2024

SfN Early Career Poster Session

Faculty For Undergraduate Neuroscience

Undergraduate Poster Session

Abstract Book

October 5, 2024, 6:30 PM - 8:30 PM

McCormick Place Convention Center Hall A

Chicago, IL

Arranged in the alphabetical order of the presenter's last name

Characterizing the Effects of Early Life Opioid Exposure on Neuronal and Astrocytic Structural Synaptic Development

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Abstract

The opioid crisis has led to an increase in neonatal abstinence syndrome, which refers to the withdrawal symptoms experienced by opioid-exposed infants after birth. Though opioid exposure has been shown to impact cells in the central nervous system (CNS), such as neurons and astrocytes, little is known regarding the impact of prenatal opioid exposure (POE) on long-term neural development. This study will model POE in mice by dosing pregnant dams with the opioid buprenorphine, and the brain tissue of the pups will be used for immunohistochemistry (IHC) staining and confocal and super-resolution (STED) microscopy. The goal is to visualize opioid-induced structural changes at the tripartite synapse to better understand how POE impacts the relationship between neurons and astrocytes. Identification of these altered cellular and molecular targets can be used to lay a groundwork for the development of future therapies targeting the issue.

This research is funded under the National Science Foundation EPSCoR Track 1 Award OIA-2242771 (West Virginia Network for Functional Neuroscience and Transcriptomics WV-NFNT), and the NIH/NIMH Grant 1R15MH126345-01."

Theme B: Neural Excitability, Synapses, and Glia

An Epileptogenic Investigation: Analyzing the Bang Sensitive julius seizure Gene and the Role Vesicular Acetylcholine & GABA Transporters Play in Seizure Susceptibility

Dabira Alonge-Oludaye[1], David Deitcher[2]

1. Pomona College
2. Cornell University

Abstract

Epileptogenesis is the study of the process by which the brain becomes seizure prone. Drosophila melanogaster is a commonly used model for studying epilepsy and mutations in the gene julius seizure (jus) during a critical developmental window was found to give rise to a type of bang-sensitivity in flies. RNAi-mediated knockdown of jus in cholinergic and GABAergic neurons gives rise to bang sensitivity. This study was carried out to visualize the vesicular Acetylcholine (VAChT) and GABA (VGAT) transporters found only in jus-expressing neurons to better understand the role that these neurotransmitters play in epilepsy. The flies used for this experiment contained a STOP cassette inserted before the coding sequence of both VAChT and VGAT, flanked on both sides of the cassette were FRT/B2RT cleavage sites, which when removed, leads to transcription of the transporters. Myc and V5 epitope tags were also added to the VAChT and VGAT genes, respectively. A jus-GAL4/UAS system was used to simultaneously express RFP (mCherry) while also expressing the recombinase that allows for transcription of the tagged transporters. The myc and V5 epitope tags were stained to localize the transporters and mCherry fluorescence was used to visualize jus-expressing neurons. This staining technique led to the first successful observation of VAChT and VGAT terminals in jus neurons. The patterns of these transporters can be distinguished and we can now detect populations of jus neurons that are GABAergic and cholinergic. This technique will be employed to detect synaptic changes in jus mutants.

Theme B: Neural Excitability, Synapses, and Glia

Synaptic control from the Pedunculopontine Tegmental Nucleus to target-defined Dopaminergic Neurons

H. Arias, L. Muzyka, and G. Beaudoin

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Abstract

Dopamine has been shown to be involved in motivation and reward-based learning via dopaminergic projections to limbic and basal ganglia structures. Our research focuses on an input brain region involved in reward-based learning, specifically, the pedunculopontine tegmental nucleus (PPN) and dopaminergic neurons that project to the dorsal and ventral striatum. The PPN sends projections to dopamine neurons throughout the substantia nigra and ventral tegmental nucleus, which is unusual given the differing roles of dopaminergic innervation of the dorsal striatum by the substantia nigra and ventral striatum by the ventral tegmental area. Electrophysiological and confocal microscopic methods will be used to assess the PPN input to the DA neurons that project to the dorsal and ventral striatum. A virus containing channelrhodopsin that is tagged with a yellow fluorescent protein will be delivered to the PPN, simultaneously Lumafluor Red Retrograde Beads will be injected in the dorsal or ventral striatum via stereotaxic surgery. Electrophysiological tests will then be done to obtain electrical recordings that quantify synaptic responses within the PPN-DA-dorsal striatum pathway versus the PPN-DA-ventral striatum pathway. Slices of the brains will be immunostained with antibodies to tyrosine hydroxylase in order to confirm recorded neurons are dopaminergic. Images of these slices will be taken via confocal microscopy in order to assess PPN input to the DA neurons that project to the dorsal and ventral striatum. This research will establish greater clarity for any future studies that seek to understand the neural network and synaptic-level processes of the PPN-DA pathway.

Theme E: Motor Systems

The impact of pregnancy on mood, cognition, and microglia function in Alzheimer's disease mice

Perla Arias, Holly C. Hunsberger

Center for Neurodegenerative Disease and Therapeutics, Rosalind Franklin University of Medicine and Science, Chicago Medical School, Rosalind Franklin University of Medicine and Science

Abstract

Alzheimer's disease (AD) impacts six-million Americans, 2/3rds of whom are women. Women are more susceptible to developing AD due to a variety of social stress factors, differences in immune responses, and a decline in estrogen. Previous research has shown that pregnancy offers protective barriers to women, reducing the likelihood of developing dementia-like disorders. Notably, pregnancy has the ability to modify a woman's inflammatory response. This interaction between pregnancy and inflammation is critical given that there is microglial upregulation to clear amyloid plaque burden in the brain. In some instances, the activation of microglia can promote the phagocytosis and clearance of those toxic proteins, but if microglia become overactivated, a surplus of inflammatory mediators are released. Here we aim to understand how pregnancy impacts cognition and microglia activation in Alzheimer's disease mice. To answer these questions, we used behavior testing and immunohistochemistry to analyze cellular activity in the hippocampal region of male and female naive and postpartum mice. We found that 1) litter-bearing mice exhibit slight memory impairment with age and 2) litter size was indicative of memory impairment in AD mice. Interestingly, the sex of the pups also impacted affective behaviors. Furthermore, immunohistochemistry using microglia markers can give insights into the complexity of microglia function in naive and litter-bearing control or AD mice. Overall, this research provides a deeper understanding of how pregnancy influences brain pathology and AD symptoms.

Theme C: Neurodegenerative Disorders and Injury

WUSTLDisruption of circadian signaling to GBM tumors desynchronizes intrinsic Per2 rhythms and slows disease progression

Nigina Aripova, Maria Gonzalez, Tatiana Simon, Erik Herzog

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Abstract

Glioblastoma (GBM) is the most deadly brain tumor in adults, with a median survival of 15 months post-treatment despite extensive research and clinical trials. Prior studies have demonstrated that murine, human, and primary GBM models have cell intrinsic circadian rhythms in expression of the core clock genes Bmal1 and Per2, and in sensitivity to chemotherapy with TMZ in vitro. In a retrospective clinical study, our lab found that taking morning TMZ increased overall survival by six months, compared to evening. This suggests that GBM has circadian rhythms that synchronize to the host's central clock, and that entrainment may regulate GBM biology and response to therapies. Here we tested whether host signaling synchronizes daily rhythms in GBM and regulates tumor growth. We transduced a murine GBM cell model with a luciferase reporter of Per2 transcription (GBM-P2L) and confirmed that these cells had circadian rhythms in clock gene expression. We next implanted GBM-P2L cells into the basal ganglia of WT C57 or arrhythmic VIP KO mice, which lack daily rhythms in locomotion and corticosterone secretion, and imaged tumor bioluminescence in vivo. We found that Per2 expression reliably peaked in the dark phase (CT16) in WT mice bearing GBM xenografts, but peaked at random times of day in VIP KO mice. Strikingly, GBM tumors grew slower in arrhythmic VIP KO mice, compared to those implanted into WT mice. Our results suggest that GBM tumors integrate into circadian circuits of the brain and depend on clock-controlled cues (i.e., VIP) to grow.

Theme F: Integrative Physiology and Behavior

Developing a Biobehavioral Assessment for Common Marmosets (Callithrix jacchus)

Grace Augustine[1], Ashwini Vivek[1], Donna Layne-Colon[2], Corinna N. Ross[2], Kimberley A. Phillips[1]

1. Trinity University, San Antonio, TX
2. Southwest National Primate Research Institute, Texas Biomedical Research Institute, San Antonio, TX

Abstract

Early life experiences, beginning with prenatal development, impact physical and mental health and development across the lifespan. While some mechanisms of this relationship have been examined in humans, the complex interactions between human physiology and sociological factors make it difficult to assess the specific effects of early life adversity on aging outcomes. To facilitate this and better characterize individual differences in research subjects, researchers at the California National Primate Research Center developed the BioBehavioral Assessment to quantify characteristics of rhesus macaques (Macaca mulatta) that may predispose the animals to certain aging or health outcomes. The BBA has identified four behavioral profiles in infant macaques. For example, biobehaviorally inhibited infants showed increased airway hyperresponsiveness later in life, similar to the association between inhibited temperament and asthma risk in humans. The study demonstrated how early-life temperament assessed by the BBA can be used to investigate potential links to specific health outcomes in adulthood. With the common marmoset (Callithrix jacchus) used as a model for human aging, it is increasingly important to characterize the animals at all stages of life to gain a more comprehensive understanding of aging and health patterns. To assist with this, we adapted the macaque BBA paradigm to assess response and adaptation, hypothalamic-pituitary-adrenal (HPA) axis regulation, and cognition in marmosets aged 3-4 months. Seven infant marmosets completed the MarBBA evaluation, which included behavioral observations, hair cortisol quantification, social preference test, social separation test, and preferential look test spread across a 5-day testing session. We performed a k-means clustering analysis with the results of each test and identified the presence of two temperament categories in our samples: reactive and behaviorally inhibited. Reactive animals showed increased locomotion during separation and autogrooming when returned; behaviorally inhibited spent more time in proximity after separation. Our ongoing research will test additional infant marmosets to increase the sample size and extend our initial findings, as we suspect there may be additional temperament categories.

