAR signaling. We previously reported that NOS1AP expression is increased in postmortem brain samples from patients with SCZ and that the long isoform of NOS1AP (NOS1AP-L) negatively regulates dendrite branching in rat hippocampal neurons. To investigate the role that NOS1AP isoforms play in human dendritic arbor development, we used hiPSC-derived neurons. We found that increased protein levels of NOS1AP decrease dendrite branching. In addition, we found that treatment of human iPSC-derived neurons with D-serine results in a reduction in endogenous NOS1AP-L protein expression. However, D-serine treatment does not reverse decreases in dendrite number mediated by overexpression of NOS1AP. Future work will focus on the identification of disease-associated biomarkers in order to aid in the development of novel therapeutics and facilitate the implementation of biologically-driven diagnostic criteria, which has the potential to improve treatment plans and patient outcomes. Cumulatively, this work has the potential to identify easy to collect, novel biomarkers of SCZ

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Poster #18

Binge sucrose/saccharin-induced neuroadaptations: A focus on the orexin/hypocretin system in female rats

Authors

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PI Name: Gary Aston-Jones

Binge eating disorder is the most common eating disorder. Animals, like humans, selectively binge on highly palatable food suggesting that this behavior is driven by hedonic, rather than metabolic signals. Behavioral and molecular adaptations induced by eating disorders share commonalities with those involved in addiction. Given that orexin/hypocretin signaling is linked to both reward processing and food intake, we examined the contribution of this system to binge-like eating in female rats. Separate groups were given intermittent (12h) or continuous (24h) access to 10% sucrose or 0.4% saccharin and food over 28 days. All the sucrose and saccharin groups exhibited an increase in the number of orexin-A peptide neurons within LH compared to the group with limited access to food only. In parallel, we found a marked increase of prepro-orexin gene expression in LH in groups with access to sucrose but not in animals with access to saccharin. This may reflect that sucrose and saccharin promote different mechanisms to increase orexin A expression, The orexin 1 receptor antagonist, SB334867 (20 or 30mg/kg), reduced binge-like intake in groups with limited access to sucrose or saccharin but not in rats with continuous access to sucrose. We are currently assessing whether binge-like sucrose or saccharin intake alters economic demand for cocaine. Altogether, our findings indicate that sucrose or saccharin bingeing alters the orexin system in LH. Our results broaden the understanding of neural alterations associated with binge-eating and point towards addictive-like properties of palatable food.

Supported by a NIAAA T32AA028254.

Poster #19

Oscillatory network spontaneously recovers the robustness in activity, which is lost due to removal of neuromodulation.

Authors

Smita More-Potdar, Jorge Golowasch

PI Name: Jorge Golowasch (NJIT)

Robust neural activity is important in networks that generate rhythmic behaviors like walking, breathing, or heart beating, especially when the animal receives various perturbations like injuries, diseases, or environmental changes. In crabs, the pyloric network generates a robust rhythm over a range of temperatures in intact neuromodulatory conditions. Removing neuromodulators (decentralization) rapidly slows down the rhythm, upsets component neurons' phases, and reduces the robustness of the rhythm. Surprisingly, the pyloric activity recovers after several hours of decentralization. However, it is unknown if robustness is also restored. We define a robust rhythm as one whose variability across perturbation levels (e.g., a range of temperatures) is low within a physiological range. We explored whether the pyloric rhythm could spontaneously regain robustness in the prolonged absence of neuromodulators. We recorded pyloric activity extracellularly in response to temperature perturbations (9ºC – 30ºC) under different modulatory conditions. We examined four activity features: burst frequency of the pyloric rhythm and three key phases of neuronal bursting. PD and LP are core bursting neurons in the pyloric network. These neurons' bursting phases describe their activity onset and termination. Our results show that pyloric phases and the frequency significantly change in response to temperature perturbations as time passes after decentralization. We further show that phase variances, but not frequency coefficient of variation, across temperature increase after decentralization and decrease approximately at 24 hours, suggesting the robustness of the rhythm is initially lost after decentralization and then recovers spontaneously over time.

Supported by funding from NSF grant DMS-1715808

Poster #20

Reading in autism shows enhanced activation of visual association cortex and greater sensitivity to imageability

Authors

Cory McCabe, Shannon Cahalan, Melanie Pincus, Mariam Mahboob, Miriam Rosenberg-Lee, William Graves

PI Name: William Graves

Individuals with autism without obvious language delays can show intact abilities to read aloud; however, retrieving word meanings can be more challenging, particularly for abstract words. Neuroimaging studies have observed an atypical involvement of sensory association cortices when processing written word meanings in autism. These patterns suggest a possibly atypical semantic organization within autistic individuals due to a focus on concrete sensory features. We examined behavioral and neural responses to word and pseudoword reading between autistic individuals and neurotypicals. Participants were 39 English speaking individuals (20 neurotypical; 19 autistic) that were matched by age, IQ, and verbal IQ. The fMRI task consisted of reading aloud 110 English words randomly intermixed with 110 pseudowords. Neural data were processed using AFNI software to contrast activations between groups in response to words versus pseudowords. Mixed-effects linear regressions were conducted for word accuracy and reaction time respectively using group status, and word imageability as covariates. Whole-brain analyses revealed greater activation for words than pseudowords in the right cuneus in autistic participants compared to neurotypicals. Linear regression analyses for reaction time (RT) to words revealed an interaction effect between group and imageability in which autistic participants showed greater reduction in RT as imageability increased. Greater activation by autistic participants compared to neurotypicals was found in the right dorsal visual association cortex, specifically the cuneus, in response to words. Taken together with faster RT when reading high imageability words, these results suggest autistic individuals may focus more on concrete sensory features of words than neurotypicals.

Supported by a Busch Biomedical Grant

Poster #21

Basic and applied research on extinction bursts

Authors

Wayne Fisher, Brian Greer, Timothy Shahan, Halle Norris

PI Name: Wayne Fisher

Discontinuation of the contingency between a response and its reinforcer sometimes produces a temporary increase in the response before its rate decreases, a phenomenon called the extinction burst. Prior clinical and basic studies on the prevalence of the extinction burst provide highly disparate estimates. Existing theories on the extinction burst fail to account for the dynamic nature of this phenomenon, and the basic behavioral processes that control response bursting remain poorly understood. In this paper, we first review the basic and applied literature on the extinction burst. We then describe a recent refinement of the concatenated matching law called the temporally weighted matching law that appears to resolve the above-mentioned issues regarding the extinction burst. We present illustrative translational data based conceptually on the model. Finally, we discuss specific recommendations derived from the temporally weighted matching law regarding procedures clinicians could implement to potentially mitigate or prevent extinction bursts.

Supported by NIH grants R01HD079113, R01HD083214, and R01HD093734

Poster #22

Blockade of the adenosine A2A receptor protects against cisplatin-induced cognitive impairments.

