Fifth Annual Rutgers Brain Health Institute Symposium

Friday, November 1st, 2019

Nokia Bell Labs
Murray Hill, NJ 07974

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. Maria Chiara Manzini (RBHS-RWJMS)*** ***"Sex-specific Signaling in Sex Bias in Neurodevelopmental Disorders"***
9.15 AM –9.25 AM	***Dr. Alexander Kusnecov (RU-NB-SAS)*** ***"Maternal T Cell Activation During Pregnancy: Impact on Postnatal Microglial and Behavioral Development"***
9.30 AM – 9.40 AM	***Dr. Ioana Carcea (RBHS-NJMS/BHI)*** ***"Oxytocin Neuromodulation in Social Behavior"***
9.45 AM – 9.55 AM	***Dr. Jeffrey D. Zahn (RU-NB-SOE)*** ***"Strategies for Promoting Controlled Neuronal Interactions for the Development of Micro-Neurocircuitry Platforms"***
10.00 AM – 10.10 AM	***Konstantinos Michmizos (RU-NB-SAS)*** ***"Towards Less Artificial Intelligence: Neuronal-Astrocytic Networks"***
10.15 AM – 10.25 AM	***Dr. KiBum Lee (RU-NB-SAS)*** ***"Direct Cellular Programming of Reactive Astrocytes into Neurons for Enhanced CNS Repair"***

10.30 AM – 10.45 AM	Refreshment Break
10.45 AM – 10.55 AM	***Dr. Pingyue Pan (RBHS-RWJMS)*** ***"Understanding Parkinson's Disease from the Synapse"***
11.00 AM – 11.10 AM	***Dr. Detlev Boison (RBHS-RWJMS/NJMS/BHI)*** ***"Adenosine for Epilepsy Prevention"***
11.15 AM – 12.15 PM	Keynote: ***Dr. Eve Marder, Victor and Gwendolyn Beinfield Professor of Neuroscience, Brandeis University, MA***. ***"Differential Resilience to Perturbation of Circuits with Similar Performance"***
12.30 PM – 2.00 PM	Buffet Lunch
2.00 PM – 2.10 PM	***Dr. David Barker (RU-NB-SAS/BHI)*** ***"Investigating Lateral Preoptic Inputs to the Ventral Tegmental Area and their Role in Motivated Behavior"***
2.15 PM – 2.25 PM	***Dr. Anna Konova (RBHS-RWJMS/UBHC/BHI)*** ***"Decision Neuroscience of Addiction"***
2.30 PM – 2.40 PM	***Dr. Chris Pierce (RBHS-RWJMS/BHI)*** ***"The Sins of the Fathers: Transgenerational Effects of Paternal Cocaine"***
2.45 PM – 2.55 PM	***Dr. Mei-heng Lin (RU-Newark-CMBN)*** ***"Cognitive Control Deficits in Childhood Leukemia Survivors"***
3.00 PM – 3.10 PM	***Dr. Brian Greer (RBHS-RWJMS/BHI)*** ***"Using Quantitative Theories of Relapse to Improve Treatments for Problem Behavior"***
3.15 PM – 4.45 PM	Post-doc and Student Poster Session
4.30 PM – 5.30 PM	Wine & Cheese Reception and Best Poster Awards

Mission Statement

The goal of the Brain Health Institute (BHI) is to develop neuroscience at Rutgers to become a highly translational and internationally preeminent research enterprise. New tools are transforming neuroscience, and these afford an unprecedented opportunity to create new treatments for central nervous system disorders. Neuroscience has been identified by Rutgers University as one of five signature areas for future focus and development. As part of this strategic plan, the 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. The BHI is the home for the overall Rutgers neuroscience initiative, and is a growing interdisciplinary institute consisting of more than 250 principal investigators with neuroscience laboratories across various campuses of Rutgers University and Rutgers Biomedical and Health Sciences. 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.

BHI Strategic Plan & Accomplishments

The development of neuroscience at Rutgers by BHI, based on current research strengths, is focused on four areas and associated disorders: *Neurodevelopment* (e.g. autism spectrum disorder and schizophrenia, Tourette's), *Neurodegeneration and Injury* (e.g. multiple sclerosis, Parkinson's disease, Alzheimer's disease, spinal cord and traumatic brain injury), *Cognitive and Sensory Neuroscience* (e.g. dementias, aging, pain, auditory disorders), and *Motivational and Affective Neuroscience* (e.g. addiction, eating disorders, obesity, depression, anxiety). Rutgers currently has numerous well-funded investigators in each of the four focus areas that study brain processes at the cellular, circuit or behavioral levels. Many Rutgers neuroscientists are focused on translating the basic science-driven discoveries into clinical therapies to treat various neurological and neuropsychiatric disorders. To further develop these four focus areas, and facilitate translational research, BHI will use an institutional perspective to help realize the full potential of neuroscience research across Rutgers. BHI will recruit new faculty to strengthen current gaps in each area, provide pilot grant funding to support collaborative research, increase the visibility of the Rutgers neuroscience programs by hosting exceptional seminar speakers, and foster collaboration by hosting workshops, inter-campus exchange seminars and an annual neuroscience symposium. BHI will develop new research initiatives in critical areas that need new research and therapeutic insights, including a new addiction research center, an Alzheimer's and dementia research center and a center for autism research, education and services (described below). The BHI will also create state-of-the-art research infrastructure such as human brain imaging center and computational cognitive neuropsychiatry center to support multi-investigator, translational research across the institution.

The Five New Centers Launched by BHI

The Rutgers Center for Autism Research, Education and Services (RUCARES): Survey reports from Federal agencies suggest that 1 in 59 children in the US is diagnosed with Autism Spectrum Disorder (ASD); the rates are ~1 in 34 in New Jersey. Given the high incidence of ASD in New Jersey and the autism research and treatment expertise available at Rutgers, a Center of Excellence in Autism Research at Rutgers is urgently needed. Rutgers has considerable strengths in basic, clinical and translational autism research, with over 50 principal investigators working to develop new autism treatments. Rutgers faculty and students also work closely with the autism community in NJ, providing educational intervention and support services through the Douglass Developmental Disabilities Center and the newly created Rutgers Center for Adult Autism Services, and developing policy and performing public outreach through the Boggs Center on Developmental Disabilities. The new RUCARES will be responsible for coordinating and fostering basic and clinical research focused on diagnosing, treating and supporting patients with ASD. The goal is to develop a world-class autism research

center engaged in cutting edge basic research to identify mechanisms and biomarkers, produce novel interventional behavioral therapies, and create new technologies and services to support both pediatric and adult ASD patient population. Dr. Wayne Fisher was recently recruited as the inaugural director of both the RUCARES at BHI and CSH-RUCARES, a clinical entity within RUCARES that is a partnership with Children's Specialized Hospital (CSH). Dr. Fisher, will hold a Henry Rutgers Endowed Chair in the Department of Pediatrics at RWJMS. He was the director of the Center for Autism Spectrum Disorders at the Munroe-Meyer Institute at the University of Nebraska Medical Center and, previously, served as executive director of the Neurobehavioral Programs at the Kennedy Krieger Institute at Johns Hopkins University School of Medicine and the Marcus Behavior Center at the Marcus Institute in Atlanta, where he built clinical-research programs in autism and developmental disabilities. He has published more than 200 papers which have been cited more than 12,000 times. He will be joined by Dr. Brian Greer, recruited by BHI as a faculty in the Department of Pediatrics in RWJMS. Brian will serve as the assistant director of CSH-RUCARES, overseeing the Severe Behavior Program. In addition, Dr. Cathleen Piazza will join Rutgers as a tenured professor in the Graduate School of Applied and Professional Psychology (GSAPP) and as a core member of the BHI. She will be the director of the Pediatric Feeding Disorders Program at CSH. As a world-renowned expert in pediatric feeding disorders, she will also join the professional teams in the small bowel/liver transplant and intestinal rehabilitation programs at CSH. The CSH-RUCARES and PFD programs will be located at 888 Easton Avenue, Somerset, NJ and begin providing clinical services in early 2020.

The Rutgers Center for Advanced Human Brain Imaging Research (CAHBIR): Advances in imaging technology now allow neuroscientists to non-invasively study structure, function and dynamical properties of the human brain. Using magnetic resonance imaging (MRI) methods neuroscientists are beginning to understand how brain structure and function are altered in disorders such as autism, schizophrenia, addiction, anxiety and depression, brain injury, neurodegeneration etc. This new knowledge is leading to the development of imaging biomarkers not only for diagnosis but also to determine efficacy and progress of treatments of various neurological and neuropsychiatric disorders. Rutgers neuroscientists have access to a diverse patient population and the expertise to carry out cutting edge analysis of brain functions and dysfunctions across the mental health spectrum. To fulfill this promise, BHI is developing a new brain imaging center (CAHBIR). The center will house a state-of-the-art 3Tesla (3T) Siemens MAGNETOM Prisma MRI instrument that will be dedicated for research. Dr. David H. Zald has recently been appointed as director of the new CAHBIR at the Rutgers Brain Health Institute. Dr. Zald will be a tenured professor and hold a Henry Rutgers Term Chair in the Department of Psychiatry in RWJMS. Currently, he is the Cornelius Vanderbilt Professor of Psychology and director of the Interdisciplinary Neuroscience Program for Undergraduates at Vanderbilt University. He has published more than 150 papers which have been cited more than 18,000 times. Dr. Zald will join Rutgers in May 2020. His responsibilities will include organizing the human brain imaging core facility to support research of faculty and trainees at Rutgers, RBHS, BHI, and the Center for Computational Cognitive Neuropsychiatry. The new research Center, which will open in Fall 2020, will be located in the Staged Research Building on the Busch campus in Piscataway. The new research-dedicated 3T MRI scanner, which measures changes in blood flow, oxygen consumption and glucose use, will support research to non-invasively measure structure and activity of the human brain. The CAHBIR will help open new frontiers in human translational neuroscience at Rutgers.