Theme F: Integrative Physiology and Behavior

Neonatal cannabidiol treatments leads to sex-specific changes in rat ultrasonic vocalization outcomes following pain exposure

Eshani Baez[1], Quinn Battagliese[1], Brian Timmerman[2], Susanne Brummelte[2], Jennifer Honeycutt[1]

1. Bowdoin College, Brunswick, ME
2. Wayne State University, Detroit, MI

Abstract

Infants born prematurely often undergo necessary procedures that have been associated with pain and concurrent neurodevelopmental changes. By exposing neonatal rats to pain, in the form of needle pokes, in combination with cannabidiol (CBD) administration, the present study examines whether CBD proves to be an effective form of pain management for neonates. We assessed distress from procedural pain via the rate, frequency, and duration of ultrasonic vocalizations (USVs) emitted by rat pups. USVs, which are emitted by rats and other rodents, serve as indicators of emotion and are used as a measure of affect in preclinical models. In pre-weanling rats, USV calls, around 40kHz, are used to solicit mother-pup interactions. It was anticipated that neonatal pain exposure would increase number and duration of neonatal USVs, while CBD administration was hypothesized to reduce number and duration of 40kHz USVs. DeepSqueak, a MatLab software utilizing deep learning, was used to detect, classify, and analyze calls. DeepSqueak analysis can distinguish between different types of USVs based on their frequency, duration, and other characteristics. The analysis and categorization of USVs is an emerging approach in behavioral research, and understanding USV output may provide insight into affective states and experiences relating to nociception, the effects of drugs in pharmacological testing, withdrawal symptoms, and animal welfare. We present findings suggesting that CBD treatment reduces USV emissions in a sex specific manner, with males showing robust decreases in USVs following treatment. This provides compelling evidence for the possible efficacy of CBD treatment in a neonatal pain model.

Theme F: Integrative Physiology and Behavior

Enhanced vulnerability to trauma-induced neurodegeneration in a Drosophila model of human tauopathy

Srivatsa Bellamkonda, Pooja Jakkampudi, Owen Kamer, Mihira Karnik, Melissa Tribley, Oyunsuvd Bat-Erdene, Joseph Figura, Lindsay Gray, Matthias Hirst, Kelly Lohr

Biology Department of Washington & Jefferson College

Abstract

Deposition of the microtubule-associated protein tau is a hallmark pathology of the family of neurodegenerative diseases known as tauopathies, including Alzheimer's disease, frontotemporal dementia, and chronic traumatic encephalopathy. Ongoing work on mechanisms of tau-mediated neurodegeneration suggest that genetic contributions interact with peripheral or environmental factors to contribute to disease onset and severity. Head trauma is an established modifier of brain health and function in human, rodent, and invertebrate models. Using an established impact injury model known as HIT, we have examined the effect of traumatic injury on behavior and neurodegenerative markers in transgenic Drosophila expressing human tau in neurons. Tau transgenic flies show worsened outcomes compared to their non-transgenic controls as shown by both locomotor activity and tissue histology. To expand upon this work, we are examining other neurodegenerative models in the HIT paradigm as well as other biochemical markers of cell death. Taken together, these data suggest that tau transgenic flies have an increased vulnerability to traumatic injury in this Drosophila model of human tauopathy.

Theme C: Neurodegenerative Disorders and Injury

The Effects of MPTP on the Spinal Locomotor Network within the Mammalian Spinal Cord

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Department of Biology, Program in Neuroscience, Bowdoin College

Abstract

The central pattern generator (CPG), localized within the lumbar region of the neonatal mouse spinal cord, generates rhythmic outputs termed fictive locomotion via exogenous application of serotonin (5-HT) and the glutamate analog NMDA. Activity of interneurons and motor neurons within the CPG can be modulated using neuromodulators. The current study assessed the effect of 1-methyl-phenyl-1,2,3,6- tetrahydropyridine (MPTP), the parkinsonism syndrome inducing drug, on locomotor-like activity generated by isolated spinal cord preparations. Here, we exposed the isolated spinal cord preparations to 10 μM, 50 μM and 100 μM of MPTP and recorded motor neuron action potential bursts from first, second and fifth lumbar ventral roots using extracellular recordings. To characterize MPTP's effect, we used three parameters: burst amplitude, burst duration, and cycle period of the locomotor pattern. The application of 10 μM MPTP led to no effects on all measured parameters. However, at 50 μM, MPTP decreases burst amplitude in ventral roots while burst duration and cycle period remain unchanged. Lastly, the application of 100 μM had a highly disruptive but reversible reduction in all parameters measured. Together, our results suggest that MPTP at 50 μM concentration selectively modulates motor neurons within the CPG by potentially via inhibitory mechanisms to decrease motor neuron recruitment without impacting interneurons/pacemaker neurons that control the excitability and speed of the locomotor network. These results have important implications on the effects of neurodegenerative disorders on neural networks that control motor function within mammals including humans.

Theme E: Motor Systems

The DNA of addiction: exploring the genetic factors in nicotine dependence and cessation

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3. Department of Psychology, Arizona State University, Tempe, AZ 85281
4. The College of Liberal Arts and Sciences, Arizona State University, Tempe, AZ 85281

Abstract

The decline in cigarette smoking from 20.9% to 11.5% between 2005 and 2021 reflects a positive public health trend. However, there is an alarming surge in e-cigarette and nicotine pouch use among youth, with a 1,733% increase among high school students from 2011 to 2019. Nicotine, a highly addictive substance, is associated with increased risks of cardiovascular, respiratory, and gastrointestinal disorders. Research into nicotine cessation is crucial for addressing the potential future health crises related to morbidity and mortality. Nicotine dependence can affect nearly anyone, but certain individuals struggle more with cessation, possibly due to upregulation of nicotinic acetylcholine receptors (nAChRs) in the brain stem and pre-frontal cortex (PFC). Exploring the genetic factors, particularly the CHRNA4 and CHRNB2 genes, could provide insights into nicotine use that is resistant to cessation. Utilizing resources like the Allen Brain Cell Atlas, we co-localized these genes to the brain stem and PFC. Further, a review of the literature and analysis of single-nucleotide polymorphisms (SNPs), behavioral survey, and electronic health record (EHR) data from the All of Us research study suggests that SNPs, such as rs2236196, may influence treatment-resistant nicotine dependence, while the SNPs rs1044396 and rs1044397 appear to be particularly responsive to Varenicline (Chantix) therapy. Additionally, the rs2072661 SNP appears consistently across all cohorts, which suggests it may play a role in nicotine dependence in general. While our findings are preliminary, they underscore the need for more comprehensive research on the genetic and epigenetic factors contributing to challenges in nicotine cessation.

Theme F: Integrative Physiology and Behavior

Synaptic transmitter and hemolymph co-modulation of the pyloric rhythm in the crab Cancer borealis

Margaret Broaddus[1], Ahmed Albayaty[1], Michael P Nusbaum[2], Daniel J Powell[1]

1. Bowdoin College
2. Univ. of Pennsylvania

Abstract

All nervous systems are modulated by signaling molecules, including amines, amino acids and peptides that are released from secretory terminals at specialized sites to circulate as hormones. An extensive body of work has elucidated the effects of hormones on single neurons and entire circuits, but these studies have primarily focused on the effects resulting from applying single or multiple neuromodulators at arbitrary, and often saturating concentrations. Thus, how co-circulating hormones collectively affect circuit flexibility and behavior remains an open question. Here we add to a nascent body of work that utilizes the hemolymph (crab blood) from a donor crab to assess the impact of the endogenous complement of hormone modulators on the isolated stomatogastric nervous system (STNS) of the crab Cancer borealis. The STNS includes the stomatogastric ganglion (STG), a well-characterized network of 26 neurons comprising two multifunctional circuits that underlie chewing (gastric mill circuit) and the passage of chewed food (pyloric circuit). These circuits are composed of motor neurons (plus two interneurons) which innervate striated muscles positioned on the exterior of the crab stomach.

In the isolated STG, but not in the complete STNS or in vivo, bulk hemolymph tends to inhibit the spontaneously active pyloric rhythm. We thus hypothesize that in the latter two conditions, other modulators must be locally released to ensure that the pyloric rhythm persists. To test this hypothesis, we are co-applying to the isolated STG hemolymph with one of several native modulators, including serotonin, a muscarinic acetylcholine agonist, dopamine, or the peptide proctolin.

Theme E: Motor Systems

Electrophysiological Signatures of Novel Language Learning in the Earliest Stages

Corey (Faith) Broersma, Megan Nakamura, Eleonora Rossi

University of Florida

Abstract

Previous research has examined the ways in which the learning of a second language in adulthood can promote cognitive and neural changes. However, little is known about the earliest stages of novel language learning in adults and how it may impact neurobehavioral signatures of language and cognition. This study aimed to investigate how the earliest neural signatures of novel language learning may be impacted by variables such as Age of Acquisition (AoA), proficiency in the second language, and general cognitive measures such as working memory and inhibitory control. Spanish-English bilinguals (n=37) participated in a 10-day mini-longitudinal study in which they completed Dutch lessons through Rosetta Stone. Event Related Potentials (ERPs) were examined at pre and post-test to investigate neural changes of Dutch language encoding using a Semantic Categorization Task (SCT). The results show a reduced N400 across learned vocabulary at post-test, indicating rapid neural adaptation. Both bilingualism factors and inhibitory control were shown to have an impact on the N400, with higher bilingual experience leading to reduced N400s for cognates, and better inhibitory control leading to smaller N400s for cognates and larger N400s for non-cognates. Working memory did not significantly affect N400 amplitude. These results suggest that bilingualism may aid in the lexicalization of similar words across languages, while higher inhibitory control can prevent cross-linguistic interference from cognates. This study demonstrates the ways in which individual differences can modulate the earliest signs of language learning and expands current literature on the neuroadaptation that occurs alongside language learning.

Theme H: Cognition

Identification of a new odorant that is detected by the AWCOFF neuron in Caenorhabditis elegans

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Abstract

Caenorhabditis elegans is a free-living nematode found commonly in compost, rotten fruit, and other environments rich with bacteria, its major food source. C. elegans uses olfaction to discriminate among odorants released by its bacterial food. In C. elegans specific neurons have been shown to be required for detecting specific odorants. However, the neuronal basis of detection of many odorants is not known. In this study, our goal was to determine which neuron or neurons are responsible for the detection of attractive odorants released by bacteria. Using a chemotaxis assay in which C. elegans can choose between the odorant diluted in ethanol and ethanol, the chemotaxis index of the nematode was calculated to reflect its attraction to odorants. We then tested several genetic mutants lacking specific neurons in chemotaxis assays. We determined that the AWCOFF neuron is likely required for the detection of one of the new odorants that we tested.

Theme D: Sensory Systems

Prolactin increases cell proliferation but not neurogenesis in the dentate gyrus of adult male rats

Mark D. Spritzer, Ugo U. Iroh, Raymond J. Grocela, E. Blaine Cunningham, **Isabella Z. Caddeau**, Kathryn A. Blek.