Authors

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PI Name: Mi-Hyeon Jang

The platinum-based chemotherapy cisplatin has been clinically reported to potentiate cognitive impairments, known as chemobrain, which affects approximately 14 million cancer survivors in the United States alone. Without a known cure, cognitive impairments are reported to occur well-after chemotherapy cessation to impair memory and mood, thus reducing quality of life in cancer survivors. To elucidate the molecular mechanisms by which chemobrain impairs cognition, we developed a mouse model resembling clinical cisplatin chemotherapy and performed RNA-seq analysis in the hippocampus, a brain structure critical for learning and memory, which revealed robust elevations in the adenosine A2A receptor (A2AR). Given that A2AR is known to play a critical role in learning, memory, and neurodegeneration, we hypothesize that A2AR inhibition can prevent cisplatin-induced cognitive impairments. We observed that cisplatin impairs adult neurogenesis, and neuronal morphogenesis of newborn neurons, including dendrite spine deficits, in the adult mouse hippocampus. Behaviorally, cisplatin potentiates learning and memory dysfunctions, as well as increases anxiety. Remarkably, pretreatment with the specific A2AR antagonist Istradefylline (KW-6002) significantly prevented the aberrant neuronal and cognitive deficits induced by cisplatin, without promoting tumor growth or interfering with cisplatin's anti-tumor activity. Mechanistically, in the mouse hippocampus and human cortical neurons derived from iPSCs, we find that cisplatin neurotoxicity, downstream of A2AR induction, is cAMP-CREB signaling dependent. Collectively, our results suggest that A2AR induction may be a key contributor to cisplatin-induced memory impairments, thus highlighting A2AR as a novel neuroprotective translational therapeutic target against cisplatin-induced chemobrain, to improve quality of life for cancer survivors.

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Poster #23

Gut infiltration of Lcn-2+ neutrophil is associated with gut dysbiosis and intestinal inflammation in a spontaneous EAE model of multiple sclerosis

Authors

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PI Name: Suhayl Dhib-Jalbut, Kouichi Ito

Intestinal inflammation and gut dysbiosis are associated with Multiple Sclerosis (MS). To determine the cellular mechanism of this association, we investigated gut infiltration of immune cells in a spontaneous experimental autoimmune encephalomyelitis (EAE) model (transgenic (Tg) mice expressing HLA-DR2a and human T cell receptor (TCR) specific for myelin basic protein peptide (MBP87-99)/HLA-DR2a complexes). Interestingly, we observed in this model, the simultaneous development of EAE and colitis, suggesting a link between autoimmune disease of the central nervous system (CNS) and intestinal inflammation. Examination of the colon revealed the infiltration of MBP-specific Th17 cells as well as recruitment of neutrophils. Furthermore, we observed that fecal Lipocalin-2 (Lcn-2), a biomarker of intestinal inflammation, was significantly elevated and predominantly produced by the gut-infiltrating neutrophils. We then extended our findings to MS patients and demonstrated that fecal Lcn-2 levels are significantly elevated in MS patients compared to healthy donors (HDs). The elevation of fecal Lcn-2 levels correlated with reduced bacterial diversity and increased levels of other intestinal inflammation markers including neutrophil elastase and calprotectin. Microbial abundance analysis showed that short-chain fatty acid producing bacteria such as Anaerobutyricum (Eubacterium) hallii, Blautia massiliensis, Clostridium hylemonae, and Roseburia sp 32368 were depleted in Lcn-2-high MS patients. This study suggests that gut infiltration of Th17 cells and recruitment of neutrophils are associated with the development of gut dysbiosis and intestinal inflammation, and that fecal Lcn-2 level is a sensitive biological indicator for gut dysbiosis and intestinal inflammation in MS.

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Poster #24

Heart rate as a predictive biomarker for severe destructive behavior

Authors

Liam H. McCabe & Brian D. Greer

PI Name: Brian D. Greer

Previous studies have examined the predictive validity of heart rate (HR) on severe destructive behavior, however such research has yet to improve clinical procedures or our understanding of physiology and destructive behavior. The purpose of this study was to examine the predictive validity of HR on varying topographies and functions of destructive behavior while controlling antecedent and consequent events through functional analyses (FA). In Experiment 1, we assessed the reliability of the Polar H10 HR monitor and the feasibility of its use in an analog FA session using a confederate participant. The results of Experiment 1 demonstrated that the Polar H10 HR monitor was a reliable measure of HR and was feasible for HR data collection during an FA session. In Experiment 2, we examined the predictive validity of HR on destructive behavior and the patterns of physiological arousal across within-session intervals of reinforcer presence or absence in four children with autism spectrum disorder (ASD). Results of Experiment 2 indicated that HR was not a reliable predictor of either automatically or socially reinforced destructive behavior. However, we found that measurement of reinforcer presence or absence was sufficient to predict socially reinforced destructive behavior. When examining HR in relation to reinforcer presence or absence, a clear pattern of HR was not identified. Although HR was not predictive of destructive behavior, we have provided a procedural framework for future assessment of other biological measures.

Poster #25

Design and computational analysis of CCL2-sequestering anti-inflammatory hydrogels

Authors

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PI Name: Jay C. Sy

Chemokine C-C motif ligand 2 (CCL2) is a cytokine known to exacerbate inflammation associated with traumatic brain injury and foreign body response around brain implants. When CCL2 binds with the receptor CCR2, it encourages monocyte chemotaxis and release of inflammatory factors such as IL-1β and TNF-α. However, CCL2 is also a critical immune system component, making it an inappropriate target for systemic therapy. We previously developed self-assembling peptide hydrogels with a CCL2-binding peptide, WKNFQTI, that could locally sequester and inactivate CCL2. With newly avaiable CCL2-CCR2 crystallography data, we set out to design de novo CCL2-binding peptides with improved affinity. We designed peptide candidates by identifying, via alanine scanning, the 11-residue sequence of CCR2 with the highest contribution to CCL2 binding (candidate aCCL-1), then mutating the sequence using two different scoring algorithms (candidates aCCL-2, Rosetta CoupledMoves and aCCL-3, BAlaS). We performed 400ns of all-atom molecular dynamics on the CCL2-peptide complexes and found that all three de novo peptides significantly outperformed WKNFQTI in number of hydrogen bonds, intermolecular contacts, and complex free energies. PCA results showed that candidate aCCL-3 demonstrated a unique interaction with residues 50-52 of CCL2 that granted the complex additional stability, making it our top performer. Our amended hydrogel is highly biocompatible, can be used as a stand-alone wound treatment or an implant coating, and its efficacy is being tested in vitro at reducing localized inflammation.

Supported by CBIR20FEL019 and NIH T32 GM135141(EDA), Busch Biomedical Grant (JCS); NIH R15 EY029504, R01DE031812, R01DE029321, R21AR079708, UL1TR003017; NSF IIP 2032392, and the URI program at NJIT (VAK).

Poster #26

Auditory discrimination learning in animals with and without developmental hearing loss is accompanied by behaviorally relevant changes to striatal auditory and motor neural activity

Authors

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PI Name: Todd M. Mowery

The way in which naïve and well-trained animals perform in the same task is dependent on differences in the evoked sensory and motor neural response to behaviorally relevant stimuli. Through many decades of research, we know that developmental hearing loss leads to permanent differences in the physiology of the auditory neuraxis. Recent work from my lab has shown that these changes extend to the auditory striatum, and that hearing loss induced deficits briefly compensate during learning. In this study, we asked how neuronal response properties in the motor and auditory regions of the dorsal striatum change during the learning of an auditory associative conditioning task as a function of developmental hearing status. Adult Mongolian gerbils were implanted with a 64-channel electrode array that spanned the sensorimotor and auditory/visual regions of the striatum. Animals were trained on an amplitude-modulated (AM) discrimination task and neural activity recorded daily as learning occurred. Significant changes within groups were compared between animals with and without a history of developmental hearing loss during the physiological emergence of the novel behaviors that are associated with increased d-prime and learning. These findings provide exciting correlations between epochs of learning and the neurophysiological processes from which novel behaviors progressively emerge. Our data show how the physiology before and after learning is significantly altered through sensory motor integration at the level of the striatum. Further, it provides novel insight into how hearing loss induced changes to underlying neurophysiology can simultaneously lead to both propagation of and compensation for learning impairments.