The Rutgers-Princeton Computational Cognitive Neuropsychiatry Center (CCNP): In spite of advances in genetics and basic neuroscience, our understanding of the brain mechanisms involved in psychiatric disorders remains in its infancy, seriously limiting our ability to develop desperately needed treatments for mental illness. Therefore, developing a better understanding of how the work that the brain does becomes disrupted, and how this leads to psychiatric problems, is now a major emphasis at the National Institute of Mental Health. It has been argued by leaders in the field that, at present, we do not fully understand the neurobiological bases for even a single symptom of a single psychiatric disorder. To address this important issue, researchers in the cognitive and brain sciences around the world forged interdisciplinary collaborations that resulted in the field of cognitive neuropsychiatry. Cognitive neuropsychiatry attempts to clarify the nature and patterns of brain activity that form the basis of specific symptoms, such as changes in mood, arousal, reality testing, threat perception, and other dimensions whose extremes represent mental illness. At the same time, great strides have occurred in computational neuroscience, a field of research that takes advantage of recent advances in computational methods and applies them to understanding brain function. Recently, a new approach has emerged from combining computational neuroscience with cognitive neuropsychiatry that is accelerating progress in this domain. This new field is called Computational Cognitive Neuropsychiatry. Computational cognitive neuropsychiatry is highly interdisciplinary and involves the use of mathematics and computer simulations to rapidly explore the effects of changes in individual biological variables, and their combinations, on the functioning of neural systems and human behavior. Computational cognitive psychiatry is very well-suited not only to understand mechanisms underlying complex normal brain functions, but also to delineate aberrant processes that underlie psychiatric disease endophenotypes, including problems in memory, attention and executive control. This exciting new field promises to provide a greater biological understanding of the complex dysfunctions that underlie psychiatric disease. The Rutgers-Princeton Center for Cognitive Computational Neuropsychiatry (CCNP) is a collaboration between the BHI and Princeton's Neuroscience Institute, created to pursue this exciting opportunity. CCNP is co-directed by Dr. Anna Konova (Rutgers) and Dr Yael Niv (Princeton Neuroscience Institute). The goal is to leverage the 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 that has the potential to bring real and rapid progress to understanding the causes of psychiatric disorders, and will lead to novel therapies for treating these mental dysfunctions. The CCNP Core facility is located in Room V01, Research Tower, 675 Hoes Lane West, Piscataway. More information about services offered at the facility can be found at - https://ccnp.princeton.edu/about-ccnp/. The center currently has a pilot grant program to support investigators interested in using the services of the facility.

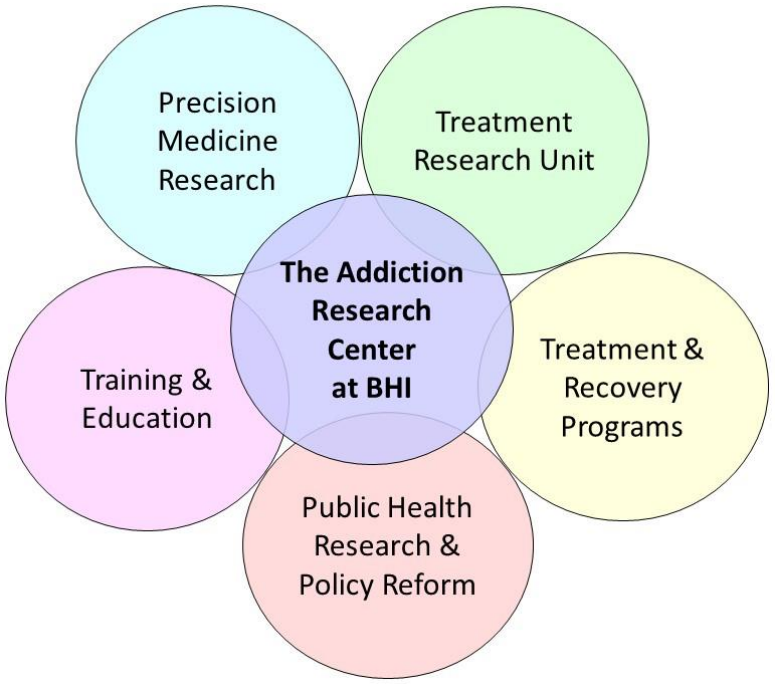
Rutgers Alzheimer's & Dementia Research Center (RUADRC): Alzheimer's disease (AD) and related dementias are a major cause of disability and death in the elderly. Approximately 6 million people have been diagnosed with AD and related dementias and the aging of America's population suggests that the number of Alzheimer's patients in the U.S. will, by 2050, increase to nearly 14 million people. Worldwide, approximately 40 million people have AD and related dementias. This number could also climb to nearly 120 million by 2050. As 5% of AD cases are familial and ~95% are sporadic, disease-modifying drugs that treat both sporadic and

familial AD are desirable. Despite recent advances in our understanding of basic biological mechanisms underlying AD and related dementias, we do not yet know how to prevent AD and related dementias, nor do we have an approved disease-modifying intervention. A major reason that these problems persist is that current animal models of AD and related dementias have not been able to predict the effectiveness of proposed therapies, so that many that have moved into clinical trials fail, which greatly slows the development of new therapies and increases their cost. Thus, there is a great need to develop the next generation of animal models (NexGeMo) of AD and related dementias to provide greater predictive power of potential therapies and thus accelerate the drug testing/clinical trial pipeline. The ultimate goals of the proposed RUADRC are:

- To develop therapies to cure AD and related dementias or, at the very least, effectively slow down the course of disease progression.
- To discover novel diagnostic and prognostic biomarkers that can forewarn the initiation of pathogenic processes before symptoms occur and also be used to monitor disease progression and treatment efficacy.

To achieve the above goals, research at RUADRC will focus 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 needed for translating research to clinic. The principal investigator at RUADRC, recruited by BHI, is Dr. Luciano D'Adamio, Herbert C. and Jacqueline Krieger Klein Endowed Chair in Alzheimer's Disease and Neurodegeneration Research, Professor of Pharmacology, Physiology & Neuroscience and Professor of Neurology at Rutgers New Jersey Medical School (NJMS) and Associate Director of Neurodegeneration and Injury at BHI. Dr. Ioana Carcea, a junior faculty recruited by BHI at NJMS, studies role of social learning in dementia by investigating oxytocin activity in aged and Alzheimer's disease rodent models. Dr. Hyung Jin Ahn, another BHI recruit, recently joined RUADRC and NJMS as a junior faculty. Dr. Ahn studies the role of cerebrovascular deficits in the etiology of AD and dementia. The Center is currently supported by multiple NIH grants and generous philanthropic support from Herbert C. and Jaqueline Krieger Klein as well as Rosalia Dattolo and Pasquale Amello Endowed Alzheimer's Research Fund established by Remember Me, Inc.

The Rutgers Addiction Research Center (RUARC): Our nation is in the midst of an unprecedented opioid epidemic. More people died from drug overdoses in 2014 than in any year on record, and the majority of drug overdose deaths (more than six out of ten) involved an opioid. The RUARC will build collaborations among scientists with the multidisciplinary expertise required to advance our understanding of the causes of opioid addiction` and other substance use disorders. As a component of the Brain Health Institute, RUARC will contain faculty in all Rutgers schools and campuses with expertise in addiction prevention, research, treatment, education, and public policy. A Treatment Research Unit (TRU), will be a key component of the RUARC. The TRU will tie together precision medicine research and clinical treatments by measuring treatment effectiveness as a function of genetics, age, gender, and environment relevant to each individual addict. The TRU will collaborate with clinical entities across Rutgers as well as with the Rutgers Health Network, an integrated network of Rutgers' affiliated hospitals, community clinics, medical groups, wellness centers, and other affiliates across NJ, to provide a wide range of inpatient and outpatient research programs for drug dependent patients. Through



the TRU, patients will benefit from substance use research while specialists advance knowledge and develop new therapies that are most effective for each of the many subsets of addiction patients. RUARC will be the only comprehensive addiction center in NJ with the capacity to impact the addiction epidemic through the diverse strengths of its members by integrating the following cutting edge approaches:

- Precision Medicine preclinical research and knowledge development that crosses multiple disciplines and addresses individual differences and needs in addiction treatment.
- Treatment and care of individuals and families coping with addiction.
- Public policy innovation and reform aimed at preventing development of drug use and at more effective avenues for addicts to obtain treatment.
- Inter-professional education of tomorrow's research, clinical, and criminal justice workforces from multiple disciplines in all aspects of addiction science.

We are recruiting a Director and other faculty for RUARC and TRU. To grow basic research in addiction at RUARC, BHI has recently recruited Dr. R. Christopher Pierce, from U Penn, as a tenured Professor in Dept. of Psychiatry at RWJMS. Other faculty, recruited by BHI, with research interests in addiction, include Dr. Anna Konova (RWJMS/UBHC) and Dr. David Barker (RU-NB, SAS-Psychology).

Building a stronger, collaborative Rutgers Neuroscience Community

Modern neuroscience is a multidisciplinary field that integrates molecular and cell biology, genetics, physiology, pharmacology, psychology, biomedical engineering, computational science, statistics and other fields of science. For breakthroughs in basic research to be translated to the clinic, interdisciplinary collaborations are a must. Rutgers currently has over 250 neuroscience investigators, spread over multiple campuses across New Jersey, with expertise that span the entire spectrum of disciplines mentioned above. BHI supports the Rutgers neuroscience community by developing key core facilities, recruiting faculty to fill institutional gaps in expertise and by facilitating communication and collaborations between these Rutgers neuroscientists. BHI-

- Develops core facilities such as CCNP and CAHBIR.
- Recruits faculty such as those associated with the above described centers.
- Organizes focus area workshops that bring together neuroscientists across Rutgers to share their work and seek collaborations.
- Provides Pilot grant funding to novel projects which have principal investigators from different Rutgers campuses and Schools. In addition to fostering interdisciplinary collaborations, a goal of this funding program is to help the investigators convert the pilot grant projects to larger projects funded by extramural awards.
- Hosts a Plenary Seminar series that brings prominent neuroscientists to various Rutgers campuses. These seminars are live webcast allowing Rutgers neuroscientists from both the host and remote sites to participate and learn about cutting-edge research in premier labs across the US.
- Holds an Annual Symposium that brings together faculty, post-docs, students and staff from neuroscience labs at Rutgers and neighboring institutions such as New Jersey Institute of Technology and Princeton. The day-long symposium includes an external Keynote speaker, talks by Rutgers faculty from various campuses, and a Post-doc/Student poster session.
- Maintains a comprehensive website (brainhealthinstitute.rutgers.edu) that is kept current with useful information and resources including a searchable faculty expertise directory, funding opportunities, upcoming neuroscience events etc. BHI also has social media presence; using Twitter (**@BHI_Rutgers**), Facebook and LinkedIn to announce events and achievements of Rutgers neuroscientists.

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The Fifth Annual
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Keynote Speaker

Eve Marder, Ph.D.
Victor and Gwendolyn Beinfield Professor of Neuroscience, Brandeis University, MA

"Differential Resilience to Perturbation of Circuits with Similar Performance"

Experimental work on the crustacean stomatogastric ganglion (STG) has revealed a 2-6 fold variability in many of the parameters that are important for circuit dynamics. Theoretical work shows that similar network performance can arise from diverse underlying parameter sets. Together, these lines of evidence suggest that each individual animal, at any moment in its life-time, has found a different solution to producing "good enough" motor patterns for healthy performance in the world. This poses the question of the extent to which animals with different sets of underlying circuit parameters can respond reliably and robustly to environmental perturbations and neuromodulation. We use both experimental and computational methods to study the effects of temperature, pH, high K+ concentrations, and neuromodulation on the networks of the STG from the crab, Cancer borealis. While all animals are remarkably robust and reliable to substantial perturbations, extreme perturbations produce "crashes". These crashes vary substantially across the animal and in models with different underlying parameter differences. The idiosyncratic nature of the crashes provides heuristic insight into the diverse nature of individuals to extreme perturbations. Moreover, models of homeostatic regulation of intrinsic excitability give insight into the kinds of mechanisms that could give rise to the highly variable solutions to stable circuit performance. The underlying parameter differences across the animals in a population and their differences in crash behavior provide a necessary substrate for evolution.