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Abstract

Neurogenesis occurs throughout adulthood in the dentate gyrus region of the hippocampus, and there is some evidence that the pituitary hormone prolactin influences adult neurogenesis. We tested the effects of acute and chronic injections of prolactin upon cell proliferation and neurogenesis within the dentate gyrus of adult male rats. Rats received either an injection of saline (control) or recombinant rat prolactin (5-800 μg/kg). In the first experiment, a single injection of prolactin was immediately followed by an injection of bromodeoxyuridine (BrdU), and brain tissue was collected 24 h after injections to assess prolactin's effects upon cell proliferation. Subsequent experiments involved either acute (4 injections at 12 h intervals prior to BrdU injection) or chronic (14 daily injections starting 24 h after BrdU injection) treatment with prolactin, and brain tissue was collected 15 days after BrdU injections. Cell proliferation and survival were assessed using immunohistochemistry and light microscopy. A low dose of prolactin (10 μg/kg) caused a significant increase in BrdU-labeled cells that were 24 h old. In contrast, neither acute nor chronic injections of prolactin had significant effects on the number of BrdU-labeled cells that survived to 15 days old. Immunofluorescent double-labeling (NeuN and BrdU) and confocal microscopy revealed that about 90% of new cells were neurons, and prolactin treatments had no significant effect on this percentage. These results suggest that there may be a selective process, unrelated to prolactin levels, which determines which newly proliferated cells stimulated by prolactin will survive to become neurons.

Theme F: Integrative Physiology and Behavior

Enriching rats prior to traumatic brain injury does not protect against subsequent neurobehavioral deficits

Haley E. Capeci, Jade A. Steber, Amogh J. Vellore, Priyal R. Goyal, Ria I. Vangala, Travis S. Mindel, Eleni H. Moschonas, Corina O. Bondi, Anthony E. Kline

Abstract

Environmental enrichment (EE) reliably produces behavioral and histological benefits when initiated after experimental traumatic brain injury (TBI). However, no benefit or prophylactic effect was revealed in a recent study where EE was provided for 2-weeks before a single controlled cortical impact (CCI) impact to the right hemisphere. The lack of protection with Pre-TBI EE may have been due to limited exposure and thus to verify the puzzling finding, the current study utilized a 4-week Pre-TBI EE paradigm to test the hypothesis that pre-TBI EE can exert a prophylactic effect. A group receiving EE before and after TBI was included to determine whether Pre-TBI EE affects the robust effectiveness of Post-TBI EE. After 4 weeks of EE or standard (STD) housing, anesthetized adult male rats were subjected to a right hemisphere CCI injury (2.8 mm deformation at 4 m/s) or sham surgery and then randomly assigned to post-operative EE or STD conditions. Beam-walk agility and acquisition of spatial learning were assessed on post-operative days 1-5 and 14-19, respectively. The Post-TBI EE groups performed better than the Post-TBI STD groups ($p<0.05$) but did not differ from each other ($p>0.05$). However, despite 4 weeks of EE prior to TBI, no prophylactic effect was observed as there were no differences between the STD-housed TBI groups regardless of whether they received EE or STD housing before surgery ($p>0.05$). These data reproduce previous findings showing that EE post-TBI is effective and replicate a recent report that providing EE prior to TBI does not confer protection.

Theme C: Neurodegenerative Disorders and Injury

Early life sleep deprivation induces autistic-like communicative deficits in C57BL/6J mice

Nicole Cofsky, Matthew S. Binder

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Abstract

Autism spectrum disorder (ASD) is defined by deficits in communication, sociability, and stereotypy. However, the most prevalent symptom is deficits in sleep, which occur in up to 83% of patients. Despite this high co-occurrence, the relationship between sleep and ASD is unclear. To assess if sleep may be contributing to the onset of communicative deficits in ASD, we induced an intermittent sleep deficit throughout early development (postnatal day (PD) 4 to 12) in C57 mice and subsequently assessed neonatal communicative behaviors, known as ultrasonic vocalizations (USVs), on PD8 and PD12. On PD8, we did not detect any significant differences in the total vocalizations produced between the early life sleep deprivation (ELSD) condition and the control condition. Additionally, no changes were found in the duration, fundamental frequency, peak frequency, or amplitude of the calls between groups. However, PD8 ELSD mice did use significantly different types of calls than control mice. On PD12, following 8 days of sleep deprivation, ELSD mice displayed numerous communicative deficits, producing significantly fewer total USVs and vocalizations of a shorter average duration. There were also significant differences in call type utilization, similar to PD8. Our study indicates that sleep deficits during early development are sufficient to induce an early life communicative deficit in neurotypical C57BL/6J mice, with a more severe sleep deficit resulting in a more severe impairment. Overall, these results suggest that sleep alterations may be a key contributing factor to the onset of core ASD symptomatology.

Theme A: Development

Student-developed in-class exercises using schematic physical models to enhance learning of functional neuroanatomy

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Abstract

Interactive in-class exercises can enhance learning and retention of course material. We developed multiple physical schematic models that emphasize nervous system function and have implemented them successfully in a large-enrollment neuroanatomy course intended for neuroscience majors and minors at the University of Pittsburgh. These models are not designed to reflect the exact structure of neuroanatomical components per se, but instead to serve as schematic "puzzles" that help students learn about the functions and potential pathology of the nervous system. Examples include models for teaching afferent and efferent pathways within the spinal cord; retinal circuitry; pathways by which visual information travels from the retina to the primary visual cortex; and functions and pathology of the basal ganglia and related structures. These models have been developed largely by undergraduate teaching assistants, which serves as a learning experience for them as they create the models and design them for effective instructional use. Our reusable, durable models are designed to be cheaply and easily constructed using common 3D printing, laser cutting, and/or similar techniques and will be made available to other instructors as open education resources under a Creative Commons license.

This work was supported by University of Pittsburgh Chancellor's Undergraduate Teaching Fellowships to AMC and MGMB and a University of Pittsburgh Provost's Open Education Resource funding award to EEF. Generous technical support was provided by the University of Pittsburgh Open Lab, including Will Hinson and Sera Thornton.

Theme J: History, Education, and Society

Verbal Fluency in Autism: Impact of Aging Across the Adult Lifespan

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Introduction: It is known that as one ages, cognitive function declines. However, cognitive aging research on adults with Autism Spectrum Disorder (ASD) is scant. Verbal fluency is a language-based executive function that is a challenge for many autistic individuals, and negatively affected by normal age-related processes. There is some cross-sectional evidence that brain regions supporting verbal fluency may experience accelerated cortical thinning in autistic adults compared to neurotypical (NT) controls, but they longitudinal trajectories of verbal fluency abilities and related brain aging are unknown.

Methods: Right-handed autistic (ASD; n=125) and neurotypical (NT; n=95) adults, ages 18 to 70 years old, were recruited for cross-sectional analyses. Participants over the age of 40 were invited to participate longitudinally with evaluations every two years (ASD, n=55; NT, n=45; follow-up duration=2.31±0.43 (1.24-3.71) years). Commonly used behavioral measures of phonemic (i.e. letter) and semantic (i.e. category) word production and cortical thickness of language-related left hemisphere areas (pars opercularis, pars triangularis, superior parietal, supramarginal, transverse temporal and anterior cingulate cortex) via freesurfer were obtained. Group differences and associations with age were investigated in fluency behavior and cortical thickness with both cross-sectional and multi-level longitudinal regression models.

Results: In the cross-sectional analysis for fluency behavior, autistic adults demonstrated persistent challenges in initiating phonemic (p=0.026) and maintaining semantic (p=0.004), but there were no diagnosis group by age interactions. For the brain, there was a diagnosis group by age interaction in the left pars opercularis where autistic adults showed a steeper negative relationship with age than NT adults (p=0.002). In the longitudinal models, no significant aging (i.e. time) effects were observed for fluency behavior or cortical thickness.

Discussion: Behavioral findings from the present study suggest that autistic adults across a wide age range have persistent difficulties with verbal fluency production, but that these abilities may not change differently from NT adults during aging. Findings from cross-sectional cortical thickness analyses suggests some vulnerability to accelerated aging in the key language production region, Broca's area, but this was not corroborated in longitudinal analyses. More research is needed to determine whether cortical language areas may be vulnerable to accelerated aging in autistic adults and implications for maintaining independence as aging ensues.

Theme A: Development

The effects of immersive visual distractor cues in virtual reality on human solutions of the Traveling Salesman Problem (TSP)

Isabelle Cote, Parisa Hariri, Rachel Blaser

University of San Diego

Abstract

The Traveling Salesperson Problem (TSP) is a combinatorial optimization problem originally of interest to mathematicians, but more recently used also in the context of cognitive and comparative psychology. Humans perform extremely well on spatial versions of this task, despite its mathematical complexity, making it an appealing tool for the study of spatial and mathematical cognition. Previously, we demonstrated that lesions of the hippocampus, and to a lesser extent, the medial entorhinal cortex (MEC), impair the performance of rats in a task analogous to the TSP. Lesions of the MEC primarily affected performance on spatial configurations that required a global strategy for efficient navigation, with little impairment on configurations for which a local strategy produced efficient performance. In the current study, we looked more closely at global vs. local strategy use in human participants. We are working toward creating a virtual reality space where participants are presented with a three-dimensional version of the TSP. The TSP can be solved by visually linking the objects in the immersive space which creates a more realistic environment in order to achieve the most pragmatic result from the participant. While the experiment is being conducted, we record the participants' gaze points to study their processing and spatial visualization. The path that the participant takes will be used in comparison to the two-dimensional version of this problem.

Theme H: Cognition

Proposing a multistage, interdisciplinary research approach to expand educational neuroscience into new cognitive territories

Carolyn DePinho, Anamaria Alexandrescu

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Abstract

Educationally relevant neuroscience research into the biological and cognitive processes that underlie the mathematical and reading abilities of atypical young learners has been a cornerstone in the evolution of educational neuroscience. The time is prime to broaden such inquiries to encompass additional cognitive domains, like scientific reasoning, and to explore other neural developmental phases, such as adolescence, across typical and atypical learners. We outline a multistage, iterative research cycle that progresses from (1) behavioral observations in educational settings to (2) behavioral and neural interrogations in cognitive neuroscience laboratories and ultimately to (3) scientifically informed educational applications. Initially, educational observations and challenges will inform novel research hypotheses and naturalistic experimental designs. These will subsequently undergo systematic testing in controlled laboratory conditions at different levels of analysis (e.g., behavioral, cognitive, neural) to achieve a mechanistic understanding of the cognitive and neurodevelopmental processes involved. The results gleaned from these investigations will inform the creation and assessment of educational practices. These neuroscience-informed educational applications will undergo iterative testing and refinement in partner research classrooms before broad implementation. Furthermore, we propose a focus on three cognitive functions that are critical for learning – attention, motivation, and decision-making – and we delineate a series of research questions and designs that employ our research approach to investigate the behavioral, neural, and developmental underpinnings of these processes. This approach promises to yield innovative, ecologically valid insights with significant empirical and theoretical contributions to both the educational and neuroscientific disciplines.