This study was supported by NIH NIDCDR01.

Poster #27

Neural mechanisms mediating optimistic beliefs about negative drug use outcomes in people with addiction.

Authors

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PI Name: Anna B. Konova

People hold biased beliefs about their future, often expecting more good things to happen to them than bad ones. While such “optimism bias” can benefit well-being, unrealistic optimism could inhibit mitigating behaviors to prevent future risk, such as reducing risky drug use. Neural circuits perpetuating optimism bias largely overlap with those involved in value-based decision-making, including drug choice. However, how this neural circuit mediates domain-specific optimism bias remains unknown. Here, we devised a task to test how a domain-specific optimism bias for negative drug outcomes is maintained in the brain. During fMRI, 19 treatment-engaged individuals with opioid use disorder (OUD) and 24 matched healthy controls estimated their likelihood of drug use-related and nondrug-related negative outcomes (e.g., overdose, insomnia) before seeing the actual base rate of each outcome for someone in their demographic. They then had an opportunity to revise their estimates. We found that subjects updated their beliefs more after receiving better-than-expected base rates (good news) than worse-than-expected base rates (bad news) ($B=0.72$, $P<0.001$), with patients tending to update their beliefs more for drug-related outcomes than controls after receiving good news ($B=-0.20$, $P=0.06$). A similar, domain-specific, optimism bias was observed neurally in the left inferior frontal gyrus where patients exhibited increased brain activity for good news compared to bad news for drug-related outcomes ($B=-0.05$, $P=0.07$). Together, these data provide initial evidence for a domain-specific optimism bias in the brain in people with OUD and a novel approach to identify neural targets that could be modulated to reduce risky drug use.

Supported by supported by grants from the National Institutes of Health (R01DA053282, PI: Konova; R25DA035161-06, PIs: Ruglass and Hien; R25GM055145, PI: Langer)

Poster #28

Role of Nociceptin/Orphanin FQ in the regulation of inflammation-induced sickness behavior

Authors

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PI Name: Alexander Kusnecov

The precursor propeptide Nociceptin/Orphanin FQ (N/OFQ) peptide is linked to behavioral changes, including anxiety, reward, and nociception. Activation of the nociceptin receptor (NOP) has been argued to oppose behavioral deficits due to stress, analgesic effects of mu-opioid receptor stimulation and systemic inflammation. Here we have examined the role of NOP in regulating the behavioral response to a proinflammatory stimulus, LPS. Behavioral testing examined a variant of a food or taste aversion paradigm in which C57BL/6 background NOP-deficient mice [NOP KO] (23F; 31M) and WT controls (20F; 22M) were treated with LPS (200µg/kg and 600µg/kg) and immediately exposed (for 90 mins) to Prosobee (a baby formula mice voluntarily consume without food deprivation).Consumption around the time of injection allowed for assessment of immediate illness effects, while recovery of consumption (or retention of aversion) was measured 24h later. Animals were also monitored for overnight food intake and body weight. Analysis of data from these experiments suggest that in NOP-deficient mice [NOP KO], in the absence of N/OFQ signaling, the systemic IL-1β and sickness response to LPS is more pronounced, and subject to sex effects (different in male and female mice). Overall, it is suggested that N/OFQ may be important for restraining inflammatory responses and attending behavioral adjustments.

Support by BHI and the Busch Biomedical grant programs

Poster #29

Impact of pain on the performance of fNIRS-based brain computer interface.

Authors

Ashwini Subramanian, Laleh Najafizadeh

PI Name: Laleh Najafizadeh

Brain computer interface (BCI) is a device that enables the control of peripheral assistive devices such as a wheelchair or a prosthetic arm using signals acquired from the brain. A key application of BCIs is in assistive systems for patients with motor disabilities. A BCI is trained prior to being used for assistive purposes. Functional near infrared spectroscopy (fNIRS) is a non-invasive neuroimaging technique that measures changes in the concentration of oxygenated and deoxygenated hemoglobin in the cerebral cortex. Recently, fNIRS has been used for brain signal acquisition in BCIs. Patients who use BCIs for assistance are usually prone to physical pain. It has been established in literature that the presence of physical pain elicits a subjective but definitive pattern of cerebral activity. This research aims to study the impact of the presence of pain on the task classification accuracy of a fNIRS-based BCI. Cortical fNIRS signals are recorded during the performance of two mental arithmetic tasks, in the presence and absence of physical pain. The BCI is then used to classify the tasks from these signals. It is observed that when the BCI is trained on pain-free data and tested on data obtained in the presence of pain, the classification accuracy drops. We also performed multi-label classification to simultaneously identify the presence of pain and classify the tasks, further demonstrating that the distinction of tasks in the presence of pain is challenging. This work highlights the importance of considering pain-induced changes in cortical activity when developing BCIs for patients.

Supported by NSF grant 1841087.

Poster #30

A deep learning framework based on dynamic channel selection for early classification of left- and right-hand motor imagery tasks

Authors

Jiazhen Hong, Foroogh Shamsi, and Laleh Najafizadeh

PI Name: Laleh Najafizadeh

Ideal brain-computer interfaces (BCIs) need to be efficient and accurate, demanding for classifiers that can work across subjects while providing high classification accuracy results from recordings with short duration. To address this problem, we present a new deep learning framework for discriminating motor imagery (MI) tasks from electro encephalography (EEG) signals. The framework consists of a 1D convolutional neural network-long short-term memory (CNN- LSTM), combined with a dynamic channel selection approach based on Davies-Bouldin index (DBI). Using data from BCI competition IV-IIa data, the proposed framework reports an average classification accuracy of 70.17% and 76.18% when using only 800 ms and 1500 ms of the EEG data after the task onset, respectively. The proposed framework dynamically balances individual differences, achieves comparable or better performance compared to existing work, while using short duration of EEG.

Supported by NSF grant 1841087

Poster #31

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

Authors

Rouba Houbeika, 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 difficulty with communication and interaction with other people. Successful social interaction requires acquisition of information presented in the environment and reconstructing those memories to behave accordingly, highlighting the importance of the hippocampus. Epidemiologic studies have demonstrated upon maternal infection, IL-6, a pro inflammatory cytokine, can cross the placenta-fetal blood brain barrier causing neuroinflammation and altering brain development. The pattern of elevated IL-6 is maintained after birth. Earlier studies evaluated the role of IL-6 using maternal immune activation mouse models that mimic infections in the first trimester of human gestation. However, epidemiological studies show that infections at the end of the second trimester pose the greatest risk for developing ASD. Unanswered is whether elevating IL-6 at the end of the second trimester will affect brain development to produce ASD-like behaviors. Therefore, we have injected mice with PBS or 75 ng of rmIL-6 on 3 consecutive days beginning on post-natal day 3, a developmental mouse stage that represents the end of the second trimester in human gestation. Our data show that as adults, IL-6 treated mice have an increase in the retention of aversive memories, social deficits and a trend towards smaller hippocampi. We also examined long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus. These studies revealed a strong trend towards increased LTP and increased LTD in the CA1 region of the dorsal hippocampus. Taken together, these data demonstrate that a transient increase in IL-6 during brain development will cause persisting behavioral changes that resemble those seen in people with ASD.