Dr. Marder received her B.A. from Brandeis University and Ph.D. at University of California, San Diego. She completed her postdoctoral training at the University of Oregon in Eugene and the École Normale Supérieure in Paris, France and then became a faculty in the Department of Biology at Brandeis University. Her work on the 30 neurons that compose the lobster STG produced many notable findings. She found that circuits can be modulated by many neuromodulators, which act on the level of populations of neurons, unlike some neurotransmitters, which only affect specific target neurons. She pioneered work on plasticity and homeostasis, revealing more about how the brain can change dramatically during learning and development yet remain structurally stable. She also developed the dynamic clamp method, which enables an experimenter to induce mathematically modeled conductances into living neurons to view the output of theoretical circuits. Her recent work examining network variability among healthy individuals shows that a variety of network parameters can produce the same behavioral outcome, challenging a long-standing goal in theoretical neuroscience to model 'ideal' neurons and neural circuits. She is a member of the Institute of Medicine, American Academy of Arts and Sciences and the National Academy of Sciences. She serves on the NIH working group for the BRAIN Initiative, and is a former president of the Society for Neuroscience. She has received the Women in Neuroscience Mika Salpeter Lifetime Achievement Award, the Gruber Award in Neuroscience, the Gerard Prize from SFN, the George A. Miller Award from the Cognitive Neuroscience Society and the Kavli Prize in Neuroscience.

POSTER ABSTRACTS

Poster #1

Acoustic Precision In Memory Is Predicted By Learning-Induced Auditory Cortical And Subcortical Neurophysiological Plasticity

Authors

Elena K. Rotondo, Kasia. M. Bieszczad

PI Name: Kasia. M. Bieszczad

Despite identical learning experiences, individuals differ in the memory formed of those experiences. For example, memory for sound formed with acoustic specificity is useful for selectively cueing subsequent sound-driven behavior, even in novel situations. With generalized memory, there is potential for novel sound cues to interfere with accurate behavioral performance. Here, a rodent model of auditory learning capitalized on individual differences in learning-induced auditory neuroplasticity to identify and characterize neural substrates for sound-specific (vs. general) memory of a training cue's acoustic frequency. Some animals revealed signal-"specific" memory behaviorally, and exhibited signal-specific neurophysiological plasticity in auditory cortical and subcortical sound-evoked responses. Response changes were stable and long-lasting over days. Learning-induced changes were not detected in animals with "general" memories. The degree of change in subcortical ($r=0.89$, $p=0.0002$) and cortical ($r=0.67$, $p=0.017$) neurophysiological responses predicted the precision of memory formation; moreover, cortical and subcortical effects were themselves correlated ($r=0.838$, $p=0.0024$). Further, pharmacologically manipulating a histone deacetylase (HDAC3) during memory consolidation promoted memory to form with acoustic precision, which significantly shifted individual variability towards greater acoustic specificity. Because HDAC3 manipulation enabled precise memory with the same characteristic neurophysiological substrates of auditory memory as untreated, "naturally"-learning subjects, it may also be relevant to extinction learning processes as a strategy to correct maladaptive behavioral responses. Preliminary data suggests that HDAC3 manipulation also promotes signal-specific extinction memory. Therefore, this work links the neurophysiological and molecular substrates of discriminative long-term auditory memories, with implications for feature-specific memory in sensory systems as a whole that drive cued behaviors.

Poster #2

Frontoparietal resting-state functional connectivity predicts alcohol use behavior change

Authors

Laura M. Lesnewich, Anthony P. Pawlak, & Marsha E. Bates

PI Name: Marsha E. Bates

Alcohol use behaviors fluctuate over time, but neurobiological predictors of these changes are not well understood. This study prospectively examined resting-state functional connectivity within the central executive neural network as a predictor of alcohol use behavior change during emerging adulthood. Neuroimaging and alcohol use data were collected at an initial time point (T1), and alcohol use was reassessed at a second time point (T2). Participants (N=33) were non-treatment-seeking emerging adults (ages 18-27 years) with a wide range of drinking behaviors. Cross-sectional analyses of T1 data revealed significant ($p < .05$) negative correlations of left posterior parietal cortex (LPPC)-paracingulate gyrus (PCG) connectivity with past year drinking quantity, past month and past year drinking frequency, and past month total binge drinking episodes. Hierarchical linear models tested the role of LPPC-PCG connectivity in alcohol use behavior change from T1 to T2, controlling for participants' age at T1. LPPC-PCG connectivity, ($p = 0.004$), time elapsed from T1, ($p = 0.002$), and their interaction, ($p = 0.001$), were significant predictors of change in past month drinking frequency. LPPC-PCG connectivity, ($p = 0.016$), time elapsed from T1, ($p = 0.001$), and their interaction, ($p = 0.003$), also were significant predictors of change in past year drinking frequency. The T1-age covariate was not significant in either model. Cross-sectional results extend previous findings that decreased frontoparietal connectivity is associated with drinking behaviors. Our prospective findings are novel and indicate that frontoparietal connectivity may contribute to temporal changes in drinking behavior observed during emerging adulthood.

This research was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA): K24AA021778, R21AA020367, and F31AA027147.

Poster#3
KNDy neuronal sensitivity to ghrelin and the impact of 17 beta-estradiol

Authors
Kristie Conde, Allison Vanschaik, Yuxiang Sun, and Troy A. Roepke

PI Name: Troy A. Roepke

The gut peptide, ghrelin, mediates negative energy homeostasis and the neuroendocrine control of reproduction by acting through its receptor, growth hormone secretagogue receptor (GHSR). GHSR, expressed in hypothalamic Kisspeptin/Neurokinin B/Dynorphin (KNDy) neurons in the arcuate (ARC), is known to regulate reproduction and energy balance. We have previously shown 17-beta–estradiol (E2) robustly increases *Ghsr* expression in KNDy neurons, enhancing their sensitivity to ghrelin. We hypothesize that E2-induced GHSR expression augments KNDy sensitivity in fasting state by elevating ghrelin to disrupt reproduction and reduce energy expenditure in females. We developed a Kiss1-specific GHSR knockout to determine the role of GHSR in ARC KNDy neurons, and found no differences in vaginal opening or estrous cyclicity. Interestingly, in ovariectomized females with or without E2 replacement, metabolic rates (V.O2, V.CO2) and substrate utilization (RER) were decreased, and food intake and activity were increased in E2-treated knockout mice. Fasting glucose levels were elevated in the knockout mice, regardless of steroid. In a separate cohort of mice, Luteinizing Hormone (LH) pulsatility was measured in fasted and ghrelin-injected knockout and controls. We observed that fasting reduced Luteinizing Hormone (LH) pulses in controls but not knockout females; ghrelin reduced LH in OVX+E2 control females about 90 min post-injection, but not in 2 of 3 OVX+E2 knockout mice. Collectively, these data suggest that GHSR activation in KNDy neurons modulates metabolism, glucose homeostasis, and LH pulsatility, illustrating a novel mechanism for E2 and ghrelin in control of KNDy neurons and their physiological functions.

Poster#4
Elevated neonatal interleukin-6 drives behavioral phenotypes reminiscent of ASD in juvenile mice

Authors
Fernando J. Velloso, Ekta Kumari, Rosamaria E. Dias and Steven W. Levison

PI Name: Steven W. Levison

Incidence of Autism Spectrum Disorders (ASD) in the US has been consistently increasing. Epidemiological studies highlight the association between maternal infections during pregnancy and behavioral deficits related to ASD. Animal models reproduced the behavioral alterations of ASD and have shown that maternal cytokines such as IL-6 can cross the placenta and the fetal blood-brain barrier. These models also indicate that the behavioral outcomes are highly dependent on developmental timing of the insult. In humans, ASD risk is greatest for infections in the early 3rd trimester, however, most studies looked at models in the mouse equivalent of the 1st trimester. Therefore, we have investigated the effects of IL-6 on neurodevelopment of newborn mice, emulating inflammation at the human equivalent of the early 3rd trimester.

IL-6 was injected into mouse pups at several concentrations to establish a paradigm of elevated serum levels similar to those observed in ASD patients. Behavior outcomes were assessed by battery of tasks. At 3 weeks of age, IL-6 injected mice showed reduced nose-to-nose and urogenital sniffing in reciprocal social tests, as well as tendency to engage in repetitive behavior. At 6 weeks, IL-6 injected mice lacked social preferences in both social approach and novel social subject protocols, exhibited increased anxiety in the elevated plus-maze, and displayed a higher sensitivity to fear conditioning. Finally, adults had deficit in olfaction-based detection of sugary food. Overall, our data support the conclusion that inflammation during pregnancy can significantly alter brain development, resulting in the behavioral alterations reminiscent of ASD.

Supported by a grant from the Governor's Council for Medical Research and Treatment of Autism awarded to Steven W. Levison.

Poster #5

Dynamin and Reverse-mode Sodium Calcium Exchanger Blockade Confers Neuroprotection from Diffuse Axonal Injury

Authors

Anton Omelchenko, Anil B. Shrirao, Atul K. Bhattiprolu, Jeffrey D. Zahn, Rene S. Schloss, Samantha Dickson, David F. Meaney, Nada N. Boustany, Martin L. Yarmush, and Bonnie L. Firestein

PI Name: Bonnie L. Firestein

Mild traumatic brain injury (mTBI) is a frequently overlooked public health concern that is difficult to diagnose and treat. Diffuse axonal injury (DAI) is a common mTBI neuropathology in which axonal shearing and stretching induces breakdown of the cytoskeleton, impaired axonal trafficking, axonal degeneration, and cognitive dysfunction. DAI is becoming recognized as a principal neuropathology of mTBI with supporting evidence from animal model, human pathology, and neuroimaging studies. As mitochondrial dysfunction and calcium overload are critical steps in secondary brain and axonal injury, we investigated changes in protein expression of potential targets following mTBI using an in vivo controlled cortical impact model. We show upregulated expression of sodium calcium exchanger1 (NCX1) in the hippocampus and cortex at distinct time points post-mTBI. Expression of dynamin-related protein1 (Drp1), a GTPase responsible for regulation of mitochondrial fission, also changes differently post-injury in the hippocampus and cortex. Using an in vitro model of DAI previously reported by our group, we tested whether pharmacological inhibition of NCX1 by SN-6 and of dynamin1, dynamin2, and Drp1 by dynasore mitigates secondary damage. Dynasore and SN-6 attenuate stretch injury-induced swelling of axonal varicosities and mitochondrial fragmentation. In addition, we show that dynasore, but not SN-6, protects against H2O2-induced damage in an organotypic oxidative stress model. As there is currently no standard treatment to mitigate cell damage induced by mTBI and DAI, this work highlights two potential therapeutic targets for treatment of DAI in multiple models of mTBI and DAI.