Characterization of Kynurenic Acid in the Nervous System of the Pond Snail Helisoma

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Abstract

The kynurenine (KYN) pathway, a major metabolic pathway in L-tryptophan (TRP) catabolism, is implicated in the formation of essential amino acids serotonin and melatonin. Dysregulation of the KYN pathway is also associated with multiple neuroinflammatory and neurodegenerative diseases, including Alzheimer's disease, schizophrenia, multiple sclerosis (MS), and various cancers. However, much is still unknown regarding KYN activity in the CNS, including the location and pathophysiological role of its metabolites. Invertebrate species provide a unique model to study neural mechanisms and behavioral processes involved in neuronal growth and localization. KYN genes have been localized in different tissues of the gastropod mollusc Lymnaea, with expression in the central nervous system as well. To date however, there have been no studies locating actual neurons containing KYN in the snail brain. We use immunohistochemical stains to locate KYN in the central nerve ring and buccal ganglia of the snail Helisoma duryi. Brains were isolated from adult snails (4-10mm in diameter), fixed using 4% PFA, and stained using anti-Kynurenine. Positive staining was found in neurons in the buccal ganglia and the circumesophageal ganglia including the cerebral, pedal, and visceral ganglia. Immunoreactivity was also found in processes such as the cerebrobuccal connectives, the buccal commissure, and nerves from the visceral and pedal ganglia. Given the importance of KYN to brain health, its localization in the snail CNS can provide a new model to study its role in the function and survival of healthy neurons.

Theme F: Integrative Physiology and Behavior

Sex-Dependent Differences in Cortisol Levels of Zebrafish (Danio rerio) are Observed After Exposure to High-Fat and Overfed Diets

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Abstract

While previous research has identified Danio rerio as a model organism for studying stress and metabolism, there is little research investigating the impact of diet-induced obesity on their sex-dependent stress response. This study induced metabolically healthy and unhealthy obesity in zebrafish by introducing over-fed or high-fat diets. Sex differences in stress responses were assessed by measuring serum cortisol levels in male and female zebrafish assigned to different dietary groups. We anticipate zebrafish placed on overfed and high-fat diets will display increases in body mass index (BMI) versus controls. We hypothesize that cortisol levels will be higher in obese zebrafish versus controls as obesity represents metabolic stress; metabolically unhealthy zebrafish will have higher cortisol levels than metabolically healthy zebrafish due to demonstrating greater metabolic derangement; and obese female zebrafish will display lower levels of cortisol compared to obese male zebrafish. Initially, we measured individual fish BMIs before randomly assigning them to a control, high-fat, or overfed diet group. After receiving the assigned diet for four weeks, we extracted blood from each fish for cortisol, triglyceride, and glucose analysis. Females displayed a significant increase in BMI within the control and high-fat diets while males did not experience any significant increases; males had significantly increased blood glucose in all diets, while females only experienced significant blood glucose increases between the control and over-fed diets; and males displayed cortisol levels that were diet-dependent while the female cortisol levels were diet-independent. This suggests diet can influence stress-related sex differences in zebrafish and requires further research.

Theme F: Integrative Physiology and Behavior

A meta-analysis of the effects of early life stress on the prefrontal cortex transcriptome suggests long-term effects on myelin

Toni Q. Duan[1], Megan H. Hagenauer[2], Duy Manh Nguyen[1], Anne Bader[1], Elizabeth Flandreau[3], Pamela Maras[1], Randriely Merscher Sobreira de Lima[4], Stanley Watson Jr[2], Michael Meaney[4], Huda Akil[2]

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Abstract

Early life stress (ELS) refers to exposure to negative childhood experiences. ELS can alter an individual's brain, leading to cognitive impairment and sensitivity to future stressors. The prefrontal cortex (PFC) is a key brain region implicated in the effects of ELS. We ran a meta-analysis of publicly available transcriptional profiling datasets to characterized the long-term effects of ELS on the PFC. We identified four datasets (GSE89692, GSE116416, GSE14720, GSE153043) that used multi-day ELS paradigms in laboratory rodents during the postnatal period. The outcome variable was gene expression in the PFC later in life as measured by microarray or RNA-Seq.

To conduct the meta-analysis, we extracted log2 transformed gene expression data and metadata from the Gemma database of curated and re-analyzed gene expression studies. We calculated ELS vs. Control differential expression using the limma pipeline. Meta-analysis was conducted by fitting a random effects model to the ELS vs. Control effect sizes and their respective sampling variances from each study.

We reached stable meta-analysis estimates for 12,152 genes. Two results survived false discovery rate correction (FDR<0.05): the downregulation of Claudin 11 (a myelin component and regulator of oligodendrocyte proliferation and migration) and the upregulation of Solute Carrier Family 30 Member 3 (a zinc transporter found in synaptic vesicles). Amongst the top results, there was a downregulation of other myelin-related genes: Myelin Associated Glycoprotein & Myelin And Lymphocyte Protein. These findings suggest that ELS during critical periods of development may produce long-term effects on the efficiency of transmission in the PFC.

Theme G: Motivation and Emotion

The Effects of Depleted Peripheral Macrophages on Alcohol Addiction Reward-Seeking Behaviors in Mice

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Abstract

Alcohol addiction is a global problem that negatively affects mental and physical health. Although previous data suggests a relationship between alcohol and immunity, significant gaps in knowledge remain in exploring how the specific functions of the immune system contribute to the formation of addiction memories. Previously published works suggest that stress and weaker immune systems play a role in addiction vulnerability. Motivated by these findings, we hypothesize that suppressing innate immune components will lead to a higher risk of addiction formation. To confirm this hypothesis, we administered Liposomal Clodronate (LC) to the mice in order to deplete macrophage function and systemically modify inflammatory responses. The behavioral aspect of the investigation was completed using a four-day drinking paradigm called Drinking in the Dark (DID) helping assess binge drinking behavior, while the Ethanol Conditioned Place Preference (eCPP) evaluated reward-seeking behaviors and identified reward memories formed due to the alcohol exposure. LC-treated groups and control groups were compared on 1) a behavioral level using the correlative relationship between the DID and eCPP scores and 2) molecular level by examining neuronal activation of specific brain regions using fos immunohistochemistry (IHC). These results may help us to understand the effects of inflammation through depletion of peripheral macrophages on alcohol related behaviors and context associations.

Theme G: Motivation and Emotion

A surface-based probabilistic atlas of the anterior medial temporal lobes: temporopolar, entorhinal, perirhinal, and parahippocampal cortex

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Abstract

The anterior medial temporal lobes (aMTL) contain a set of cortical areas providing an interface between association cortex and the hippocampal formation, thought to be critical for long-term memory. These include entorhinal cortex (ER), with direct connections to the hippocampus, as well as perirhinal (PR) and parahippocampal cortex (PH), with connections to ER. A less well-characterized component of this system is temporopolar cortex (TP), a primate-specific brain area situated just anterior to PR, with a similar pattern of inputs to ER. Identifying the anatomical locations of these areas in individual human brains is a critical precursor to studying their function. However, existing atlases of aMTL areas have several limitations: 1) they are derived from relatively small sample sizes; 2) they typically do not include TP; and 3) they are volume-based, and subject to potential inaccuracies of volumetric normalization methods. Here, we develop a surface-based probabilistic atlas of aMTL regions TP, PR, ER, and PH derived from hand drawings of gross anatomical boundaries in N = 100 young adult participants. Data were .7mm-resolution T1-weighted anatomical MR images from the Human Connectome Project (HCP) dataset. Regions were hand-drawn bilaterally on volumetric images using a protocol based on previously described sulcal and gyral landmarks corresponding to cytoarchitectonic boundaries between areas. Regions were then converted to standardized cortical surface coordinates (fsLR space) using the HCP normalization approach: cortical surface reconstructions for individual participants were generated using Freesurfer; regions were resampled to individual surfaces using ribbon-constrained mapping; and normalized to fsLR space using multimodal surface matching. Lastly, data were combined across participants to produce a probabilistic atlas specifying the likelihood of each area existing at a given surface coordinate. This work provides a useful tool for researchers studying the anatomy and functional of aMTL areas, and especially the poorly understood area TP, using surface-based analysis.

Theme I: Techniques

Yoga intervention improves ADHD and cognitive measures in emerging adults with ADHD

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Abstract

Attention Deficit/Hyperactivity Disorder (ADHD) is a chronic neurodevelopmental condition that is characterized by elevated levels of inattention, hyperactivity, and impulsivity. Adult ADHD often presents with disruptions to social life and work, as well as impairments in executive function.

The negative side-effects of pharmaceutical treatment led to a need to focus on non-pharmaceutical approaches. Yoga has been shown to enhance memory and emotional regulation (Basso et al. 2019), and improve attention and processing speed (Gothe & McAuley, 2015) in adults not diagnosed with ADHD. A recent meta-analysis suggests that yoga practice may be an effective form of intervention for children and adolescents with ADHD (Chimiklis et al. 2018). Yet, studies investigating the effectiveness of yoga on adult ADHD symptoms are mixed (Friz & O'Connor 2022, Dinu et al. 2023).

To address these gaps, we investigated the effectiveness of an 8-week yoga intervention on cognitive measures (continuous performance task, N-back, Stroop), and affective and attention self-report scales (ADHD, daily function, interoception, affect, sleep, stress, mindfulness). A total of 41 college students with ADD/ADHD participated. 22 received the intervention, 19 did not.

Preliminary analysis found that participants in the yoga group decreased their self-reported ADHD measures on the ASRS-v1.1 $z=3.76$, $p<0.001$, increased their interoception levels on six MAIA scales, $z=2.16$, $p<0.03$, and improved on number-correct in the 2-back task, $t=2.43$, $p<0.03$, over the 8-week time frame. An interpretation of these measures and comparisons to the control condition will be discussed.

Theme H: Cognition

Pathogenicity Assessment of Three Newer Alpha-Synuclein Mutants Under Varying Expression Levels in Yeast Reveals Differential Toxicity

Kate Feist, Shanamon Chandavimol, Sebastian Gacek, Federica Bertolotti, Amanda Grassel, Carris Borland, Shubhik DebBurman

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Abstract

Parkinson's Disease (PD) is the second most common neurodegenerative disorder characterized by the death of midbrain dopaminergic neurons. This selective cell death is linked with the misfolding and accumulation of the protein, □-synuclein. Six □-synuclein mutants previously linked with early-onset familial PD (A30P, E46K, H50Q, G51D, A53T, A53E) are extensively well-studied for their mechanism of toxicity. In contrast, three newer □-synuclein mutants linked with familial and sporadic PD (A18T, A29S, and A53V) are less well-understood for their underlying toxicity mechanisms. We characterized these three mutants in a budding yeast (S. cerevisiae) model and report that A18T, A29S, and A53V are all differentially toxic in yeast, with A53V being the most toxic, followed by A18T, and A29S. The level of mutant toxicity is correlated with □-synuclein aggregation, with A29S significantly less aggregated than the other two mutants. Each mutant's toxicity is also expression-dependent: at lower concentrations, all three mutants become less toxic and equalize to each other's level and lower than that of wildtype □-synuclein. These new mutants also reveal greater toxicity differentiation in several altered cellular/environmental conditions linked with PD: while all three are equally sensitive to altered SUMOylation, A18T and A53V are more sensitive to nitrative stress. We are currently evaluating whether the loss of the original amino acid (alanine) or the gain of the mutant amino acid (T, S, or V) is key to the toxicity of A18T, A29S, and A53V mutants. Specifically, the A53 position, we find more support for the gain of a new mutant rather than the loss of A, with toxicity linked with substitution mutants N, G, R, but not D. We are also testing the combinatorial impact of double mutants (A18T/A29S, A29S/A53V, A18T/A53V) and a triple mutant (A18T/A29S/A53V). Overall, our studies add new insight into the nature of toxicity of each of these rare mutants linked with PD.