Supported by Governor's Council for Medical Research and Treatment of Autism (CAUT22AFP009) to FJV.

Poster #32

Roles of top-down projections in gating plasticity in dendrites and coordinating learning in hierarchical circuits

Authors

Alessandro Galloni, Ajay Peddada, Aaron D. Milstein

PI Name: Aaron D. Milstein

Here we consider a central problem in biological learning called the “credit assignment problem” - how does the outcome of a behavior adjust the right synaptic connections across multiple layers of neuronal circuitry to improve future performance? Artificial neuronal networks are typically trained by direct gradient descent to minimize the error in the output of the network with respect to its synaptic weights. In contrast, biological networks are thought to implement unsupervised Hebbian learning rules, which do not prescribe a mechanism for learning to be coordinated across multiple layers. Recent work has demonstrated that neurons with extended dendrites may have special features that are advantageous for supervised learning. In addition to feedforward connections that transmit sensory information “bottom-up” from the periphery, biological neurons also send information backwards along a hierarchy of neuronal circuitry through extensive “top-down” feedback connections. These feedback connections typically impinge on distal neuronal dendritic compartments where they can evoke a special type of event called a “dendritic calcium spike.” This event both increases the output of a neuron and induces a non-Hebbian form of plasticity called “behavioral timescale synaptic plasticity” (BTSP). We will show evidence from a computational model that regulation of dendritic spiking and plasticity by top-down feedback signals can effectively coordinate plasticity across multiple layers of a neuronal network during pattern recognition learning

Supported by NIMH and EMBO grants.

Poster #33

The role of Tex15 in the alteration of singular olfactory receptor gene choice in mouse olfactory sensory neurons

Authors

Nusrath Yusuf, Giorgia Merolli, Mallika Ravi, Alina Irvine, Kevin Monahan

PI Name: Kevin Monahan

The incredible specificity with which we can discern a vast diversity of smells emerges from how olfactory sensory neurons (OSN) express olfactory receptor (OR) genes, which encode the proteins that bind chemical odorants. Each OSN stochastically transcribes only one allele of an OR gene. The choice of an OR gene occurs as immediate neuronal progenitor (INP) cells mature into OSN. Recent work has revealed remarkable remodeling of the local chromatin during this period, but the molecular mechanisms governing these processes and their connection to singular OR allele expression remain unknown. We show that testis expressed 15 (Tex15), a protein that has only been studied in the testes where it regulates methylation and silencing of transposons, is crucial for stochastic OR gene choice. We find that when Tex15 is knocked out there is a dramatic reduction in the diversity of expressed OR genes with a few OR genes dominating stochastic choice. Strikingly, Tex15 is transiently expressed at the INP stage of OSN differentiation. We hypothesize that Tex15 is epigenetically controlling stochastic OR gene choice, either by regulating DNA methylation or other aspects of OR gene chromatin structure. Our experiments on primary OSNs from Tex15 KO mice aim to address the timing and patterning of methylation marks deposition in Tex15 KO mice. In parallel, we will analyze the chromatin structure and 3D organization of OR genes Tex15 KO OSNs. This work will reveal the key molecular underpinnings for our sense of smell, while also uncovering a new and unexpected role for Tex15.

Supported by NIGMS R35, Rita Allen Foundation

Poster #34

Impact of copy number variants on early development in patients with treatment resistant psychosis

Authors

Matthew K Harner, Tyler Dietterich, Martilias Farrell, Lisa Bruno, Allison Britt, Rose Mary Xavier, Jennifer Mulle, Patrick Sullivan, Richard Josiassen, and the PASH Collaborative Group

PI Name: Jennifer Mulle

Rare disease-associated copy number variants (CNVs) occur at increased rates in patients with treatment-resistant psychosis. Phenotypic expression of these genomic disorders has been documented throughout childhood and adolescence but remains largely unexplored in the context of adult psychiatry. Here, we used archival medical records to retrospectively document the early development of CNV carriers (n=25) and non-carriers (n=25; matched for age, sex, and ancestry) from a cohort of patients with treatment-resistant psychosis. Neurodevelopmental burden (cumulative score ranging from 0-5 based on the presence (1) or absence (0) of any symptoms of autism, developmental delay, ADHD, intellectual disability, and learning disability) was compared between groups using a Wilcoxen Rank Sum test. Carriers of specific CNVs (duplications of 15q11.2-q13.1 and 16p11.2) were examined in depth to identify shared and distinct phenotypic characteristics. CNV carriers had a significantly greater burden of early-life neurodevelopmental symptoms compared to controls. 15q11.2-q13.3 duplication carriers were more commonly affected by early behavioral symptoms (i.e., ADHD, impulsivity, aggression), whereas 16p11.2 duplication carriers had a high rate of mood and psychosis symptoms in early life (i.e., depression, social withdraw, paranoid delusions). Combined with previous findings, these data support the hypothesis that specific CNVs increase the burden of disability across multiple domains including early neurodevelopmental phenotypes and long-term outcomes such as treatment-resistance in psychotic disorders. Rare variants may therefore be a rich substrate for studying the interaction between early developmental cognitive burden and treatment outcomes in adult psychiatry.

This work was supported by the National Institute of Mental Health (K01 MH108894); H. Lundbeck A/S; the Vernik Family Trust; and the Samuel and Paul Lofgren Family Trust

Poster #35

Visual-motor integration deficits in 3q29 deletion syndrome

Authors

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PI Name: Jennifer Mulle

3q29 deletion syndrome (3q29del) is associated with neuropsychiatric and neurodevelopmental phenotypes. We previously reported that graphomotor weakness is present in up to 78% of individuals with 3q29del. We have now explored nuances of the graphomotor phenotype and its association with other comorbidities in this population. Participants were recruited from the online 3q29 registry (3q29deletion.org) for two days of deep phenotyping. 32 individuals with 3q29del (62.5% male) were evaluated with the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) to assess visual-motor integration. Participants were also evaluated with measures of cognitive ability, executive function, adaptive behavior, and school function. Males with 3q29del performed significantly worse than females on the VMI and Motor Coordination subtest. VMI performance was significantly associated with ADHD diagnosis and cognitive ability. Compared to published data from individuals with 22q11.2 deletion syndrome, individuals with 3q29del showed significantly more impairment. The 3q29 deletion is associated with substantial deficits in visual-motor integration, Visual Perception, and Motor Coordination. Our data suggests that 3q29del may qualify as a nonverbal learning disability. Future studies should assess whether individuals with 3q29del would benefit from early interventions, including occupational therapy.

Supported by NIMH R01 MH110701 (PI Mulle)

Poster #36

Neuron-to-neuron transfer of proteins and organelles via tunneling nanotubes: Relevance to neurodegenerative diseases.