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Poster# 6

Impact of OPRM1 A118G on ethanol sensitivity in stem cell derived human neurons

Authors

Matthew S Scarnati, Marisa Joel, Mavis Swerdel, Jay A. Tischfield, Ron P. Hart and Zhiping P. Pang

PI Name : Zhiping Pang

Alcohol use disorders (AUDs) are among the most prevalent mental disorders worldwide. Yet, the mechanism(s) that can promote dependence in humans, in addition to the synaptic basis of AUDs in the context of opioid signaling, remains poorly understood mainly due to the difficulty in obtaining and studying live human tissue. The objective of this project is to utilize human neuronal cells (iNs) generated from induced pluripotent stem cell lines to study the molecular, cellular, and synaptic mechanism(s) of single nucleotide polymorphism (SNP) rs1799971 (OPRM1 A118G) in the μ-opioid receptor (MOR) which results in the N40D amino acid substitution. The working hypothesis is that the D40 variant of MOR has a defect in N'-glycosylation which might impair MOR trafficking, ligand binding, and expression, ultimately altering opioid and alcohol sensitivity on synaptic regulation, increasing the likelihood to develop an AUD. Acute application of EtOH caused a significant increase in sIPSC and mIPSC frequency for N40 harboring iNs, while only a modest increase was observed in D40 human iNs. Interestingly, application of the MOR agonist DAMGO, following acute EtOH treatment, reduced the frequency of inhibitory events to a greater extent in D40 containing iNs. These data in combination with paired pulse stimulations suggest that iNs containing D40 MOR allelic variants have a lower initial synaptic release probability, and a higher affinity for opioid agonists. In addition, we observed a significant increase in inhibitory synaptic release exclusively in iNs harboring D40 MOR allelic variants following a 10-day chronic intermittent ethanol (CIE) exposure paradigm. Finally, EtOH treatment alone indicates a differential sensitivity to acute and chronic treatment between genotypes.

Research is supported by grants from NIH-NIAAA R01 AA023797 as well as Collaborative Studies on the Genetics of Alcoholism/COGA 5U10AA008401-26. MS is supported by NIH-NIAAA T32 AA028254.

Poster#7
Self-Healing Hydrogel Coatings for Improving Brain Implant Biocompatibility

Authors
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PI Name: Jay Sy

Many neurodegenerative diseases can be treated by methods involving implanted electrodes. However, the effectiveness of these electrodes is hampered by the endogenous foreign body response (FBR) to the implant. Especially concerning is gliosis, the formation of glial scar tissue surrounding the implant, which insulates the electrode and displaces neurons, reducing signal clarity. Gliosis is exacerbated by micromotion, the movement of brain tissue relative to the implant due to physiological rhythmic activities (e.g. respiration and blood circulation), and mechanical mismatch in elastic moduli between the implant (~100 GPa) and brain tissue (~10 kPa). These factors result in high strain at the tissue/implant interface, triggering FBR. To attenuate this, many investigators have looked into hydrogel coatings for electrodes to better approximate brain tissue and absorb strain energy. Studies have focused on covalently-linked hydrogels (e.g. PEG) due to their availability and biocompatibility; however, these systems are limited in their capacity to absorb energy since high strains can sever the covalent bonds. Our lab is instead investigating non-covalent hydrogels, including hydrophobic-hydrophilic polymer networks and self-assembling peptides. These systems form coatings that are shear-thinning and self-healing, meaning they absorb energy and disassemble under high strain and reassemble post-strain. To further characterize these systems, we have developed a novel bioreactor that simulates micromotion *in vitro*, enabling us to investigate how these hydrogel systems affect the strain field around implants. The most effective variations of each system will be tested in rodent models, where we also plan to attempt anti-inflammatory drug delivery via these hydrogel coatings.

Supported by the Rutgers Biotechnology Training Program Fellowship (NIH T32 GM008339), NIH R00 EB016690, and the Busch Biomedical Grant Program.

Poster#8
Neuronal Network Changes After *In Vitro* Stretch Injury

Authors
Catherine Rojvirat, Tuan Nguyen, Joshua Berlin

PI Name: Joshua Berlin

Acute mild traumatic brain injury (mTBI) is a major health problem in the United States that causes significant patient morbidity. However, effective treatments are still lacking. Changes in neuronal network function could underlie acute sequalae that follow acute mTBI. To date, however, direct measures of network properties have not been investigated in acute mTBI settings. The goal of this project is to investigate the changes in neuronal network function, both directly and indirectly, immediately after mTBI using an in vitro stretch injury model. To accomplish this, we are using cultured embryonic rat cortical neurons to measure neuronal population activity with calcium imaging and neuronal connections with single-cell photolysis of caged glutamate.

Consistent with prior literature, our data show that spontaneous neuronal network activity is generally depressed following mild stretch injury, as measured by decreases in participation rate, amplitude and frequency of synchronized calcium transients that result from spontaneous bursting activity in cultured cortical neurons. In the presence of reduced spontaneous network activity, the number of active neuronal connections can be decreased, but can also be unchanged. In order to understand how decreased spontaneous activity can occur without a decrease in connectivity, we examined the effect of injury on neuronal excitability using single cell photolysis of caged glutamate. These experiments demonstrate that excitability is decreased after injury. Thus, to date, our experiments suggest that mild traumatic injury can depress network activity in two ways, first by decreasing neuronal excitability and second by decreasing the number of active synaptic connections between neurons.

Supported by NIH, NJCBIR

Poster #9
Role of Orexin neurons in Hypoglycemia Unawareness

Authors
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PI Name: Vanessa Routh

Hypoglycemia is a serious side effect of intensive insulin therapy used to prevent diabetic hyperglycemia. Powerful neuroendocrine and behavioral responses evolved to prevent and correct hypoglycemia. Recurrent insulin-hypoglycemia (RH) impairs these mechanisms leading to life threatening conditions known, respectively, as hypoglycemia associated autonomic failure (HAAF) and hypoglycemia unawareness (HU). As a result of HAAF and HU, glucose levels drop without detection to dangerously low or lethal levels. Blocking the orexin receptor mimics HU suggesting a role for the glucose-inhibited (GI) perifornical hypothalamus (PFH) orexin neurons. Thus, we hypothesized that HU reduces activation of PFH orexin-GI neurons in low glucose. To test this hypothesis, we performed whole cell patch clamp recording on PFH orexin neurons from animals treated with 3 consecutive daily saline (control) or insulin (RH) injections. Glucose sensing by PFH orexin neurons persisted in the presence of tetrodotoxin (TTX; n=5) indicating a postsynaptic response. Additionally, TTX (n=5) and bicuculline (n=1) amplified the response to low glucose indicating tonic presynaptic inhibition. Excitation in low glucose was inhibited by 2.5 mM 2-deoxy glucose (non-metabolized form of glucose; n = 5) but not when ATP concentration in the recording pipette was increased from 2mM to 5mM (n=10). This suggests that these neurons sense the glucose molecule per se vs glucose metabolism. As we hypothesized, RH blunted activation of PFH orexin-GI neurons in 0.1 mM glucose in both males ($P < 0.001$) and females ($p<0.05$). These data suggest that impaired activation of PFH orexin-GI neurons during hypoglycemia may contribute to HU.

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Poster #10
Intermittent access to the opioid fentanyl induces a multifaceted addiction-like phenotype that is associated with an increased number of orexin neurons

Authors
Jennifer E. Fragale, Morgan H. James, & Gary Aston-Jones

PI Name: Gary Aston-Jones

Clinical data indicate that human addicts rarely maintain stable drug use patterns over extended periods. To better model abuse patterns in human addicts, the IntA self-administration paradigm was established and has since emerged as a powerful preclinical model of drug addiction. IntA to cocaine results in an escalation of cocaine intake, increased motivation for cocaine in a behavioral economics (BE) procedure, increased compulsive responding, and greater cued and drug-primed reinstatement compared to traditional short (ShA) and long-access (LgA) models. Despite the utility of the IntA model, it has yet to be applied to the study of opioid addiction. Here, we extend our characterization of the IntA model to the opioid fentanyl. Male rats were either given ShA (1h), LgA (6h) or IntA to fentanyl for 14 days. Like IntA to cocaine, we found that IntA to fentanyl causes escalation of fentanyl intake, increased motivation for fentanyl, persistent drug seeking during abstinence, and increased cue-induced reinstatement compared to rats given ShA or LgA to fentanyl. We have shown that IntA to cocaine is associated with an increase in the number of lateral hypothalamic orexin neurons. To determine if IntA to opioids produces similar changes in orexin expression, rats previously given ShA or IntA to fentanyl were sacrificed following 3mo of abstinence. Rats given IntA to fentanyl exhibited increased orexin cell numbers compared to rats given ShA to fentanyl. Unlike IntA to cocaine, these differences were apparent in both the lateral and medial hypothalamic orexin cell fields. Together, these results indicate that the IntA paradigm can serve as a strong preclinical model of opioid addiction and that IntA-induced behaviors may develop through persistent changes in orexin expression.

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Poster #11
How Different is Different Enough: Quantifying Difference Across Neuromodulators

Authors
Elizabeth Cronin

PI Name: Dirk Bucher

Neural circuits are modified by many neuromodulators. Neuromodulation is typically studied with the expectation that the modulator configures the circuit to produce a specific output. In most systems, however, many modulators have overlapping and often convergent effects. Additionally, neural circuits are always subject to actions of multiple modulators at any time. Yet, the behavioral needs of the animal require that circuits produce consistent outputs. If multiple neuromodulators have convergent effects with the same sign, but also diverge on their targets, it is reasonable to assume that co-modulation results in a similar circuit output, even if, in each case, the circuit is not exposed to the same combination of neuromodulators. We therefore propose that convergent co-modulation increases the inter-individual consistency of circuit output.We examined this hypothesis in the triphasic oscillatory pyloric circuit of the crab stomatogastric ganglion (STG). The STG is modulated by an astounding number of neurotransmitters and hormones. In this system, multiple peptide and muscarinic modulators converge to activate a single ionic current and enhance synaptic interactions. Yet, these modulators target distinct subsets of neurons and have different dose-dependent effects. In our protocol, we use three peptides and bath apply them in singlets and doublets at increasing concentration: low (1 nM), medium (30 nM) and high (1 uM). We compare circuit activity using the five phases of activity, #spikes/burst and spike frequency. We ask: How different individual modulatory outputs are from each other and as you increase the number of modulators, does the circuit output become more similar?