Theme C: Neurodegenerative Disorders and Injury

Triangulating Neural Correlates of Consciousness

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Abstract

For decades the desire to understand the brain basis of subjective experience has been a major goal of neuroscience. Pioneering efforts by Christof Koch and Francis Crick resulted in the idea of neural correlates of consciousness (NCCs) which can be defined as the "minimal neural mechanisms that are together necessary and sufficient for experiencing any conscious percept." Previous approaches at identifying NCCs, such as backward masking, have seemed to successfully identify many candidate NCCs, but have had difficulty in distinguishing manipulation-specific effects from general features of subjective experience that would be required of a "necessary and sufficient" correlate. This project introduces a method of "triangulation" which should more accurately identify universally applicable NCCs. Our approach contrasts three distinct visual perception manipulations - backward masking, dichoptic color fusion, and inattentional blindness - all within the same experimental framework. By comparing electroencephalography (EEG) responses to seen and unseen visual stimuli across three different manipulations in the same subjects, we are able to focus on overlapping neural correlates. The identification of these common features will help to isolate those NCCs that are consistent across all three experimental paradigms. By employing machine learning to the analysis of EEG data, the triangulation method represents a significant advance in identifying the neural correlates of conscious visual experience.

Theme H: Cognition

A shortened chronic variable stress paradigm does not alter anxiety or motivated behaviors in female C57BL/6 mice

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Abstract

The chronic variable stress (CVS) paradigm has been used to model the effects of chronic stress in rodents. This intervention introduces mild, unpredictable, and ongoing stressors to rodents. Prior studies report a stress response after 4-8 weeks of CVS, varying depending on the frequency of the stressors or the specific animal used. In female C57BL/6 mice, 6 weeks of CVS elicits increased hypothalamic pituitary adrenal (HPA) axis responsivity. We hypothesized that a shortened CVS paradigm (23 days) would also increase HPA axis responsivity without altering behavioral measures of anxiety and motivation. We used 24 adult female C57BL/6 mice, 12 in a control condition that received no stressors, and 12 in the CVS condition. Mice in the CVS condition were exposed to 1-2 randomly assigned stressors each day of the study, including empty cage, damp bedding, light disturbance, white noise, novel object exposure, social stress, predator odor, and cage tilt. At the end of 23 days, behavior was measured in the elevated plus, open field, social motivation, marble burying, and sucrose preference tests. After behavior testing, mice were given an acute restraint stress prior to euthanasia, and blood was collected to measure cortisol levels. Overall, mice who underwent a shortened CVS paradigm did not differ from non-stressed mice on most behavioral measures. Ongoing analyses will compare cortisol levels between stressed and non-stressed mice. Ultimately, these data suggest a shortened CVS paradigm does not elicit robust behavioral changes in female C57BL/6 mice, which can be applied to future studies.

Theme F: Integrative Physiology and Behavior

Pathogenicity Assessment of Three Newer Alpha-Synuclein Mutants Under Varying Expression Levels in Yeast Reveals Differential Toxicity

Sebastian Gacek, Kate Feist, Shanamon Chandavimol, Federica Bertolotti, Amanda Grassel, Carris Borland, Shubhik DebBurman

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Abstract

Parkinson's Disease (PD) is the second most common neurodegenerative disorder characterized by the death of midbrain dopaminergic neurons. This selective cell death is linked with the misfolding and accumulation of the protein, alpha-synuclein. Six alpha-synuclein mutants previously linked with early-onset familial PD (A30P, E46K, H50Q, G51D, A53T, A53E) are extensively well-studied for their mechanism of toxicity. In contrast, three newer alpha-synuclein mutants linked with familial and sporadic PD (A18T, A29S, and A53V) are less well-understood for their underlying toxicity mechanisms. We characterized these three mutants in a budding yeast (S. cerevisiae) model and report that A18T, A29S, and A53V are all differentially toxic in yeast, with A53V being the most toxic, followed by A18T, and A29S. The level of mutant toxicity is correlated with alpha-synuclein aggregation, with A29S significantly less aggregated than the other two mutants. Each mutant's toxicity is also expression-dependent: at lower concentrations, all three mutants become less toxic and equalize to each other's level and lower than that of wildtype alpha-synuclein. These new mutants also reveal greater toxicity differentiation in several altered cellular/environmental conditions linked with PD: while all three are equally sensitive to altered SUMOylation, A18T and A53V are more sensitive to nitrative stress. We are currently evaluating whether the loss of the original amino acid (alanine) or the gain of the mutant amino acid (T, S, or V) is key to the toxicity of A18T, A29S, and A53V mutants. We are also testing the combinatorial impact of double mutants (A18T/A29S, A29S/A53V, A18T/A53V) and a triple mutant (A18T/A29S/A53V). Overall, our studies add new insight into the nature of toxicity of each of these rare mutants linked with PD.

Theme C: Neurodegenerative Disorders and Injury

Evidence of Active-Forgetting Mechanisms? Blocking Arachidonic Acid Release May Slow Forgetting of Sensitization in Aplysia

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Abstract

Long-term sensitization in Aplysia is accompanied by a persistent up-regulation of mRNA encoding the peptide neurotransmitter Phe-Met-Arg-Phe-amide (FMRFa), a neuromodulator that opposes the expression of sensitization through activation of the arachidonic acid second-messenger pathway. We completed a preregistered test of the hypothesis that FMRFa plays a critical role in the forgetting of sensitization. Aplysia received long-term sensitization training and were then given whole-body injections of vehicle (N = 27), FMRFa (N = 26), or 4-bromophenacylbromide (4-BPB; N = 31), a phospholipase inhibitor that prevents the release of arachidonic acid. FMRFa produced no changes in forgetting. 4-BPB decreased forgetting measured 6 d after training [ds = 0.55 95% CI(0.01, 1.09)], though the estimated effect size is uncertain. Our results provide preliminary evidence that forgetting of sensitization may be a regulated, active process in Aplysia, but could also indicate a role for arachidonic acid in stabilizing the induction of sensitization.

Theme H: Cognition

Establishing directionality of information flow during post-retrieval monitoring in episodic memory

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Abstract

The cognitive processes of episodic memory retrieval and monitoring the quality of the retrieved information require extensive coordination and communication between distinct brain regions. The role of these regions, including the frontal cortex, parietal cortex, and hippocampus, in these memory processes has been well established through previous research. Prior studies have also highlighted the left inferior parietal cortex (IPC) and right dorsolateral prefrontal cortex (dlPFC) as critical areas of interest for post-retrieval monitoring. Interactions between these regions are regulated by theta oscillations (3-8 Hz), allowing for the formation of transient functional neural networks that facilitate the performance of complex cognitive tasks. Despite an established understanding of the structural and functional connectivity of the hippocampal-parietal-frontal network during episodic memory retrieval, the directionality of the information flow within this network is not yet understood. This in-progress study employs electroencephalography (EEG) to record participants performing a source retrieval task. Renormalized partial directed coherence (rPDC), a method derived from Granger causality analysis, is used to determine the direction of information flow. In addition, source localization is improved by obtaining three-dimensional scans of each participant's head, enabling us to capture individualized scalp electrode positions. Based on previous research, we expect to find left IPC to right dlPFC information flow at theta frequency during post-retrieval monitoring of episodic memory. The results obtained from this study will advance our current understanding of the functional networks underlying episodic memory retrieval and provide new insights into the mechanisms of cognitive control and coordination across different brain regions.

Theme H: Cognition

Decoding learned content during sleep: A representational similarity approach

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Abstract

Memory reactivation during sleep is known to play a vital role in memory consolidation, but finding evidence of reactivation in human sleep is still challenging. This study aims to use representational similarity analysis (RSA) to investigate whether EEG activity recorded during sleep carries information about the category of content learned prior to sleep. Participants completed two separate study visits where they engaged in learning about animals associated with either scenes or objects. Following the learning session, participants took a nap while their brain activity was recorded using EEG. We will extract neural patterns of activity from each sleep stage, in each nap (post-scene and post-object learning naps), and in each participant. We will assess representational similarity by correlating brain activity patterns between participants. We predict that if learning content is being reprocessed during sleep, there will be higher within- than between-category similarity, suggesting that brain activity is more similar between participants when they learned about animals paired with the same category than a different category. This study has the potential to advance our understanding of how learning shapes neural activity during subsequent sleep and can inform future work investigating how memory reprocessing during sleep sculpts long-term memory.

Theme H: Cognition

Antinociceptive effects of dual fatty acid amide hydrolase and soluble epoxide hydrolase inhibitors in rat models of inflammatory pain

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Abstract

Pain is a common reason people seek medical attention, yet many long-term treatments such as opioids produce both dangerous and unpleasant side effects. New treatments that target novel mechanisms of action are required to improve both safety and efficacy. Fatty acid amide hydrolase (FAAH) and soluble epoxide hydrolase (sEH) are two pain-related enzymes. Simultaneous inhibition of FAAH and sEH promotes endogenous anti-inflammatory molecules to reduce pain synergistically. This approach achieves alleviation of a greater amount of pain compared to single-target methods. We hypothesized that dual inhibition of FAAH and sEH using one compound will alleviate inflammatory pain mediated by two different neuroanatomical systems in male and female rats. We synthesized several analogs of dual FAAH/sEH inhibitors and used two variations of the formalin test to induce acute inflammatory pain in the paw and orofacial region of rats. Rats were pre-treated with varying doses (0.1-3 mg/kg) of our dual inhibitor, vehicle, or a positive control drug (ketoprofen for hind paw inflammation, sumatriptan for orofacial inflammation). Our dual inhibitors alleviated hind paw inflammation to an equal degree as ketoprofen, although at lower doses. However, the effects of dual FAAH/sEH on orofacial inflammation varied on the dual inhibitor, dose, and dosing regimen. Dual FAAH/sEH inhibition may be sufficient to inhibit hindpaw inflammation but not orofacial inflammation potentially due to the lack of blood-brain barrier (BBB) penetration by the inhibitors. Future studies will determine the efficacy of BBB-penetrant dual FAAH/sEH inhibitors on orofacial and hindpaw inflammation in rats.