Authors

Priya Vaid and Virgil Muresan

PI Name: Virgil Muresan

Alzheimer's Disease (AD), a severe form of dementia that causes brain damage and cognition loss at old age, is characterized by accumulation of toxic protein species - amyloid-β peptide (Aβ) and hyperphosphorylated Tau protein (pTau) – in a small population of neurons in the entorhinal cortex and/or the locus coeruleus. As the disease progresses, the toxic protein species gradually spread throughout the brain, likely through a process that involves neuron-to-neuron transmission. It was proposed that the transfer of the toxic species from the neuron where they have been generated to the recipient neuron could occur through thin, channel-like connections, known as tunneling nanotubes (TNTs). TNTs are known to be generated via two different mechanisms: (1) extension of a filopodium from one cell to another, followed by membrane fusion; and (2) membrane fusion between two cells in close contact. Using metabolically stressed, locus coeruleus-derived neuronal cells (CAD), we have identified a novel mechanism of generation of TNTs. We found that TNTs could form between daughter cells that fail to complete cytokinesis after mitosis and remain permanently connected. Such TNTs increase in length as the cells migrate in different directions and withstand extreme mechanical stress. We showed that these TNTs contain microtubules, actin filaments, and neurofilaments. They also contain a large variety of proteins and protein aggregates typically present in AD and other proteinopathies (e.g., phosphorylated Tau, TDP-43, SOD1, FUS, α-synuclein). These findings are consistent with the possibility of neuron-to-neuron propagation of these potentially pathogenic species via the newly identified TNTs..

This study was supported by Connecticut Science Fund/Vanguard Charitable Grant

Poster #37

Type I interferon signaling drives microglial dysfunction and senescence in human IPSC models of Down syndrome and Alzheimer's disease

Authors

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PI Name: Peng Jiang

Microglia are critical for brain development and Alzheimer's disease (AD) etiology. Down syndrome (DS) is the most common genetic origin of intellectual disability and the most common risk factor for AD. Surprisingly, little information is available on the impact of trisomy of human chromosome 21 (Hsa21) on microglia in DS brain development and AD in DS (DSAD). Using our new induced pluripotent stem cell (iPSC)-based human microglia-containing cerebral organoid and chimeric mouse brain models, we report that DS microglia exhibit enhanced synaptic pruning function during brain development. Consequently, electrophysiological recordings demonstrate that DS microglial mouse chimeras show impaired synaptic functions, as compared to control microglial chimeras. Upon being exposed to human brain tissue-derived soluble pathological tau, DS microglia display dystrophic phenotypes in chimeric mouse brains, recapitulating microglial responses seen in human AD and DSAD brain tissues. Further flow cytometry, single-cell RNA-sequencing, and immunohistological analyses of chimeric mouse brains demonstrate that DS microglia undergo cellular senescence and exhibit elevated type I interferon signaling in response to pathological tau. Mechanistically, we find that shRNA-mediated knockdown of Hsa21encoded type I interferon receptor genes, IFNARs, rescues the defective DS microglial phenotypes both during brain development and in response to pathological tau. Our findings provide in vivo evidence supporting a paradigm-shifting theory that human microglia respond to pathological tau by exhibiting accelerated senescence and dystrophic phenotypes. Our results further suggest that targeting IFNARs may improve microglial functions during DS brain development and prevent human microglial senescence in DS individuals with AD

Supported by NIH (R01NS102382, R01NS122108, and R01AG073779 to P.J.). We thank the UCI-ADRC, which is funded by NIH/NIA Grant P30AG066519 and the Brightfocus Foundation (BFF17-0008), for providing us with DSAD and Cont human brain tissues.

Poster #38

Potential therapy for a rare subset of Parkinson's Disease due to deficiency of Pten-Induced Putative Kinase (PINK1)

Authors

Tianxia Xiao

PI Name: Joshua D. Rabinowitz (Princeton)

A new therapeutic pathway for the genetical rare disease, Parkinson's disease type 6, is proposed with a poly-peptide lead compound as the starting point of structure-based design. The pharmacokinetics is discussed with reference to the chemical nature of the lead compound and methods for IND-enabling studies are suggested. Particularly, we review the theoretical rationale of using intranasal (IN) drug delivery via olfactory neuronal distribution pathways. As preliminary research for a potential start-up venture, we also provide the rational for first in human dose and design of first clinical trial. Following the traditional model in pharmaceutical drug development, we explain the proof-of-concept in patients. Competitive concerns with related therapeutics are addressed in the end.

Poster #39

The Role of TRPM3 Ion Channels in Opioid-Induced Pruritus

Authors

Nawoo Kim, Yevgen Yudin, Songxue Su, Tibor Rohacs

PI Name: Tibor Rohacs

Neuraxial administration of morphine has the distressing side effect of pruritus. Common anti-itch therapies are ineffective; therefore, a more target-specific treatment for morphine-induced pruritus is needed. Pruritus from morphine is caused by the inhibition of inhibitory neurons, while analgesia is caused by inhibition of excitatory neurons in the spinal cord. Morphine acts on opioid receptors which couple to heterotrimeric Gαi-proteins exerting acute effects on downstream ion channel targets to inhibit neuronal activity. This project aims to investigate if the transient receptor potential melastatin 3 (TRPM3) ion channels are involved in opioid-induced pruritus. TRPM3 is a non-selective, heat-sensitive cation channel expressed in neurons that is inhibited upon opioid receptor activation. This inhibition is mediated by direct binding of Gβγ to a 10-amino acid binding site on TRPM3, encoded by an alternatively spliced exon. We created a genetically mutated mouse line (TRPM3DEx17) in which TRPM3 channels lack this exon. Upon intrathecal injection of morphine, the TRPM3DEx17 mice experienced less scratching compared to wild-type (WT) mice. Exogenously activating TRPM3 with intrathecal co-injection of pregnenolone sulfate (PS) along with morphine decreased scratching. Intrathecal injection of the TRPM3 antagonist, primidone, caused spontaneous itch. As TRPM3 shows higher level of co-expression with the μ-opioid receptors in the inhibitory neurons responsible for the pruritic pathway compared to the excitatory neurons for the analgesic pathway, the results show that the activation of TRPM3 can decrease morphine-induced itch without significant side effects. This study provides evidence for a potential new therapy to relieve morphine-induced pruritus by targeting TRPM3.

Supported by R01NS055159-12 and F31NS125940

Poster #40

State dependent control of feeding behavior by a BNST⟶LHA pathway

Authors

Kuldeep Shrivastava, Tess Kowalski, Mark A. Rossi

PI Name: Mark A. Rossi

Overeating is a major issue in modern society, resulting in numerous health problems, including obesity. The bed nucleus of the stria terminalis (BNST), a component of the extended amygdala has been previously identified as the key brain structure that regulates diverse motivational states through its interactions with various synaptic targets, including the ventral tegmental area (VTA) and the lateral hypothalamus (LH). The BNST comprises primarily GABAergic cells, and consumption of food activates BNST neurons. It has been previously reported that $BNST^{GABA \rightarrow LHA}$ activation increases feeding by inhibiting LHA glutamatergic (LHA^{Vglut2}) neurons. Furthermore, recent studies have shown that LHA^{Vglut2} activation suppresses feeding and is aversive but effect of motivational state on feeding behavior remains uncharacterized. Here, we discover that optogenetic activation of the BNST⟶LHA pathway promotes frequency dependent sucrose seeking. In addition, we found that chronic HFD exposure diminish BNST⟶LHA induced sucrose seeking behavior. The effectiveness of stimulation depends on motivational state and is not sufficient to overcome aversion. These results shed light on possible neural pathway mechanisms underlying complex disease states characterized by feeding abnormalities

This work was supported by R00DK121883 and the Robert Wood Johnson Foundation (grant #74260)

Poster #41

Irisin: An insight into sex differences in glucose usage during submaximal endurance exercise