Funded by NIH Grant MH060605

Poster #12
Emergence of cellular and network degeneracy through the balance between intrinsic and synaptic properties

Authors
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PI Name: Jorge Golowasch

Many behaviors critical for survival, such as locomotion and respiration, must be robust and consistent across an individual's lifespan and different individuals. However, the networks that generate these behaviors display significant variability at the level of neuronal and synaptic properties. This work addresses the question of how and under what conditions neuronal networks, with variable cellular and network properties, generate similar activity. We hypothesize that neural networks maintain similar outputs by dynamically balancing neuronal intrinsic and synaptic properties. We test this hypothesis with two approaches. One approach is to ask how single neurons may gain similar attributes of activity from an activity-based homeostatic rule that acts on neuron intrinsic properties. The second approach examines how neurons that have similar attributes of activity in isolation may or may not preserve those when placed in a network coupled with either chemical or electrical synapses. Taken together, we show that the newly emerged network activities depend not only on the participating neurons ionic conductances but also the type of synaptic connectivity and the maximal synaptic strength.

Supported by NSF-DMS 1715808 (HGR & JG)

Poster #13
Role of corticotropin-releasing factor in the lateral habenula in anxiety-like behaviors in rats withdrawn from chronic alcohol drinking

Authors
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PI Name: Jiang-hong Ye

Corticotropin-releasing factor (CRF) regulates glutamatergic transmission through its receptors (CRF1R & CRF2R) and plays an important role in alcohol addiction. The lateral habenula (LHb) acts as an interface between stress- and alcohol-related processes. We previously found increased glutamatergic transmission in LHb neurons of rats withdrawn from chronic alcohol exposure (EtOH-WD). In the current study, we assessed whether: 1) CRF regulates the excitatory drive to LHb neurons; 2) chronic ethanol drinking alters CRF's effects; and 3) manipulation of LHb CRF function alters alcohol consumption and anxiety-like behaviors during withdrawal. Bath application of CRF (0.1-200nM) increased glutamate release with an inverted U-shape dose-dependent curve in LHb neurons of both EtOH-WD and Naïve rats. Selective activation of CRF1Rs caused a greater enhancement in the EtOH-WD compared to Naïve rats. However, selective activation of CRF2R produced inhibition in the EtOH-WD but not naïve rats. Acute ethanol induced enhancements on glutamate release were attenuated by the CRF1R-antagonist but further potentiated by the CRF2R-antagonist in EtOH-WD rats, suggesting that chronic ethanol exposure and withdrawal could enhance CRF signaling, which preferentially binds to CRF1R that in turn increases glutamate transmission, and thus contributes to the hyper-glutamatergic state during withdrawal. Importantly, EtOH-WD rats exhibited an elevated anxiety level, which was attenuated by intra-LHb infusion of a CRFR1-antagonist or a CRFR2-agonist. These compounds also significantly reduced alcohol intake. However, CRFR1-agonist, but not CRFR2-antagonist exacerbated anxiety-like behaviors without altering ethanol consumption in EtOH-WD rats. These results indicate that CRF regulates the excitatory drive to LHb neurons, which is altered by chronic ethanol drinking; and manipulation of LHb CRF function alters alcohol consumption and anxiety-like behaviors.

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Poster #14
The role of p75NTR in inducing axonal degeneration after injury

Authors:
Laura E. Montroull, Bryan J. Pfister and Wilma Friedman

PI Name: Wilma Friedman

Expression of p75NTR is induced in numerous Central Nervous System (CNS) neurons after damage in the adult brain and has been shown to regulate neuronal cell death in several injury models. While the neuropathological consequences of TBI are heterogeneous, diffuse axonal injury is ubiquitous at all severity levels, leading to deficits in connectivity that may or may not recover over time. p75NTR has been widely studied in the Peripheral Nervous System in various injury and cell-death paradigms, as well as in developmental axonal pruning and degeneration. However, the role of this receptor in mediating axonal degeneration in the CNS after TBI remains unclear. To determine the role of p75NTR in this process we subjected adult mice to mild traumatic injury using lateral fluid percussion brain (LFP) injury model. We found that one day after LFP, p75NTR is upregulated in axons and this increase is maintained 3 days after the injury. The co-localization of p75NTR with βAPP, suggest that those axons are degenerating. To understand the mechanisms of p75NTR in mediating axonal degeneration and to examine axon-specific signaling mechanisms, cortical neurons subjected to 45% or 60% of axonal stretch injury. We found an increase in p75NTR expression in axons after 45min and a significant increase in the axonal fragmentation index one day after stretch injury. On the contrary, cortical neurons cultured from p75NTR-/- rats showed less axonal degeneration than neurons cultured from WT animals one day after injury suggesting the participation of this receptor in inducing axonal degeneration.

Poster #15
Differential innervation of striatal microcircuitry by primary somatosensory and primary motor cortex

Authors
Branden Sanabria, Sindhuja S. Baskar, Christian R. Lee, and David J. Margolis

PI Name: David J. Margolis

The striatum is the main input nucleus of the basal ganglia. We identified differential functional innervation of striatal medium spiny neurons (MSNs) and fast spiking interneurons (FSIs) by primary somatosensory (S1) and primary motor (M1) cortex. Input from M1 produced equally large postsynaptic potentials in both FSIs and D1 or D2 dopamine receptor expressing MSNs while S1 inputs produced larger postsynaptic potentials in FSIs. Additionally, optogenetic activation of M1 or S1 corticostriatal inputs had opposite effects on behavior with M1 input promoting motor responses and S1 input suppressing responses. Here, we sought to determine whether there are differences in the structural innervation of striatal neuron subtypes by S1 and M1.
We injected AAVs with Ruby2 or GFP spaghetti monster (sm) inserts into S1 and M1 followed by whole cell current clamp recordings of striatal neurons with biocytin filling to allow for labeling of single striatal neurons and corticostriatal inputs. Slices were processed with immunohistochemistry for the two sm-proteins as well as biocytin. Confocal z-stacks were acquired and data were analyzed using Imaris software.
Corticostriatal processes from both neocortical regions were observed to course through the striatum and terminate in puncta. Puncta making close approximations to filled neurons were quantified and the corresponding distance from the soma calculated. Preliminary results indicate an increased density of inputs originating from M1 than from S1 on striatal MSNs. These results suggest that one mechanism underlying the stronger functional innervation of MSNs by M1 than S1 is the increased density of synaptic inputs from M1.
Initial studies were supported by grants from the Rutgers Brain Health Institute Pilot Grant to both DJM and JMT, the National Institutes of Health (RO1NS094450 to DJM and RO1NS034865 to JMT), and present work was supported by the National Science Foundation (IOS-1845355) and NIH (R01NS094450) to DJM

Poster #16
Repetitive TBI in rats with diffuse closed head impacts

Authors
Vedad Delic, Katherine J. Stalnaker, Julia A. Burton, Kevin C. Pang, Kevin D. Beck, and Bruce A. Citron

PI Name: Bruce Citron

Traumatic brain injury (TBI) is associated with an increased risk of developing chronic traumatic encephalopathy (CTE) and Parkinson's disease (PD) that together impact millions of people. Whether TBI causes these diseases or accelerates their underlying pathology remains unknown. Increased focus on the role of inflammation in pathogenesis of neurodegenerative diseases and the extensive use of rats in studying PD necessitated the development of a rat model of TBI that does not involve preparatory surgeries, which themselves can elicit strong immune system responses. Moreover, repetitive TBIs, which are associated with the highest risk for neurodegenerative diseases, have not received sufficient attention in rats, while closed head weight drop models have been used for decades in mice. We therefore created a simple weight drop model, building on our previous work and models developed by Buchele, Marmarou, and Pick, that is able to cause closed head TBI with repetitive blunt trauma to the skull. The rats are placed on a sponge that allows rapid rotational acceleration in addition to the impact injury. Injury titration was performed up to 2.0 kg. Spatial memory deficits were found after injury. The optimal repetitive injury was determined to be with a 1.5 kg weight drop, and these injuries were mild and did not produce locomotor deficits. Repetitive mTBI (r-mTBI) did however cause astrocyte infiltration into the substantia nigra pars compacta (SNpc). Our future work will determine the potential effect of repetitive TBIs to induce or accelerate neurodegenerative disorders most closely linked to TBI, such as PD.

This work is supported by Department of Veterans Affairs (Veterans Health Administration, Office of Research and Development (I01RX001520, I21BX003815)), the Assistant Secretary of Defense for Health Affairs through the Congressionally Directed Gulf War Illness Research Program (W81XWH-16-1-0626), and the Veterans Bio-Medical Research Institute.

Poster #17
Chemogenetic inhibition of locus coeruleus promotes exploration and enhances phasic signaling

Authors
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PI Name: Gary Aston-Jones

Chemogenetic approaches are increasingly used throughout neuroscience as a way to modulate neuronal activity via endogenous signaling mechanisms (i.e. G-proteins). While chemogenetic actuators such as hM4Di, an inhibitory DREADD (Designer Receptor Exclusively Activated by Designer Drug), have been validated in vitro, in vivo validation is still sparse. Importantly, the in vivo effects of hM4Di is likely dependent on the neuronal circuit in which it is expressed and thus validation is necessary for each new application. Here, we describe a method for selectively expressing the inhibitory DREADD hM4Di in the rat locus coeruleus using viral vectors and a transgenic rat line. We report the effect of LC-hM4Di on c-fos expression, LC-dependent exploratory behavior, and single unit neural activity as measured in the awake and behaving rat. Our preliminary results indicate that in LC, hM4Di disinhibits neuronal activity and promotes exploratory behavior. Rather than simply silencing LC altogether, hM4Di may be inhibiting basal activity of the nucleus and switching LC-modulated circuits into an alternate mode of activity. These results provide us with a unique tool for manipulation LC function and reinforce the importance of validating tools for use in new applications.