Theme F: Integrative Physiology and Behavior

Cholinergic mechanisms of Pavlovian conditioned approach behavior in rats

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Abstract

Co-use of nicotine and alcohol is common in humans, with alcohol cues often functioning as Pavlovian conditioned stimuli. Pavlovian conditioned approach behavior can be displayed through sign- and/or goal-tracking. Previous studies have yielded contrasting results regarding nicotine's effects on sign- and goal-tracking behavior. We addressed this conflict by training rats under identical parameters with different rewards that were equated for caloric content. Male and female rats were exposed to 15% ethanol in an intermittent access 2-bottle-choice procedure. Subsequently, rats received 24 training sessions in which a CS+ lever, paired with a reward (15% ethanol or 21.3% sucrose), and a CS- lever, not paired with a reward, were presented. Prior to each conditioning session, rats were injected with nicotine (0.4 mg/kg) or saline (1 mL/kg). Sign-tracking behavior was measured by CS+, relative to CS-, lever presses and goal-tracking behavior was measured by entries into the reward receptacle, normalized for pre-CS baseline entries. Nicotine enhanced sign-tracking discrimination between the CS+ and CS- levers, and the sucrose group showed quicker sign-tracking discrimination across sessions, although this did not interact with drug treatment. Nicotine also affected goal-tracking discrimination, such that the nicotine group learned to discriminate between the CS+ and CS- levers whereas the saline group did not. This effect depended on reward identity. There were no effects of sex on either measure. These results demonstrate that nicotine can augment both sign-tracking and goal-tracking to reward-associated cues, and hence underscore the importance of nicotinic acetylcholine receptors in modulating various forms of learned behavior.

Theme G: Motivation and Emotion

Generalization between two types of reward learning in β-arrestins 2 knockout mice

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Abstract

Dopamine signaling in the striatum is essential for animals to properly learn. As part of learning, animals must be able to discriminate between different stimulus-reward contingencies, as well as properly generalize (but not over-generalize) their previous learning to novel environments. β-arrestins are scaffold proteins that desensitize G-protein coupled receptors and serve as an important temporal modulator of dopamine signaling. Here, we tested the ability of β-arrestin 2 knockout (BA2KO) mice to (1) learn and discriminate short and long cues (2) generalize their previous learning to the opposite cue type. We trained naive BA2KO in an appetitive Pavlovian learning paradigm that tested their ability to learn to predict a sucrose reward based on either a short cue (10s light signal) or a long cue (2 minute light signal) over a two-week period. After one week of hiatus, the same mice were then trained on the opposite conditioning paradigm for an additional two weeks (task switch). In the first task, both BA2KO and littermate controls learned both the short and long cue tasks to equal proficiency. After the task switch, both BA2KO and littermate controls were likewise able to learn both tasks even after their initial training. However, BA2KO mice that were first trained on the long cue task displayed an apparent generalization of that training when they were then switched to the short cue task that warrants further investigation. We hope these results will further an understanding of the mechanisms underlying adaptive behavior and dopamine-dependent learning processes.

Theme F: Integrative Physiology and Behavior

Time On Task is More Predictive of Undergraduate Success in a Neuropharmacology Course than Visual Spatial Ability

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Abstract

In general education neuropharmacology courses, students are introduced to new content without prior knowledge requirements. These courses rely on spatial reasoning to help students visualize complex concepts like neuronal pathways, synapses, electrochemical signaling, and receptor population changes. While spatial reasoning is known to predict success in STEM fields such as engineering, chemistry, biology, and mathematics, its influence on success in neuroscience is less understood. To help students better grasp neuropharmacology concepts, we created assignments using BioRender, a software tool that allows users to create high-quality scientific and biomedical illustrations with customizable elements. We measured students' visualization skills with the Purdue Spatial Visualization Test-Visualization of Rotations (PSVT:R), a timed test that challenges students to mentally rotate three-dimensional objects based on complex illustrations. Female students in our study scored lower on the PSVT:R, consistent with previous research. Our study explored the relationship between visual-spatial reasoning test scores and the time spent on BioRender assignments as predictors of student performance on neuropharmacology exams, which included both illustration and multiple-choice questions. We found that the percentage of completed BioRender assignments was a stronger predictor of student success than their innate visual-spatial ability (PSVT:R). Additionally, we used the Visual, Auditory, Reading, or Kinetic (VARK) test to determine students' preferred learning styles. However, we found no correlation between visual learning preference and visual-spatial ability or exam scores. Our findings suggest that time invested in BioRender assignments was a more significant factor in student success than natural visual-spatial abilities, regardless of preferred learning style.

Quantifying Behavioral Response to Alarming and Novel Stimuli in Larval Zebrafish

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Abstract

Consistent increases in global temperatures due to climate change is predicted to have critical implications on the habitat of aquatic animals like the Danio rerio. Previous works produced inconsistent results on the effect of raising in high temperatures on behavioral response to alarming and benign cues. Some papers suggested that elevated temperatures during zebrafish development reduces locomotion, while others reported increased swimming distance and speed. To reduce inconsistency, we recorded fear responses to benign or alarming olfactory and visual stimuli for zebrafish raised in normal (28° Celsius) and raised (32° Celsius) temperatures. Fear responses include increased motility after exposure. For olfactory response, we used an alarming stimulus known as schreckstoff (chemical cue released by injured conspecifics) and glutamic acid, a benign cue. For visual response, we used a looming stimulus as an alarm cue and a rotating pinwheel as a benign cue. Results indicate minimal difference in fear response to the cue versus control. Comparing temperature groups, 32° C raised fish exhibit reduced locomotive response for both stimuli modalities. Differences in responses between temperature groups are likely supported by a difference in neuronal activity patterns as zebrafish are presented with stimuli. Light bead microscopy provides preliminary evidence of reliable recordings from multiple brain areas. Future analysis of fear response should consist of imaging the olfactory bulb and optic tectum during cue exposures. Future directions should evaluate downstream pathways which are developmentally affected by increased temperatures, such as the habenula, which is implicated in zebrafish experience-dependent regulation of fear responses.

Theme F: Integrative Physiology and Behavior

Stress-Evoked Astrocyte-Neuron Dynamics in the Lateral Hypothalamus

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Abstract

The lateral hypothalamus (LH) is a critical region for regulating sleep, wakefulness, feeding, and stress responses. Despite extensive research on neuronal functions within the LH, the role of astrocytes and their interactions with neurons in this region remains underexplored. This study investigates how neurons and astrocytes in the LH modulate acute stress responses. To that end, we performed dual-color fiber photometry in the LH to simultaneously measure neuronal and astrocytic calcium dynamics as mice underwent tail suspension, elevated zero maze, and fear conditioning. We found that neurons and astrocytes in the LH are independently tuned to key events and/or behavioral state transitions in each acute stressor task, but also become more synchronous in their activity to each other compared to non-stressful, home cage conditions. Our findings demonstrate that astrocytic activity in the LH is specifically recruited during functionally relevant instances, playing a complementary and non-redundant role to neuronal activity in modulating behavioral responses to acute stress. These interactions may yield crucial, real-time insights into the contribution of different cell types in the brain and their impact on stress-related behaviors.

Theme F: Integrative Physiology and Behavior

Effects of Post-Training Dopaminergic and Beta-adrenergic Antagonism on Sensitization

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Abstract

Memory consolidation processes contribute to conditioned hyperactivity and sensitization. However, the underlying neural systems that mediate memory consolidation, and their impact on conditioned hyperactivity and sensitization are poorly understood. The present experiments examined if antagonism of the dopaminergic and noradrenergic systems, specifically the dopaminergic D2 and beta-adrenergic receptors, respectively, disrupted memory consolidation and subsequently blocked the development of conditioned hyperactivity and sensitization. Following 4 weeks of acclimation, male, Swiss Webster mice received either a single injection (intraperitoneal, i.p.) of physiological saline (vehicle) or methamphetamine (2.0 mg/kg) prior to a single 30-minute locomotor activity session (Conditioning). Immediately or 2 hours after the conditioning session, mice received ether an injection (i.p.) of physiological saline (vehicle) or the dopaminergic D2 receptor antagonist, haloperidol (40 mg/kg; Experiment 1), or distilled water (vehicle) or the non-selective (β1/β2) receptor antagonist. propranolol (16 or 32 mg/kg; Experiment 2), and then returned to their home cages. Following the conditioning session, tests for conditioned hyperactivity (CR Test) and behavioral sensitization (Methamphetamine Challenge Test) occurred after a delay of 6 and 7 days, respectively. An injection of physiological saline or methamphetamine (1.0 mg/kg) occurred on the CR Test and Methamphetamine Challenge Test, respectively. Distance traveled served as the dependent measures of locomotor activity. A single injection of methamphetamine produced robust conditioned hyperactivity and sensitization. Neither immediate post-injection of haloperidol nor propranolol disrupted conditioned hyperactivity but propranolol dose-dependently attenuated sensitization. Taken together, these results indicate that neither dopaminergic nor beta-adrenergic antagonism disrupted memory consolidation and subsequent conditioned hyperactivity whereas post-training antagonism of beta-adrenergic receptors disrupted development of sensitization through a non-memory consolidation process(es).

Theme G: Motivation and Emotion

Sex, drugs, and working memory: The effect of sex differences and MK-801 administration on learning in the delayed alternation task in the rat

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Abstract

The prefrontal cortex (PFC) is implicated in working memory (WM) processing in both humans and rats. Impaired working memory function is a common symptom in patients with Schizophrenia (Jannus et al 2023, Wozniak et al 1990). Past research suggested that the deficit in schizophrenia patients may be associated with an inability to accurately encode information to be held in working memory (Lee and Park, 2005). This raises the question of whether working memory deficits seen in patients with schizophrenia or models of the disease are an acute effect of working memory performance, or an effect of impaired learning due to the chronic nature of the disorder.

In order to answer this question, we have employed the non-competitive NMDA receptor antagonist MK-801 to create a chronic learning impairment (LI) in one group of rats which we will compare to a control (C) group given saline injections. We used 18 Long-Evans rats (10 F, 8 M) to compare the effects of sex on WM and drug effects, due to the historical prevalence of male rats in neuroscience research. We trained both groups of rats to perform a delayed alternation lever press task under the differential drug conditions, followed by 2 test phases. In phase 1, all animals performed the WM task with saline injections to compare the effect of LI without acute drug effects. In phase 2, all groups received MK-801 to assess the effects of LI combined with drug effects in both groups.