Authors

Gwyndolin M. Vail and Vanessa H. Routh

PI Name: Vanessa H. Routh

Regulation of energy usage is a tightly controlled homeostatic function that often differs depending upon sex. For example, submaximal endurance exercise stimulates lipid oxidation more so in females than in males, where glucose utilization is initially dominant. The brain is a likely source for this sex difference, as it maintains energy homeostasis. One way the brain does this is through glucose inhibited (GI) neurons in the ventromedial hypothalamus (VMH). VMH-GI neurons increase activity when glucose decreases to restore peripheral glucose levels. Using mouse brain slice patch-clamp techniques, we exposed VMH-GI neurons to irisin, a myokine released by muscle during exercise. We hypothesize that irisin acts as a sex-dependent signal of exercise to the brain. Consistent with this, irisin had no significant effect on VMH-GI neuronal activation in males as glucose decreased from 2.5 to 0.1 mM. However, in females irisin decreased the depolarization and the change in input resistance of VMH-GI neurons in low glucose by 4 ± 1 mV and 60 ± 11%, respectively. These data suggest that during exercise, low glucose activates VMH-GI neurons to a lesser extent in females vs males, perhaps explaining female preference for lipids over glucose during exercise. Additionally, post hoc analysis revealed that the effects of irisin were not significant during proestrus, when circulating estrogen peaks. This implies an estrogenic regulation of exercise-induced sex differences in substrate utilization. Understanding how sex and hormones influence energy usage will allow for more personalized approaches to nutritional strategies, which are especially important in diabetic and pre-diabetic patients.

Supported by NIH IRACDA Grant 1K12GM093854 (GMV) and NIH R01DK103676 (VHR)

Poster #42

Pathogenic LRRK2 regulates centrosome cohesion via Rab10/RILPL1-mediated CDK5RAP2 displacement

Authors

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PI Name: Sabine Hilfiker

Mutations in LRRK2 increase its kinase activity and cause Parkinson´s disease. LRRK2 phosphorylates a subset of Rab proteins including Rab8 and Rab10, which allows for their binding to RILPL1. The phospho-Rab/RILPL1 interaction causes deficits in ciliogenesis and interferes with the cohesion of duplicated centrosomes, including in patient-derived peripheral cells. We show here that the centrosomal deficits mediated by pathogenic LRRK2 can also be observed in patient-derived iPS cells, and we have used transiently transfected cell lines to identify the underlying mechanism. The LRRK2-mediated centrosomal cohesion deficits are dependent on both the GTP conformation and phosphorylation status of the Rab proteins. Pathogenic LRRK2 does not displace proteinaceous linker proteins which hold duplicated centrosomes together, but causes the centrosomal displacement of CDK5RAP2, a protein critical for centrosome cohesion. The LRRK2-mediated centrosomal displacement of CDK5RAP2 requires RILPL1 and phosphorylated Rab proteins, which stably associate with centrosomes. These data provide fundamental information as to how pathogenic LRRK2 alters the normal physiology of a cell and may form the basis for assays to stratify PD patients who benefit from LRRK2-related therapeutics.

Supported by Michael J. Fox Foundation for Parkinson's research, and intramural funding from Rutgers University.

Poster #43

Role of a potassium ion channel mutant in neuronal development

Authors

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PI Name: Federico Sesti

Potassium channels regulate neuronal excitability and are capable of eliciting intracellular signal cascade in the central nervous system. Voltage-gated potassium channel subfamily B member 1 (KCNB1) is associated with integrins (IKCs) that is important for converting its electrical properties into a signal transduction that results in cell proliferation. Mutations of KCNB1 are associated with epileptic disorders. Particularly, a substitution mutation for Arginine to Histidine at position 312 in the KCNB1 gene ($KCNB1^{R312H}$) has been identified in children presenting early-onset epileptic encephalopathies. Children affected by this disorder present recurrent seizures and intellectual delays. To investigate this neurological condition, we generated a CRISPR knock-in (KI) murine model harboring the $KCNB1^{R312H}$ gene variant. Although KCNB1 is embryonically expressed, its role in neurodevelopment is unknown. Furthermore, since the $KCNB1^{R312H}$ subunit of the IKCs complex may affect its signal transduction, we hypothesize the mutant channels to elicit an aberrant effect during neuronal development. We analyzed the KI mouse model at different developmental stages via immunohistochemistry, Golgi staining, western blots, and coimmunoprecipitation to analyze its role in neocortex development. Immunohistochemistry showed under-migration in upper cortical layers; Golgi staining revealed hyper arborization and lack in middle cortical layers; western blot and coimmunoprecipitation suggest variations in the macromolecular IKCs complex and its pathway. Our results support the hypothesis that defective IKCs, formed with the mutant $KCNB1^{R312H}$, can affect neurodevelopment. Our data reveals a previously unknown neurodevelopmental mechanism in which potassium channels affect the fundamental neuronal processes through mechanisms that do not directly depend on its current conducting properties.

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Poster #44

Cortical circuits controlling maternal care

Authors

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While pharmacological and lesion studies in rodents have shown that the prefrontal cortex is involved in maternal care, we lack information about specific cell types and connectivity from this region. Using transgenic mice, we describe that the neuronal projections positive for the gastrin releasing peptide (GRP) are involved in maternal care. Antero and retrograde tracing strategies showed that GRP cells in the medial prefrontal cortex (mPFC) project to the medial preoptic area (mPOA), a major area controlling maternal care. Optogenetic activation of GRP cells expressed in the mPFC or in the mPFC-mPOA circuits induced maternal care. Altogether our study shows that the mPFC can enhance maternal care by its projections to the mPOA. Describing the mPFC circuits related to maternal care is critical for understanding deficient maternal care in women with mood affections as some of these disorders are linked to deficient activity in this brain region.

Supported by the American Association of University Women (AAUW), the New Jersey Autism Research Council, Busch Grant, and R01MH107555 from NIH.

Poster #45

Elimination of intravascular thrombi prevents early mortality and reduces gliosis in hyper-inflammatory experimental cerebral malaria

Authors

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PI Name: Robin Stephens

Cerebral malaria (CM) is the most lethal outcome of Plasmodium infection. Inflammatory cytokines, severe coagulopathies, and mortality are correlated in human CM. Mechanisms of mortality driven by inflammation and coagulation and poorly understood. Mice deficient in the regulatory cytokine IL-10 (IL-10 KO), infected with P. chabaudi succumb to a hyper-inflammatory response and lethal outcome preventable by neutralization of the systemic inflammatory cytokine tumor necrosis factor (TNF). Behavioral dysfunction and microglial activation in infected IL-10 KO animals is suggestive of neurological involvement driven by inflammation. To understand the relationship of intravascular inflammation to parenchymal dysfunction, we studied the relationship of glial cell activation to congested vessels in the brain. There is severe thrombotic congestion in infected IL-10 KO animals combined with immune cells (CD45, CD11b, CD4), microglia (Iba-1), and astrocytes (GFAP) that often colocalize with thrombi. Despite containment of both pathogen and leukocytes within cerebral vasculature, activated microglia and astrocytes were prevalent in the parenchyma, particularly clustered near vessels with thrombi. Finally, we investigated the roles of inflammatory cytokine tumor necrosis factor (TNF) and coagulation on cerebral pathology using neutralizing antibodies and low-molecular weight heparin to inhibit inflammation and coagulation. Neutralization of either TNF, or coagulation, significantly reduced both thrombus formation and gliosis and prevented mortality. These findings support the contribution of inflammatory cytokines to coagulation and neuropathology in cerebral malaria. Localization of inflammatory leukocytes within intravascular clots suggests a mechanism for interaction by which cytokines could drive local inflammation without considerable cellular infiltration into the brain parenchyma.