Supported by NIH grant R01-DA006214, F31-DA047068-01A1

Poster #18
DBS-like optogenetic stimulation of accumbens dopamine D2 receptor-containing neurons attenuates cocaine reinstatement

Authors
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PI Name: R. Christopher Pierce

Previous work indicated that deep brain stimulation (DBS) of the nucleus accumbens (NAc) shell attenuated reinstatement of cocaine-seeking in rats. However, the potential differential impact of DBS on specific populations of neurons to drive the suppression of cocaine-seeking is unknown. Medium spiny neurons in the NAc are differentiated by the expression of dopamine D1 receptors (D1DRs) or dopamine D2 receptors (D2DRs), activation of which promotes or inhibits cocaine-seeking behavior, respectively. We tested the hypothesis that DBS-like optogenetic stimulation of D1DR-containing neurons in the NAc shell would potentiate cocaine-primed reinstatement, whereas DBS-like optogenetic stimulation of D2DR-containing neurons in the NAc shell would attenuate cocaine-primed reinstatement. We used transgenic rat lines that express Cre recombinase selectively in D1DR-containing or D2DR-containing neurons in combination with a Cre-dependent adeno-associated viral vector expressing channelrhodopsin or yellow fluorescent protein (eYFP) to deliver high frequency optogenetic stimulation selectively to each population of neurons in the NAc shell. High frequency, DBS-like optogenetic stimulation of D2DR-containing neurons attenuated reinstatement of cocaine seeking in male rats, whereas DBS-like optogenetic stimulation of D1DR-containing neurons did not alter cocaine-primed reinstatement. In rats which only expressed eYFP, intra-accumbens optogenetic stimulation did not alter cocaine reinstatement relative to sham stimulation, indicating that the effect of DBS-like stimulation to attenuate cocaine reinstatement is mediated specifically by channelrhodopsin rather than as a consequence of prolonged light delivery. Collectively, these results suggest that DBS of the NAc attenuates cocaine-primed reinstatement through the selective manipulation of D2DR-containing neurons.

Supported by NIH grants R01 DA015215 and T32 DA028874.

Poster #19
A knock-in rat model of Trem2^{R47H}

Authors
Marc Tambini and Luciano D'Adamio

PI Name: Luciano D'Adamio

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia in the elderly. The evidence that microglia cells surround amyloid-plaques -both in AD patients and plaque-bearing mice- and influence synaptic plasticity via synapse remodeling suggested a link between microglia and AD pathogenesis. Genetic evidence directly implicates microglia function as genome-wide association studies have uncovered rare variants of *triggering receptor expressed on myeloid cells 2* (*TREM2*), whose expression in the central nervous system is restricted to microglia, that increase the risk of developing AD. To extend the mutational analyses to animal model organisms, several groups generated *Trem2^{R47H}* knock-in (KI) mice via CRISPR/Cas9. Analysis of *Trem2* expression in these models revealed a reduction in *Trem2* levels that resulted from the generation of a new splice site which introduces a premature stop codon. Here, we report the generation of a new *Trem2^{R47H}* KI rat model that faithfully replicates *Trem2* expression levels seen in wildtype rats. Our findings put forward a rat KI model of *Trem2* as a viable model for the investigation of Trem2-R47H.

Supported by funding from NIA to LD: R01 AG033007, R01 AG052286, R01 AG063407

Poster #20
Disruptions of learning, memory and experience-induced auditory cortical plasticity in a NexGenMo rat model of Alzheimer's disease

Authors
Andrea Shang, Sean Tsaur, Sooraz Bylipudi, Dylan Sullivan, Luciano D'Adamio, Kasia M. Bieszczad

PI Name: Kasia M. Bieszczad

Hearing loss in midlife has been identified as a risk factor for progression to Alzheimer's disease (AD), and central auditory processing disorders can precede AD onset by 5-10 years, which posits auditory function as a possible early biomarker for later-life progression to dementia. While the primary auditory cortex (A1) is a key site for learning-dependent sensory neuroplasticity that contributes to long-term memory formation, the relationship between auditory system function and cognition remains largely understudied in animal models of AD. Here, we used a next-generation model (NexGenMo) of AD to examine auditory cognitive function and cortical plasticity in a CRISPR-mediated point mutation knock-in (KI) rat. KI introduces one (AppS/H; n = 6) or two copies (AppS/S ; n = 6) of a familial Swedish mutation to the amyloid precursor protein (APPswe), vs. controls with the humanized sequence knocked-in (AppH/H; n=6). Animals were trained on a 2-tone associative/auditory discrimination (2TD) task, which requires them to respond (by bar press; BP) to one tone (5.0 kHz) for reward, and to inhibit BPs to another tone (11.5 kHz). Successful auditory learning and cue-selective memory formation has been shown to depend on learning-induced A1 plasticity that sharpens and strengthens acoustic representation of learned cues in long-term memory. We hypothesized that APPswe would produce disrupted learning and memory due to failures of normal learning-induced cortical plasticity. 2TD learning and performance levels were delayed and blunted in animals with APPSwe. A memory test immediately after reaching performance criterion revealed that the memory formed for the rewarded tone was less precise with APPswe. Another memory test 5 weeks later showed that time-dependent consolidation processes that sharpen auditory memories were also disrupted with APPSwe. Electrophysiology revealed normal auditory brainstem responses (ABRs) and cortical physiology to support that learning deficits were not due to hearing loss or atypical A1 organization. However, learning-induced A1 tuning bandwidth changes paralleled the learning and memory delays with APPswe. This is the first report on the behavioral and neurophysiological consequences of this NexGenMo of AD on auditory associative learning, and the first of few studies examining memory-related sensory cortical function in AD.

Supported by Busch Biomedical Grant to KMB

Poster #21
Effects of a mGluR agonist, CHPG, in the triple transgenic mouse model of Alzheimer's Disease

Authors
Talia M. Planas-Fontanez; Jean Z. Honeywell; Yangyang Huang; Cheryl F. Dreyfus

PI Name: Cheryl F. Dreyfus

Previous work in our laboratory indicates that stimulation of metabotropic glutamate receptors (mGluRs) by injection of the agonist ACPD or CHPG directly into the corpus callosum elicits an increase in brain derived neurotrophic factor (BDNF) and in myelin proteins following a cuprizone elicited demyelinating lesion (Fulmer et. al., 2014). More recently, we find that this effect of CHPG can be elicited by an intraperitoneal (ip) injection to a cuprizone treated mouse (Saitta personal communication). In the present study, we sought to determine if mGluR agonists could have similar protective effects in an Alzheimer's Disease (AD) mouse model, in which pathologies include neuronal and oligodendrocyte degeneration. Examination of the basal forebrain (BF) from triple transgenic (3xTg) AD mice demonstrated that at 12 months there is a significant decrease in BDNF compared to control mice as well as in the myelin proteins MBP and MAG. These deficits are reversed after administration of exogenous BDNF (0.5ug/uL) into the lateral ventricle. These losses are also reversed by an ip injection of CHPG, (40 mg/kg; 3X/week) for one week. Significant increases in BDNF, PLP and MAG were detected in the BF of AD, but not control mice. Similar increases in the hippocampus were accompanied by increases in numbers of myelinated axons in the CA1 region and the fornix. These studies suggest that CHPG may have a protective effect on demyelination in multiple models of neurodegeneration.

Mice were provided by F. LaFerla (UC Irvine); Supp. NIH NS036647

Poster #22
Lentiviral vectors for expressing human amyloid precursor protein or apolipoprotein E gene variants associated with increased risk of Alzheimer's disease.

Authors
Ayeshia Morris, Lara Tablieh, Petronio Zalamea, Mavis Swerdel and Ronald P. Hart

PI Name: Ronald Hart

Variants of two human genes are associated with the greatest risk of late-onset Alzheimer's disease (AD)—the E4 allele of apolipoprotein E (APOE) and the Swedish mutation of amyloid precursor protein (APP). Studies suggest that risk is related to dosage, in that APOE E4/E4 has higher risk than E4/E3 or other APOE genotypes, and overexpression of APP, including APP-Swe, leads to enhanced AD pathology. Furthermore, co-expression of mutant presenilin 1, a subunit of γ-secretase associated with early-onset AD, would enhance processing of APP into the more toxic Aβ42 product. Therefore, we constructed a library of lentiviruses designed to express selected variants of each gene. The plasmids co-express either the expression marker mCherry or a drug-selectable resistance gene, each separated by a "self-cleaving" T2A peptide sequence. The APP plasmids include the wild-type human sequence modified with the Swedish mutation (KM670/671NL). The human APOE plasmids express E2, E3, or E4 variants. The human PSEN1 plasmids express either the M146V or the del9 mutations. We transduced HEK293 cells and detected expression by mCherry fluorescence in live cells, by Western blotting, or using immunocytochemistry. Transduced cells provide a source of extracellular APOE suitable for co-culture with neurons or preparation of conditioned medium. Transduction of neurons with APP and/or PSEN1 produces oligomeric A□ in the medium which is expected to alter AD pathways. Lentiviruses could also be injected into mouse brain for chronic in vivo experiments. These lentiviruses provide effective tools for studying AD mechanisms in cultured cells or in vivo.

Supported by NIH 5T32ES007148, R01ES026057 and R01AA023797.

Poster #23

Phf8- mediated epigenetic dysregulation of mTOR signaling/autophagy increases amyloid beta level and cognitive deficits in hyperhomocysteinemic and bleomycin hydrolase-deficient mice

Authors

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PI Name: Hieronim Jakubowski

Hyperhomocysteinemia (HHcy) is associated with Alzheimer`s disease (AD). The mechanistic target of rapamycin (mTOR) signaling/autophagy pathways and the Hcy-thiolactone-hydrolyzing enzyme bleomycin hydrolase (Blmh) are linked to AD. We tested a hypothesis that HHcy causes amyloid beta (Aβ) accumulation and cognitive impairment *via* epigenetic effects on brain mTOR signaling/autophagy. *Blmh*$^{-/-}$5xFAD mice harboring a human transgene with mutations in the *APP*/*PSEN1* genes. HHcy was induced with 1% methionine in drinking water for 4-12 months. Control mice received plain water. Neurological deficiencies were assessed by behavioral testing. Brain Aβ, mTOR/autophagy proteins, and *Phf8* histone demethylase and Lys20 methylation in histone 4 (H4K20me1) were quantified by Western blotting. *Blmh*$^{+/+}$5xFAD and *Blmh*$^{-/-}$5xFAD fed with an HHcy diet for 1 year showed significantly impaired activity (beaker test), cognition (novel object recognition test), and locomotion (gait test) relative to *Blmh*$^{+/+}$5xFAD mice fed with control diet. *Blmh*$^{+/+}$5xFAD and *Blmh*$^{-/-}$5xFAD fed with an HHcy diet showed significantly increased accumulation of Aβ, phosphorylated forms of mTOR, decreased autophagy markers Beclin1, Atg5, Atg7 relative to *Blmh*$^{+/+}$5xFAD mice fed with control diet. In HHcy 4-12-month-old mice relative to *Blmh*$^{+/+}$5xFAD on control diet we observed significantly decreased level of the histone demethylase Phf8 and increased H4K20me1 which are involved in mTOR regulation. Epigenetic up-regulation of mTOR signaling and down-regulation of autophagy by HHcy, mediated by increased H4K20 methylation, causes Aβ accumulation and the cognitive and neuromotor impairments in mice. Similar changes in the Phf8/H4K20Me1->mTOR->autophagy pathway induced by Blmh deficiency suggest the involvement of Hcy-thiolactone in epigenetic dysregulation of mTOR/autophagy and neurological impairment.