Theme H: Cognition

Investigating the effects of Parkinson's disease-associated mutations on alpha-synuclein protein aggregation in vivo

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Abstract

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder affecting approximately 1% of the population over 60 years of age (Tysnes & Storstein, 2017). The mechanistic origins of PD remain a mystery, thus therapies can only mitigate Parkinson's symptoms without halting the progression of the disease. A definitive clinical diagnosis requires a post-mortem autopsy revealing Lewy bodies: aggregated alpha-synuclein protein that cluster in the cytoplasm of neurons. Alpha-synuclein is a 140-amino-acid-long protein that regulates neurotransmitter release, vesicle cycling, and has been linked to the DNA repair processes (Spinelli et al., 2014, Schaser et al., 2019). However, the mechanisms of aggregation and the role of Lewy bodies in PD remain poorly understood. Familial forms of PD, which make up less than 10% of cases, have revealed at least six alpha-synuclein point mutations, all of which result in autosomal dominant synucleinopathies (Klein & Westenberger, 2012). These mutations have been suggested to either promote or inhibit protein aggregation in vitro. Our approach uses various forms of transiently expressed human alpha-synuclein tagged with GFP (green fluorescent protein) in live zebrafish larvae. We then use in vivo Fluorescence Recovery After Photobleaching (FRAP) at 4 days post fertilization to measure the mobility of human A53E-alpha-synuclein, E56K-alpha-synuclein, and wild-type alpha-synuclein. This methodology will provide real-time insights into the aggregation dynamics of these mutations. Understanding the etiology of PD at the level of alpha-synuclein aggregation may be a crucial step toward ultimately developing an effective treatment to halt disease progression.

Theme C: Neurodegenerative Disorders and Injury

Cannabinoid receptor 2 deficiency directs sex-specific increase in tau phosphorylation in organotypic brain slice cultures

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Abstract

Cannabinoid receptor-2 (CB2) is an endocannabinoid receptor expressed in peripheral immune cells and activated microglia and upregulated in postmortem patient tissue and animal models of Alzheimer's disease (AD). Studies pharmacologically targeting CB2 show improved cognitive function and reduced amyloid plaque burden in amyloid-driven AD animal models suggesting the CB2 activation has ameliorative effects. However, there is limited data evaluating the role of CB2 in tau aggregation as found in tauopathies. Therefore, we evaluated tau accumulation and solubility in organotypic brain slice cultures transduced with AAVs to overexpress human mutant tau (P301L) from WT-CB2-expressing (n=10) and CB2-deficient (n=10) mice. Fractions collected post-transduction (28 days) were evaluated using western immunoblotting for total tau (T44), phosphorylated tau (ptau; AT8), and inflammation (NFκB, TMEM119). Initial findings evaluating human tau across fractions demonstrated the largest accumulation was found in the first two fractions, suggesting a model with greater soluble forms of tau. The evaluation of these fractions yielded significantly higher human ptau (p=0.037) and mouse ptau (p=0.015) in female CB2-deficient mice compared to WT in the high-salt fraction, whereas in the triton-X fraction, mouse ptau levels were significantly higher in female slices (p=0.008), independent of genotype. Furthermore, we found a trend for lower levels of NFκB (p=0.087), TMEM119 (p=0.0730) in CB2-deficient female cultures independent of genotype in the triton-X fraction. Results suggest CB2 alters tau phosphorylation in a sex-dependent manner, potentially by modifying microglial responses. Future studies will evaluate a model with greater insoluble tau accumulation, extending findings to a model of toxic tau aggregation.

Theme C: Neurodegenerative Disorders and Injury

The Fish Brain Response to Injury Elicits Differential Expression of the Pim Kinase Proto-Oncogenes

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Abstract

In response to injury, the brain repair capability of mammals is severely limited due to an inability to replace lost cells. In contrast, fish have tremendous brain repair capacity and in response to injury, the fish brain undergoes a tremendous amount of cell proliferation. The serine/threonine pro-survival Pim kinase proto-oncogenes are well-known promoters of cell proliferation. To examine whether the Pim kinases may be involved in the brain reparative process of fish, we characterized their temporal gene expression levels during the brain response to injury in the mummichog (Fundulus heteroclitus) over the course of four days, focusing on the midbrain/diencephalon (MB/DI). In addition, we followed the temporal expression profiles of proliferating cell nuclear antigen (pcna) gene, a marker of cell division, as well as neurod2, a marker of neurogenesis (to examine the state of neural differentiation), and finally, cyclin-dependent kinase inhibitor 1 (cdkn1), as Pim kinases promote cell proliferation in tumors by inhibiting its expression. Over the course of four days, relative pim kinase expression increased, peaking at two days post-injury (2DPI) and subsiding by four days post-injury (4DPI). The levels of pcna increased at 2DPI and subsided at 4DPI, while neurod2 and cdkn1(bb) gene expression levels remained low. Differential expression patterns of the pim kinase genes and pcna suggest that Pim kinases may influence cell proliferation in the brain repair process of fish by inhibiting the transcription of cdkn1(bb). Supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number P20GM103499.

Theme C: Neurodegenerative Disorders and Injury

Cognitive effects of intra-striatal injection of alpha-synuclein preformed fibrils in young versus aged rats

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Abstract

Alpha-synuclein is a protein that has commonly been implicated in Parkinson's disease (PD). Intra-striatal injections of alpha-synuclein preformed fibrils (PFFs) in rats are used to model cognitive and motor symptoms of Parkinson's disease but aged animals are rarely used despite age being the major risk factor for PD. We studied the effects of alpha-synuclein PFFs in young versus aged rats. Sixty-three male Fischer 344 x Brown Norway F1 hybrid rats, either young (6 months) or aged (20 months), received injection of alpha-synuclein PFFs (experimental group) or alpha-synuclein monomers (control group) into bilateral striatum. Two months post-surgery, rats were tested on a delayed response working memory task followed by a probabilistic reversal learning task. We hypothesized that working memory and cognitive flexibility would deteriorate more rapidly in aged compared to young rats injected with PFFs. Data to date show that aged PFF rats perform numerically worse on the working memory task in comparison to the other groups, especially at long retention delays. Results from the reversal learning task were consistent with the working memory data, and show that aged but not young PFF rats completed fewer reversals than monomer-injected controls (three-factor, repeated measures ANOVA, group X age interaction, $F(1,16)=8.49$, $p=.01$). The initial results suggest that this aged rat model can replicate cognitive deficits seen with progression of PD and other synuclein-associated dementias.

Theme C: Neurodegenerative Disorders and Injury

Modulation of Vertebrate Spinal Locomotor Activity via Temperature and Ion Channel Function

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Abstract

Mammals depend on intact sensorimotor systems to adapt and respond to changes within their external and internal environments to maintain homeostasis. Specifically, temperature sensation via ion channel function allows organisms to adapt their physiology to extreme heat or cold conditions and to monitor fever and inflammatory responses to infection or injury. While it is known that dysregulation of temperature sensation clearly influences human health, the causes and specific cellular mechanisms responsible for this dysregulation and the direct effects of temperature on neural motor networks are relatively unknown. To study the effects of temperature on mammalian spinal central pattern generator (CPG) networks, spinal cords from postnatal mice one to six days old (P1 – P6) were used. Extracellular recordings were obtained from L2 (flexor) and L5 (extensor) ventral roots. Once stable locomotor-like activity was achieved with the application of serotonin and NMDA, we applied either capsaicin (to activate heat receptors) at a concentration of 1microM or menthol (to activate cold receptors) at a concentration of 200microM. Interestingly, we found an age-dependent effect on the modulation of these temperature-mediated channels by both capsaicin and menthol. The most significant increase in spinal network excitability was seen in younger pups (0-3 days old) after capsaicin application and the greatest decrease in neural excitability in the oldest age group (4-6 days old) after menthol application. Thus, the early postnatal age of mammals appears to play a role in the ability for motor neural networks to respond and adapt to temperature fluctuations.

Theme E: Motor Systems

The Effect of Thyroid Hormone Levels on Brain-wide Response to Acute Social Stressors in Mice

Rexhebije Kadriu, Jovian Cheung Sanjeev Janarthanan, Laura Lynch, Alissa Le, Danielle Roberts, Shannon Bennett, Annegret Falkner, Catherine Peña

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Abstract

Thyroid dysfunction during adulthood affects behavior, while early life suppression could have effects on brain development that also lead to later behavioral changes. Specifically, thyroid hormone production contributes to brain development and thyroid hormone levels in adulthood are known to influence mood, although little is known about how different brain circuits may be impacted by developmental or adult thyroid dysregulation. This project focuses on the manipulation of thyroid hormones and its effects on brain-wide responses towards acute stressors. We hypothesize that suppression of thyroid hormone levels, either during early life and/or in adulthood, alters brain circuit-level response to social defeat stress in mice.

Theme A: Development

Phosphorylated Peptide Enrichment for Phosphoproteome Analysis in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is characterized by cognitive decline and neuropathological changes attributed to the aggregation of extracellular amyloid-beta plaques and intracellular tau-containing neurofibrillary tangles. Abnormal phosphorylation may contribute to neurotoxicity by altering protein structure and function. In addition to tau hyperphosphorylation, global phospho-dependent signaling cascades are implicated in AD pathogenesis. Phosphoproteomics allows for the enrichment and identification of proteins from these pathways to describe biomarkers and putative therapeutic targets. However, the study of phosphoproteins is often difficult due to their low abundance and co-existence with their non-phosphorylated isoforms in the cell. Immobilized metal affinity chromatography followed by label-free liquid chromatography-tandem mass spectrometry (LC-MS/MS) was implemented to investigate the phosphoproteome in this study. The inclusion criteria for the human AD brain tissue were based on pathological scoring, such as amyloid burden and tau pathology. Brain lysates from AD and non-demented control frontal cortex were digested and underwent phospho-peptide enrichment with re-charged magnetic Fe3+-NTA beads before LC-MS/MS analysis. MS raw files were searched with FragPipe to identify proteins, missing values were imputed, and statistical tests were performed to derive differentially enriched proteins and gene ontology groups. Consistent with prior studies, 14-3-3 binding proteins were highly phosphorylated in AD brain tissue. Future studies will scale up and automate phosphopeptide enrichment in brain tissue and additional biofluids, such as in cerebrospinal fluid (CSF) and plasma, to further understand AD biomarkers and mechanistic pathways. A deeper understanding of brain tissue, CSF, and plasma biomarkers may allow for non-invasive AD diagnoses and reveal novel therapeutic pathways.