Supported by R01NS106597.

Poster #46

Behavioral screening of Celsr3 mutant mouse models for Tourette-like phenotypic features

Authors

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PI Name: Max Tischfield

Tourette Disorder (TD) is a prevalent neurodevelopmental syndrome characterized by motor and/or vocal outbursts known as ‘tics’. TD is hypothesized to result from developmental perturbations to cortico-striato-thalamo-cortical (CSTC) networks, but efforts to address the underlying circuit mechanisms have been impeded by a lack of animal models. Our lab is developing preclinical animal models for TD based on exome sequencing data from over 800 TD simplex trios that identified multiple de novo mutations in high-confidence TD genes. CELSR3 is an adhesion protocadherin G protein-coupled receptor and currently the most frequently mutated gene found in TD. CELSR3 plays important roles in axon guidance, neurite outgrowth, and synapse formation. However, circuit mechanisms pertaining to CELSR3 and its dysregulation in TD are unknown. We have now generated three novel mouse models engineered to express human mutations in CELSR3. With this powerful allelic series of animal models, we are currently applying mouse behavior, electrophysiology, and anatomical approaches to understand how mutations in Celsr3 affect development of key CSTC and basal ganglia circuits. Screening Celsr3 models for behavioral changes using motion sequencing (MoSeq), pre-pulse inhibition (PPI), open field, and fixed ratio (FR1) reinforcement learning has revealed TD-like behavioral phenotypes. Furthermore, we have identified changes to dendritic patterning and the firing activities of cholinergic interneurons, important modulators of striatal dopamine release. Our combined approaches in animal models will build novel mechanistic frameworks to elucidate circuit mechanisms that underlie TD, which will help guide the development of more efficacious treatments.

Supported by TSA, NJ Center For Tourette Syndrome, BRF, BBRF (MAT) & R01MH115958 (JAT, GAH).

Poster #47

Cardiac responses to pain as biomarkers for pain-induced stress in autism

Authors

Mona Elsayed, Elizabeth Torres.

PI Name: Elizabeth Torres

Pain sensation often goes unnoticed in nonverbal individuals such as those with autism spectrum disorder (ASD). The goal of this work is to uncover biomarkers of pain by exploring cardiac signals from the autonomic nervous systems (ANS). We target the neurotypical (NT) population to understand signature responses to pain that can be used to objectively assess when those with physical pain and/or neurodevelopmental disorders demonstrate such responses under normal conditions. NT subjects performed various motor-cognitive tasks such as resting, walking, and pointing to a target under control and pain conditions while ASD subjects performed the same tasks only under control conditions. Electrocardiographic (ECG) signals representing cardiac activity (via the ANS) were characterized via clinically relevant heart rate variability (HRV) metrics to assess sympathetic and parasympathetic NS activation along with more personalized analyses. Preliminary findings suggest unique statistical patterns in cardiac responses during the pain condition that are comparable to the signals observed in ASD subjects at baseline. In NT subjects, the pain condition elicits a unique cardiac response that is associated with elevated sympathetic (fight-or-flight) activity and/or decreased parasympathetic tone commonly observed in ASD subjects. Results from personalized parameterization also followed consistent patterns with time & frequency domain HRV metrics. Overall, this work has several implications in developing a clearer neurophysiological understanding of pain by objectively detecting internal levels of pain and pain-related stress/anxiety in autistic individuals and the general population - ultimately allowing for earlier diagnosis and treatment.

Supported by the Governor's Council for Medical Research and Treatment of Autism (CAUT14APL018)

Poster #48

Chronic stress and its effects on behavior, RNA expression of the bed nucleus of the stria terminals, the M-current of NPY neurons.

Authors

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PI Name: Troy Roepke

Women are more susceptible to the development of stress-related mood disorders, suggesting a sex difference in stress processing. The bed nucleus of the stria terminalis (BNST) is a region of the brain that is essential for the central stress response and is also sexually dimorphic in expression. This suggests that it may be a cause of this sex difference. Additionally, Neuropeptide Y (NPY) is highly expressed in the BNST and is active in stress signaling. For this study, experimental mice experienced six weeks of a chronic variable mild stress (CVMS) paradigm prior to behavior, RNA sequencing, and whole-cell patch clamp electrophysiology. Behavior tests were the open field test (OFT), elevated plus maze (EPM), light/dark box (LDB), and novelty suppressed feeding (NSF). We hypothesized that stress would result in behavioral differences, sex-dependent differences in the transcriptome, and a decreased M-current in NPY neurons. In the OFT, stressed mice spent less time in the center and more time in the corners. In the EPM, stressed mice spent more time in the closed arms and females had more open arm crossings. In the LDB, male mice had significantly more stretch attend postures than females. In the NSF, no significant effects were observed. Stress did not affect the M-current in the NPY neurons, nor was there a sex difference. The RNA sequencing data did not result in major expression differences regarding stress. This suggests that CVMS is an effector of behavior, but BNST NPY neurons may not be a regulator of chronic stress.

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Poster #49

Repetitive mild TBI develops pTau aggregation in nigra and does not affect preexisting fibril induced Parkinson-like pathology burden

Authors

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PI Name: Vedad Delic

Traumatic brain injury (TBI) is associated with an increased risk for Parkinson's Disease (PD). Among U.S. Veterans, those with a history of TBI are at a 56% higher risk to develop PD later in life. The most common type of TBI is mild (mTBI) and can occur repeatedly in athletes, military personnel, and victims of domestic abuse. PD can be characterized by deficits in fine motor movement control, caused by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). To investigate whether repetitive mTBI nucleates PD pathology or accelerates prodromal PD pathology, an injury device was constructed to deliver surgery free r-mTBI to rats. PD was modeled in rats by intracranial injection of recombinant αSyn preformed fibirils to cause progressive human-like PD pathology. At a 3-month endpoint, encephalomalacia was detected throughout the brain of r-mTBI rats, accompanied by astrocyte expansion and microglial activation. Pathology closely associated with PD was produced only by fibril injection. 8x r-mTBIs did not cause or accelerate preexisting PD pathology initiated by PFF injection. r-mTBI caused aggregation of phosphorylated Tau (pTau) protein in nigra with and without pre-existing PD-like pathology. Furthermore, pTau aggregation colocalized with PFF induced αSyn Lewy body-like inclusions without r-mTBI. These findings suggest that r-mTBI induces pTau aggregate deposition in dopaminergic neurons, creating an environment conducive to eventual seeding of αSyn pathology.

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Poster #50

Cortical brain injury causes retrograde degeneration of afferent basal forebrain cholinergic neurons via the p75ntr.