Supported in part by grants from the National Science Center, Poland (2016/21/D/NZ4/00478, 2018/29/B/NZ4/0071) and the American Heart Association (17GRNT32910002).

Poster #24

The absence of p75^{NTR} in granule cell precursors of the cerebellum increase cell proliferation and anxiety levels

Authors

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PI Name: Wilma Friedman

The external granule layer (EGL) of the cerebellum is a transient proliferative layer were the granule cell precursor (GCP) undergoes clonal expansion to originate the granule neurons. Besides its role in balance and posture, recent functional and anatomical evidence has demonstrated that the cerebellum is also required for cognitive tasks such as reward anticipation and anxiety.

The p75 neurotrophin receptor (p75^{NTR}) is expressed in the EGL. Previously, we demonstrated that the absence of p75^{NTR} promotes a delay in GCP cell cycle exit, producing an abnormally large cerebellum that persisted into adulthood, with motor consequences.

In the present work, we observed that the absence of p75^{NTR} increases the cell cycle speed of the GCP and this mechanism involves RhoA. We also demonstrated, that deleting p75^{NTR} specifically from the EGL, induced an increase in Purkinje cell fairing properties, most likely due to an excess excitatory input. Finally, the network alteration observed promotes an increase in anxiety levels in these animals.

Our results suggest that p75^{NTR} must be spatiotemporally regulated during cerebellar development. The absence of p75^{NTR} in the EGL promotes a deregulation in cell cycle affecting neuronal network that ultimately leads to increase anxiety in adult animals.

Poster #25

Sex Differences in Motivation for Cocaine: Role of Progesterone and Oxytocin

Authors

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A key feature of drug abuse is pathologically high motivation for cocaine. We investigated the role of ovarian hormones on motivation for cocaine in female rats using a within-session threshold behavioral economics (BE) procedure. We quantified demand elasticity (α, inverse motivation) and free consumption (Q_0, hedonic setpoint) in females across the estrous cycle and in ovariectomized (OVX) and hormone-replaced females. Females showed lower demand elasticity (greater motivation) for cocaine compared to males. Females in proestrous showed greater demand elasticity (lower motivation) for cocaine compared to all other cycle phases. Cycle phase accounted for 70% of the variance between data points, obscuring individual differences in demand. Serum progesterone (P4) predicted decreased cocaine motivation, whereas estradiol (E2) correlated to greater intake (Q_0). Hormone replacement in OVX females with either E2 (0.09 mg/kg; 44-48hr prior to testing) and/or P4 (4.0 mg/kg; 4-6hr prior to testing) showed that E2 increased motivation in females, while P4 decreased motivation. Thus, P4 mitigates motivation for cocaine (e.g. estrus cycling or OVX). We then investigated the effects of cocaine self-administration on estrous cyclicity. By 13 weeks, proestrous epochs are absent. We tested the effects of oxytocin (0.1 mg/kg; 0.3 mg/kg) to reduce cocaine demand. Oxytocin was effective in reducing demand for cocaine in females and restored proestrous epochs in previously acyclic females. Thus, P4 signaling is a key modulator of cocaine demand in females that may underlie previously observed sex differences in addiction phenotypes, and oxytocin may be a relevant therapeutic.

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Poster #26

The role of the RNA binding protein Celf4 in the specification of the first synapses during early neocortical development

Authors

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The balanced formation of distinct synaptic subtypes within a prenatal neocortex lays the foundation for the organization of complex circuits, which encode complex behaviors specific to the neocortex. Initial synapses are found within the prenatal neocortices of both mice and humans located in two specialized zones, the marginal zone and the subplate zone. However, the concept of molecular and cellular mechanisms for these unique synapses to form in either of the two zones is not fully understood. We found that RNA binding protein, Celf4, is linked to the development of proper balance of distinct neocortical synapses in the marginal zone and the subplate, possibly by the regulation of mRNA translation. In addition, this novel mechanism is susceptible to the effects of exposure to prenatal stress.

Poster #27
Altered perineuronal nets and synaptic plasticity in the hippocampus in neurofibromin deficiency in mice

Authors
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PI Name: Ozlem Gunal

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumorigenic neurodevelopmental disorder associated with autism spectrum disorder (ASD) and intellectual disability (ID). Abnormalities in perineuronal nets (PNNs), a specialized extracellular matrix, have been linked to several neuropsychiatric conditions, but have not been investigated in mouse models of neurodevelopmental disorders associated with ASD and ID. In this study, we explored PNNs in the hippocampus in NF1 heterozygous mouse model ($Nf1^{+/-}$) compared to wild type controls. Because hippocampus is associated with synaptic plasticity, cognition and social behavior, we focused our analyses on CA1 and CA2 subregions of the hippocampus. Using lectin, Wisteria floribunda agglutinin (WFA) to label PNNs, we found increased WFA labeled PNNs in the CA2 of $Nf1^{+/-}$ mice compared to controls. Hippocampal gelatinase enzymatic activity, which remodels extracellular matrix proteins, is also reduced in $Nf1^{+/-}$ mice compared to wild type animals, associated with increased PNN formation. Additionally, we showed that Schaffer collateral-CA1 LTP is impaired in $Nf1^{+/-}$ mice, whereas long-term depression (LTD) is enhanced compared to wild type mice. Behavioral characterization suggests impaired long-term social learning and inhibitory avoidance learning in $Nf1^{+/-}$ mice compared to wild type controls. Our data show that PNN abnormalities might contribute to synaptic plasticity and behavioral deficits associated with ASD and ID.

Poster #28
Characterizing the Impact of Prenatal Drug Exposure on Emotion Processing: Findings from the ABCD study

Authors
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Prenatal drug exposure has shown to alter the trajectory of neurodevelopment and put an individual at risk for impairments long before functional disorders arise. Adolescence is a period where atypical development becomes apparent in behavior and brain function that can lead to psychiatric illnesses including mood and anxiety disorders, and substance abuse. However, the current literature on precise neural underpinnings of prenatal drug exposure and their manifestations on behavior is sparse, ambiguous, and primarily based on small cohort studies. Therefore, here we leverage data from the Adolescent Brain Cognitive Development (ABCD) study to determine the effects of prenatal drug exposure on working memory and emotional arousal and the underlying brain activity. From 8,829 children with fMRI data in the ABCD cohort, we defined groups by extent of prenatal drug exposure based on mothers' self-report of drug use during pregnancy: continued exposure (CDE; continued use after pregnancy confirmation), limited exposure (LDE; discontinued use after pregnancy confirmation), and no exposure (NDE). The N-back fMRI task with emotionally-salient stimuli was used to assess emotion processing during a task which demanded working memory. The primary outcomes were task performance, and brain activity of pre-selected (based on a prior systematic review) regions of interest (inferior frontal gyrus, dorsolateral prefrontal cortex, ventromedial prefrontal cortex, and amygdala). After adjusting for the mother's age at birth, task performance showed main effects of Memory [$F(1,8578)=225.7$, $p<0.001$)], Emotion [$F(2,8577)=4.9$, $p=0.007$)], Stimulus [$F(2,8577)=699.7$, $p<0.001$)], and Exposure [$F(2,8578)=5.008$, $p=0.007$)] as well as Stimulus*Exposure [$F(4,17156)=4.6$, $p=0.001$)] and Memory*Stimulus*Exposure [$F(4,17156)=3.2$, $p=0.001$)] interactions. These differences in task performance as well as in regional brain activations are being further explored and will be included in the final presentation. Although previous studies show that prenatal drug exposure is associated with differences in brain function, those findings should be replicated in a larger study. The ABCD study presents an opportunity to answer important questions about the effects of prenatal drug exposure on development

The ABCD Study is supported by NIH partners as well as the Centers for Disease Control and Prevention

Poster #29
Minimizing resurgence of destructive behavior using behavioral momentum theory

Authors
Wayne W. Fisher, Brian D. Greer, Ashley M. Fuhrman, Valdeep Saini, Christina A Simmons, and Madeleine Keevy

PI Name: Wayne Fisher

Many individuals diagnosed with intellectual and developmental disabilities display destructive behavior (e.g., aggression, self-injury, property destruction). Epidemiological studies and meta-analyses have revealed that interventions based on the results of a functional analysis (FA; Iwata, Dorsey, Slifer, Bauman, & Richman [1982/1994]) are more effective than similar behavioral interventions not based on the results of an FA (Campbell, 2003; Didden, Duker, & Korzilius, 1997; Iwata, Pace, et al., 1994). One such intervention informed by the results of an FA is functional communication training (FCT), which combines differential reinforcement of alternative behavior (DRA) with extinction to teach an alternative form of communication that replaces destructive behavior (Carr & Durand, 1985). While FCT is effective (Greer, Fisher, Saini, Owen, & Jones, 2016), the resurgence of destructive behavior can occur during FCT if the alternative response contacts a challenge (e.g., extinction). Behavioral momentum theory (BMT) suggests that refinements to FCT could mitigate resurgence of destructive behavior during periods of extinction. Following a functional analysis and treatment with FCT for four children with autism spectrum disorder, we combined three refinements to FCT (i.e., the use of a lean schedule of reinforcement for destructive behavior during baseline, a lean schedule for the alternative response during FCT, and an increase in the duration of treatment) and compared the magnitude of resurgence relative to a condition in which FCT was implemented in a traditional manner. Results suggested that the combination of these three refinements to FCT was successful in decreasing the resurgence of destructive behavior during an extinction challenge.

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Poster #30
Tracing functional network alternations following injury

Authors
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PI Name: Laleh Najafizadeh

Accurate diagnosis of mild traumatic brain injury (mTBI) is challenging. Reasons include rapid recovery of acute symptoms and absence of evidence of injury in typical static neuroimaging scans (MRI/CT). However, early diagnosis of mTBI is important to ensure that patients get the right medical treatment at the right time to prevent further progression of injury-induced effects. Finding reliable and accurate biomarkers which can detect mTBI and predict patient's recovery rate has been recently the subject of extensive research. In this work, we investigate alterations in brain's functional connectivity networks after the injury and during the recovery using graph-based analysis. Widefield optical imaging technique is utilized to record cortical activity of GCaMP6s transgenic mice prior to, as well as 20 minutes and 3 days after inducing the injury. By employing graph-based analysis, different characteristics of brain's functional networks are computed, and changes in network measures after the injury are studied. Network measures obtained from the injury and control groups are statistically compared and group differences across sessions are studied. These measures are also passed to classifiers (e.g. SVM, logistic regression, and kNN), and an accuracy of 90.05% is obtained when distinguishing control and injury groups. Our study demonstrates the potential of graph-based network analysis in capturing brain's functional changes after the injury.

Supported by grants from NSF, NJCBIR

Poster #31
A Novel Human Brain Organoid Platform for Virus-Host Interactions

Authors
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PI Name: Peng Jiang, Zhiping Pang

The objective of this study is to develop a human brain organoid model to better understand Human Immunodeficiency Virus (HIV-1) infection of the central nervous system (CNS) and elucidate how virus-host interactions contribute to neuropathology. We use human pluripotent stem cells differentiated into microglia precursors and Neural Progenitor Cells (NPCs) that are combined in low-adherence conditions. These cells then aggregate into 3D spheres that mature into functional cerebral organoids. We evaluate organoid maturity using immunostaining to track developmental marker progression as well as patch-clamp electrophysiology to assess neuronal functional maturation. We use a brain-derived macrophage-tropic HIV strain, JR-FL, to infect microglia precursors; to validate successful infection we use PCR-based detection of 2-long terminal repeat (LTR) circular DNA in addition to ELISA-based detection of viral p24 protein. Our data indicate that human stem cells were efficiently differentiated into microglia precursors and NPCs that can mature into functional cerebral organoids. Patch-clamp electrophysiology reveals functional maturation of neurons within organoids supported by immunohistochemistry results. We show that stem-cell derived microglia can be infected by JR-FL HIV-1 and give rise to productive infection, based on the presence of 2-LTR circles and p24 production. Finally, we present our preliminary work on our spiked chamber fluidic system for circuit analysis study. An HIV-organoid model presents a unique in vitro platform for investigating the consequence of HIV infection on the neural microenvironment, virus-host interactions at large, and how these lead to functional alterations in human neurons.

Supported by R21HD091512, R01NS102382 and Rutgers BHI pilot grants

Poster #32
Microtubule-associated proteins and corticosterone levels in a blast-induced mild traumatic brain injury mouse model with PTSD-like symptoms

Authors
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PI Name: Gleb P. Shumyatsky

Post-traumatic stress disorder and prolonged neuroendocrine deficits are observed in veterans returning from the war that suffered a mild traumatic brain injury (mTBI) caused by a blast. Works using mainly rats have reported that mTBI alters levels of proteins that interact with microtubules (e.g. β-amyloid peptide, tau, and stathmin). The variety of genetic resources and tools that allow the in vivo observation and manipulation of neuronal activity make the mouse an attractive option to study mTBI. We tested a mouse model of mTBI by using experimental conditions previously established in rats. Mice were evaluated 6 months after blast injury and showed a mild increase in anxiety but, no changes were observed in fear and contextual memory or in depressive-like symptoms as compared to the sham group (n=12 mice per group). Corticosterone was also measured in urine samples and, no statistical differences were found. However, lower levels of corticosterone were correlated with less depressive symptoms; the lowest levels of corticosterone were observed in injured mice. Preliminary histological analysis of individual mouse brains showed that stronger expression of stathmin in the prefrontal cortex and hippocampus was correlated to higher levels of anxiety. Furthermore, stronger stathmin expression in the hippocampus was correlated to higher depressive symptoms. Overall, stronger levels of stathmin were observed in mice that received the blast. Our results suggest that high expression of stathmin in the brain and low urine levels of corticosterone might be involved in the behavioral affections observed in blast-treated mice.

Supported by a grant from New Jersey Commission on Brain Injury.

Poster #33
Computational Astrocyence: The computational role of astrocytic-neural interactions

Authors
Ioannis Polykretis, Vladimir Ivanov, Konstantinos Michmizos

PI Name: Konstantinos Michmizos

Astrocytes process and modulate neuronal activity, yet the functional implications of these interactions on neuronal network information processing remain elusive. To suggest possible functional roles for astrocytes at the network scale, we are developing biologically-constrained, large-scale neural-astrocytic network (NAN) models. We developed a NAN model which suggested that astrocytes direct neuronal network activity away from destructive epileptiform activity and towards the computationally optimal, critical regime. The model consisted of biophysical, point process neurons and astrocytes. The neuronal network mimicked cortical connectivity statistics with spike-timing dependent plasticity (STDP). Astrocytes were integrated into the network with two-way signaling: 1. Slow, large-scale astrocytic integration of neuronal synaptic signals 2. Astrocytic, Ca2+ driven, slow inward current (SIC) stimulation of the network. The joint interaction of neuronal STDP with astrocytic SIC stabilized the network at criticality; a dynamical regime implicated in memory, learning, etc. Our model proposes that astrocytes monitor and modulate neuronal network activity toward critical dynamics as a way to optimize information processing in the brain. In our second NAN model, astrocytes switched the neuronal firing mode from regular spiking to bursting in an activity-dependent manner. Astrocytes detected and encoded intense presynaptic activity into their membrane depolarizations. They responded by releasing a Ca2+ buffer, which decreased the extracellular [Ca2+]. Low [Ca2+]e upregulated the neuronal persistent Na+ current, which enhanced membrane afterdepolarizations, giving rise to spike bursts. Bursting emerged periodically and its frequency increased with neuronal input intensity, endowing neurons with pacemaker properties. With bursting implicated in electrical signaling, long-term synaptic plasticity, rhythmogenesis, information transmission, and synchronization, our model proposes a mechanism, through which astrocytes can orchestrate neuronal activity from the synaptic to the behavioral level. Our models can be used for determining computational roles of astrocytic mechanisms in brain function and dysfunction, including effects on optimal network information processing and neuronal firing mode.

Supported by Rutgers BHI Pilot grant

Poster #34
Theta-band resonance in a neocortical microcircuit computational model

Authors
Rodrigo FO Pena, Horacio G Rotstein

PI Name: Horacio G Rotstein

The neocortex is a region of the brain responsible for many higher-order functions. Sensory signals arrive from different areas are integrated into the neocortex. Oscillations at certain frequency bands function for coordination of activity in many areas. Recent work showed the role of inhibition on the control of theta (4-11 Hz) oscillations through resonance. Optogenetic activation of interneurons (inhibitory) induced theta-band-limited spiking in pyramidal (excitatory) neurons. Although it is clear that this pattern is neuronal specific, the network architecture responsible for this resonance and how this is related to the correct gating of the signals in such a network is currently unknown. We address this problem with a computational model of the neocortex. We consider pyramidal cells (PYR), parvalbumin-positive (PV), and somatostatin-expressing (SOM) interneurons. These cells are interconnected with exponential decaying event-driven synapses where short-term depression/facilitation is present when appropriate. Every cell receives a noise input process to simulate in vivo synaptic barrage. By applying oscillatory stimulation in PVs, theta-band resonance was induced in PYRs whereas direct stimulation of PYRs did not present resonance, as it was experimentally reported. Our results show that SOMs, adaptation, depression, and facilitation regulate these resonance effects. Our results highlight the importance of the combined activity of different neocortical cells in flexibly selecting inputs.

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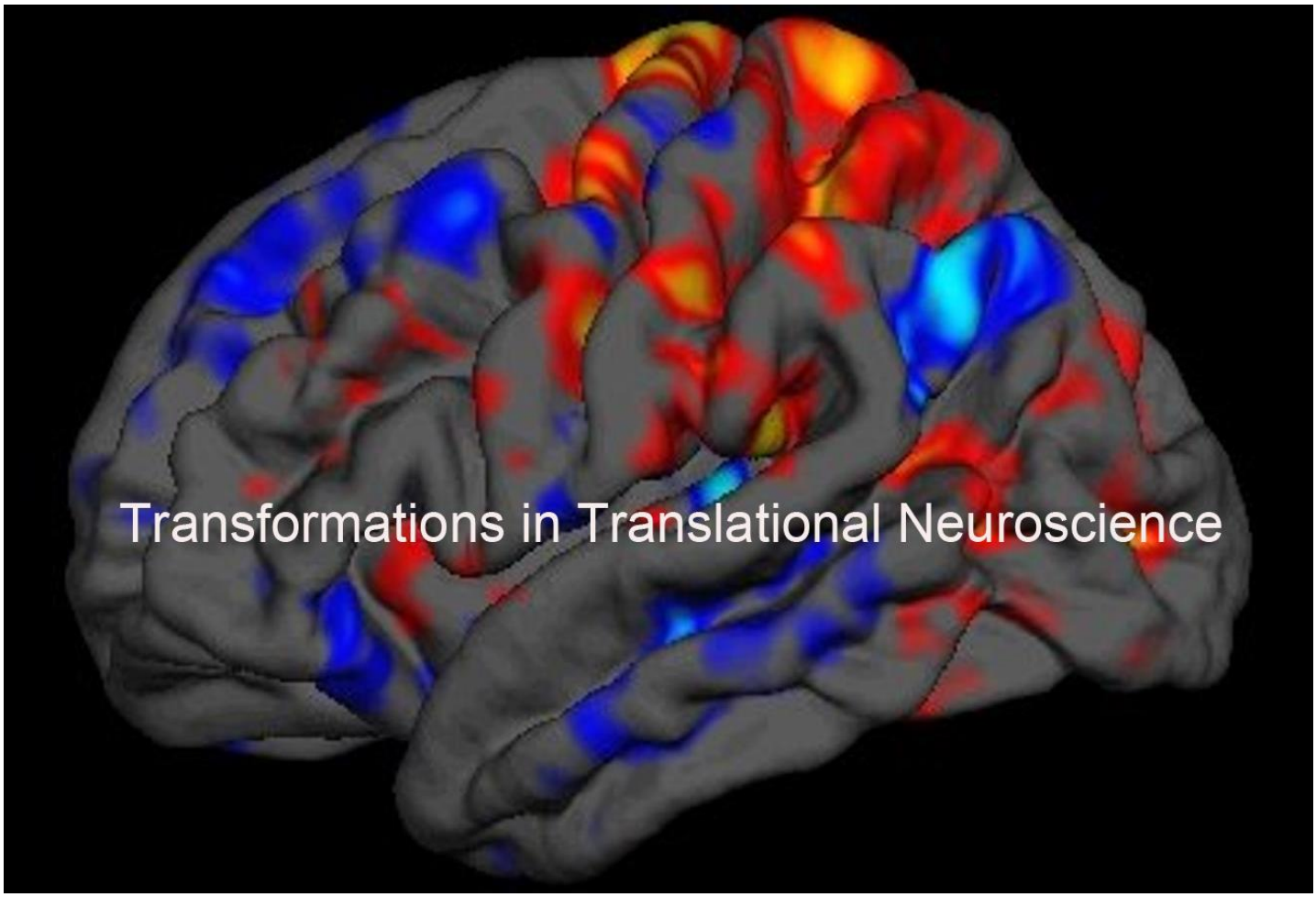
Notes



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