Authors

Srestha Dasgupta, Laura Montroull and Wilma Friedman

PI Name: Wilma Friedman

Basal forebrain cholinergic neurons (BFCNs) extend long projections to multiple targets in the brain to regulate cognitive functions and are compromised in numerous neurodegenerative disorders. To assess how injury to the target region of these neurons affects their viability in vivo, we are using the Fluid Percussion Injury (FPI) model to test the effects of injury at the cortex on the afferent BFCNs. Our studies show significantly fewer BFCNs ipsilateral to the injury compared to the contralateral side of the brain 7 and 14 days after the injury, an effect which is absent in p75 knockout mice, suggesting a retrograde degenerative effect of the cortical injury on the projecting BFCNs through p75NTR. Basal forebrain survival, growth, synaptic maintenance, and apoptosis is governed primarily by neurotrophins (NT). Treatment of BFCN neurons with pro-neurotrophins (pro-NT) trigger apoptosis via p75NTR. Interestingly BFCNs express all the neurotrophin receptors throughout life and may access NTs locally or from their targets such as the cortex and hippocampus. We have observed an induction of proBDNF and proNGF in the cortex and hippocampus after cortical FPI suggesting that the induction of these factors my contribute to BFCN loss. To determine the effects of proNT signaling directly on BFCN viability, we are using microfluidic cultures to segregate BFCN soma and axons in vitro allowing for compartmentalized treatment with proNTs. Our studies show that stimulation of BFCN axon terminals with proNTs elicits retrograde degeneration of the axons and cell death of these neurons in vitro. The knowledge of how proNTs affect axonal integrity and retrograde BFCN death will shape our understanding of the role of proNTs in conditions of neurodegeneration.

Poster #51

Insular and striatal correlates of uncertain risky reward pursuit in schizophrenia.

Authors

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PI Name: David Zald

Risk-taking in specific contexts is beneficial, leading to rewarding outcomes. Schizophrenia is associated with disadvantageous decision-making, as subjects pursue uncertain risky rewards less than controls. However, it is unclear whether this behavior is associated with more risk sensitivity or less reward incentivization. Matching on demographic and IQ, we determined whether risk-taking was more associated with brain activation in regions affiliated with risk evaluation or reward processing. Subjects (30 schizophrenia/schizoaffective disorder, 30 controls) completed a modified, fMRI Balloon Analogue Risk Task. Brain activation was modeled during decisions to pursue risky rewards and parametrically modeled according to risk. Groups differed in risky-reward pursuit despite prior aversive outcomes (Explosions; $F(1,59)= 4.06, p=.048$) but not average risk-taking discontinuation point (Adjusted Pumps; $F(1,59)=2.65, p=.11$). Less activation was found in schizophrenia via whole brain and region of interest (ROI) analyses in right ($F(1,59)=14.91, p<0.001$) and left nucleus accumbens (NAcc; $F(1,59)=16.34, p<0.001$) during decisions to pursue rewards relative to riskiness. Risk-taking correlated with IQ in schizophrenia, but not controls. Path analyses of average ROI activation determined less statistically-determined influence of anterior insula upon dorsal anterior cingulate bilaterally (left: $\chi 2=12.73, p<.001$; right: $\chi 2=9.54, p=.002$) during risky reward pursuit in schizophrenia. NAcc activation in schizophrenia did not differentiate according to the relative riskiness of uncertain rewards as much as controls. Lack of activation differences in other regions suggest similar risk evaluation. Less insular influence on anterior cingulate may relate to attenuated salience attribution during risky reward pursuit or inability for risk-related brain regions to collaborate and sufficiently perceive situational risk.

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Poster #52

Preclinical Brain Imaging at Rutgers University Molecular Imaging Core.

Authors

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

PI Name: Edward Yurkow

The Rutgers University Molecular Imaging Core (RUMIC), located on the Busch Campus, provides a non-invasive 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, PET/CT, Micro-CT, Optical/X-ray Imaging and High-Resolution Ultrasound Technologies. The facility allows 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 Core is adjacent to animal holding facilities for serial imaging, anesthesia, surgery, and veterinary care. In addition to consultation and experimental services, the Core offers 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 at the Core 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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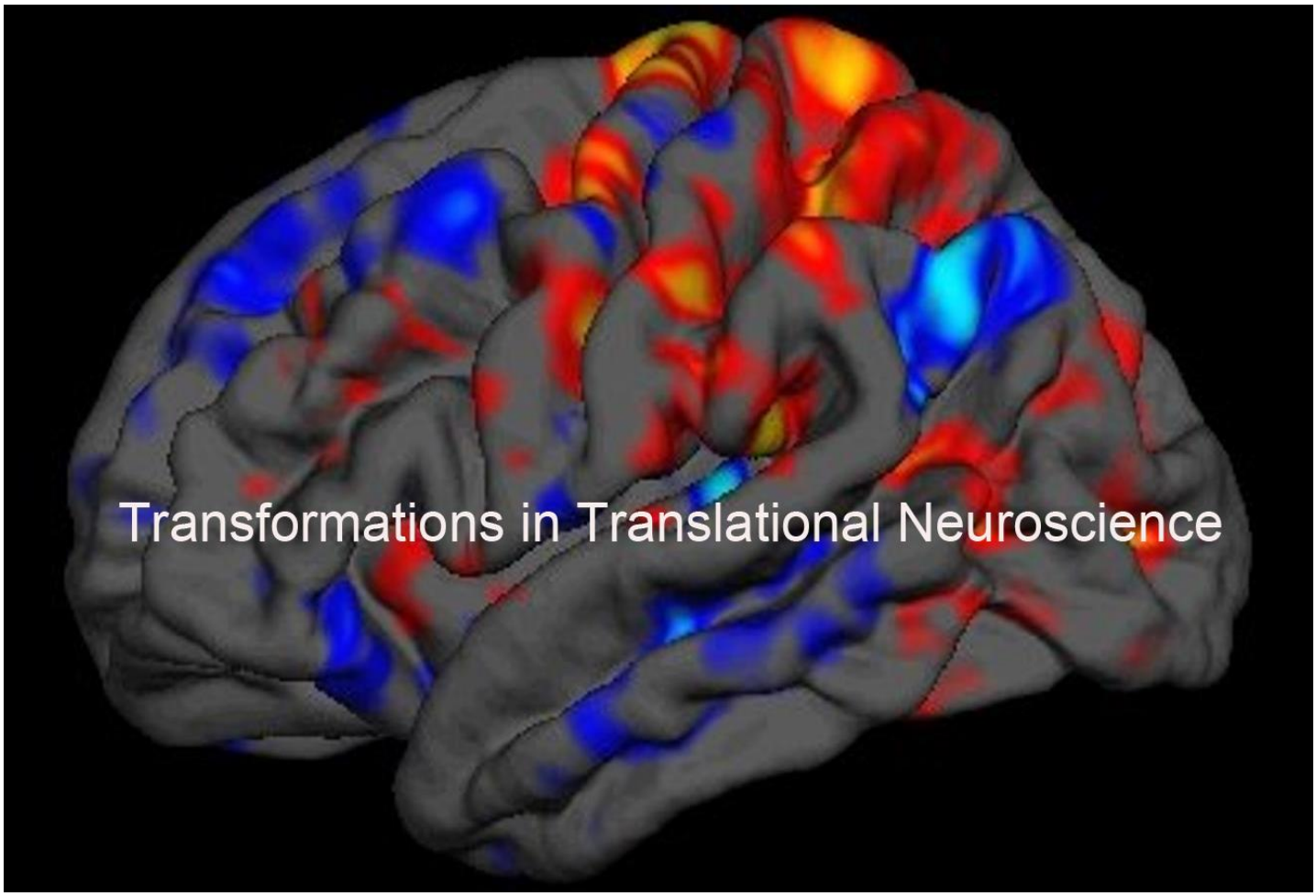

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