Synucleinopathies: Molecular Determinants of β-Synuclein and γ-Synuclein Toxicity in a Yeast Model

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Abstract

Synucleinopathies, a group of disorders characterized by the abnormal folding and aggregation of proteins from the synuclein family (including α-, β-, and γ-synuclein), encompass Parkinson's Disease (PD), the second most prevalent neurodegenerative condition. While α-synuclein's role in PD is well-researched, less is understood about the involvement of β- and γ-synucleins in neurodegeneration and toxicity. However, two mutations in β-synuclein (P123H and V70M) are associated with Dementia with Lewy Bodies (DLB), and γ-synuclein inclusions are linked with ALS pathology. At SfN2023, we reported that -synuclein are differentially toxic, whereas γ-synuclein is non-toxic in our Saccharomyces cerevisiae (budding yeast) PD model system. Here, we further evaluated the toxicity potential of β- and γ-synuclein by looking at their toxicity, localization, and expression using yeast assays. We evaluated substitution mutants for disease- causing β-synuclein mutations V70M and P123H, by changing the original amino acid with a different hydrophobic residue (V70), and with other polar and basic residues (P123). We expressed mutants swapping known familial mutations in α- and β-synuclein onto each other (α-, β- and γ-synuclein). We report that: 1) Substitution mutants show evidence for the gain of polar and basic amino acid cause toxicity in P123H-β-synuclein mutant, while hydrophobicity is key for V70M-β-synuclein toxicity; 2) α-synuclein familial mutations when swapped into β-synuclein show that amino acids A18, A29, A30, E46, G51, and A53 can regulate β-synuclein toxicity; 3) however, γ-synuclein's non-toxicity is unaltered when swapped with α-/β-, familial mutations at A18, A30, E46, and V70. This study highlights the usefulness of yeast models in better understanding β- and γ-synuclein pathogenicity in neurodegeneration.

Theme C: Neurodegenerative Disorders and Injury

Molecular and functional profiling of vagal sensory neurons

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Abstract

Dysregulation of cardiac autonomic motor or sensory circuits can result in arrhythmias. Yet current surgical or pharmacological treatments primarily target motor circuits but not cardio-sensory neurons. Studying the role of cardio-sensory circuits in mammals has been challenging because in vivo neural activity measurements in vagal sensory neurons (the major conduits of viscerosensory information) require invasive procedures and anesthesia. Here, we leverage the larval zebrafish optical and genetic accessibility to track the function and development of vagal sensory neurons in 5 to 12 days post-fertilization fish. We have developed experimental protocols and techniques for molecular and functional profiling of the entire sensory vagus system in larval zebrafish throughout development. Our study sets the stage for systems-level studies of molecularly defined groups of vagal sensory neurons and their involvement in cardiac arrhythmia, as well as modulation of brain activity and behavior.

Theme F: Integrative Physiology and Behavior

Rescuing sustained attention capability in aged rats using a combined therapy of nicotinic acetylcholine receptor allosteric modulation and environmental enrichment after experimental brain trauma

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Abstract

Traumatic brain injury (TBI) is a leading cause of death and disability and poses significant challenges for elderly populations, often exacerbating existing age-related cognitive decline. Empirical evidence suggests disruptions in cholinergic neurotransmission following TBI may contribute to cognitive deficits. Therapies that enhance acetylcholine (ACh) transmission may ameliorate cognition, especially in conjunction with noninvasive rehabilitation, which is akin to the real world. We have shown that a parietal cortex TBI induces deficits of complex attention in young adult rats, males and females. We predicted that parietal injury in aged (15-16 months old) male rats will augment sustained attention deficits compared to young adults. We then hypothesized that chronic NS-1738, a novel positive allosteric modulator (PAM) of the α7 nicotinic ACh receptor (α7-NAChR) will improve sustained attention post-TBI in aged rats, alone and in combination with environmental enrichment (EE), a pre-clinical neurorehabilitation model. Aged male rats were trained in the 3-choice serial reaction time task (3-CSRT) prior to a right parietal controlled cortical impact (2.8 mm cortical deformation depth) or sham injury. They required more sessions to reach criterion than young adults, especially as cue durations shorten. Following a controlled cortical impact (CCI) of moderate severity to the right parietal lobe or sham injury, rats were randomized to daily NS-1738 (5 mg/kg) or vehicle, as well as daily EE (24h) or standard housing for a month starting post-injury day (PID) 1. 3-CSRT retrials occurred on PID 17-27. Statistical analysis utilized repeated measures ANOVAs with Newman- Keuls post hoc tests. Anxiety-like behavior was assessed via the well-validated open field test (OFT) on PID 28. Cortical lesion volumes were assessed post-sacrifice. TBI-induced cognitive deficits were pronounced in aged rats ($p<0.05$) and were rescued by chronic NS-1738 ($p<0.05$). Moreover, NS-1738+EE rendered an additive effect on restoring accuracy and lowering omissions ($p<0.05$). TBI reduced OFT center exploration without reductions in ambulation ($p<0.05$). NS-1738 and EE housing individually restored center exploration, suggestive of ameliorating anxiety-like behavior ($p<0.05$). While both NS-1738 and EE rendered trends on reducing the extent of cavitation, the combined therapy was ineffective at promoting tissue preservation in preliminary findings. Our findings reflect the vulnerability of the elderly following TBI and support benefits of α7-NAChR PAM and/or EE treatment after experimental brain trauma on sustained attention through cholinergic neurotransmission.

Theme C: Neurodegenerative Disorders and Injury

The Effect of Synthetic Alarm Substance (C5H4N4O2) on Established Zebrafish Shoals

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Abstract

Zebrafish (Danio rerio) are a valuable model for studying social behavior due to their highly gregarious nature, which includes shoaling. Shoaling occurs when members of a group of fish congregate loosely, with limited coordination of movement among the members. When a predator attacks a shoal member, the injured fish releases an epithelial alarm substance which serves as a threat signal to other shoal members. Previous studies indicate that exposure to alarm substances disrupts shoaling and elicits anti-predatory responses, including freezing, darting, and bottom-dwelling. The present study explored the responses of small mixed–sex shoals (n = 4, 2 males & 2 females each) exposed to an alarm-substance as part of a Open-Tank Free-Swim Test (OTFST). Adult wild-type zebrafish were used in control and experimental shoals in 5L tanks flanking either side of the tank holding a single subject for a related study (SfN Abstract #9862, PSTR122). The experimental shoal was exposed to 1.5 nM concentration of the synthetic alarm substance; the control shoal remained unperturbed. Digital video recordings were obtained during the OTFST and subsequently analyzed using EthoVision XT 15.0. While shoals demonstrated considerable variability in intraindividual movement and shoal density, there are pronounced differences between intact and alarmed shoals. Compared with members of intact shoals, members of alarmed shoals spent substantially less time in the upper half of the tank, a behavioral marker of anxiety in fish. Understanding these responses in regard to fear contagion has implications regarding anxiety, fear responses, and potentially research on neurodevelopmental disorders of social development.

Theme F: Integrative Physiology and Behavior

Localization of dopamine D2a and D1Aa receptor expression in the central auditory system of a vocal fish

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Abstract

The plainfin midshipman is a seasonally reproducing, vocalizing fish with robust increases in peripheral auditory sensitivity during the summer breeding season that enhance the detection of social acoustic signals for reproduction. In the summer, decreases in dopamine innervation of the inner ear coupled with decreased expression of the inhibitory dopamine D2a receptor contribute, in part, to their enhanced auditory sensitivity. Seasonal changes in catecholaminergic innervation of central auditory nuclei are also observed, however, the functional role of dopamine in these areas remains unclear, particularly its role in modulating auditory processing. As a first step towards elucidating the function of dopaminergic action on the central auditory system, we utilized fluorescence in situ hybridization to characterize the expression of inhibitory dopamine D2a and excitatory dopamine D1Aa receptor transcripts in the brains of reproductive adult female midshipman fish. Our preliminary data suggests both D1Aa and D2a receptor expression in telencephalic (medial area dorsalis of the telencephalon, supracomissural nucleus), diencephalic (anterior tuberal nucleus, central posterior nucleus of the thalamus), midbrain (torus semicircularis), and hindbrain (descending octaval nucleus) auditory nuclei, with D2a receptor expression generally being predominant. Robust D2a but not D1Aa expression appears to be localized to the dopaminergic neurons in the periventricular posterior tuberculum, responsible for driving the seasonal changes in dopamine innervation of the inner ear and, in part, other central auditory centers. These findings provide a first step towards understanding the modulatory role of dopamine in the central auditory system of a seasonally reproducing vocal vertebrate.

The Role of the Main Olfactory Epithelium During Motherhood

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Abstract

Motherhood is associated with significant, behavioral, emotional, and physiological changes. Offsprings require significant parental care, making appropriate maternal behavior essential for their survival. Focusing on the main olfactory epithelium (MOE), we aim to investigate whether molecular changes in the MOE could enhance olfactory-guided maternal behaviors. For this purpose, we will use pup urine as a chemosensory cue and a neutral odor on opposing sides of a track in a tri-chamber to test both mothers at postpartum day 5 (PPD5) and virgin females preference. Using behavioral testing, RNA scope, and immunohistochemistry, we will determine 1) if the MOE is involved in enhancing mothers' preference toward pup olfactory chemosensory cues, and 2) whether two known genes, important for establishing maternal behavior in the brain, mainly prolactin receptor (prlr) and paternally expressed gene 3 (peg3), are also present at the level of the MOE and could play a key role in modulating maternal behavior in response to pup related olfactory cues. Our results indicate that mothers, unlike virgin females, prefer pup odor at PPD5 but not during pregnancy. Moreover, we have demonstrated that prlr and peg3 are both differentially expressed in the MOE during the transition of motherhood. These findings point to the adaptability and responsiveness of the MOE to both internal changes, such as hormonal variations, and external stimuli, including pup olfactory chemosensory cues, thereby facilitating maternal adjustment and behavior.

Theme F: Integrative Physiology and Behavior

Resocialization Rescues Deleterious Sleep Effects of Developmental Isolation in Drosophila melanogaster

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Abstract

The intense—and lengthy—social isolation of the Covid-19 pandemic inflicted unknown consequences on our brains and behavior. Young children may have been the most affected, isolated during critical periods of neurodevelopment. A previous study demonstrated the deleterious effects of larval social isolation on sleep in the fruit fly Drosophila melanogaster. To further isolate critical periods of social development on sleep, this experiment examined sleep in adult fruit flies that experienced isolation at distinct stages of development. Flies were isolated as eggs, at the 2nd larval instar, or left in group housing for development. Upon pupation, half of each group was re-socialized with their group-mates. The egg isolation group showed the shortest and most fractured sleep (supporting previous literature), but adult resocialization afterward rescued those sleep effects. Inconsistent with previous studies, Group-housed flies that were isolated from pupation into adulthood showed no significant sleep differences from wholly group-housed flies. Future experiments will investigate neural mechanisms of these sleep effects, beginning by visualizing the possible differences in socially-implicated dopamine neurons in isolated flies.

Theme A: Development

Evolutionary algorithms and diverse neuronal classes support learning in recurrent spiking neural network models of the brain

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4. Physics Department, Harvey Mudd College, USA

Abstract

Task-trained recurrent spiking neural network models (RSNNs) can offer insights into how the brain learns to perform spike-based computations over time. Training RSNNs with backpropagation through time (BPTT) is challenging due to the non-differentiable nature of spiking functions, requiring gradient approximations. Evolutionary Algorithms (EAs) offer an alternative by generating and selecting model populations, thus optimizing non-differentiable functions and exploring broader solution spaces. We observe that RSNNs trained with BPTT show greatest changes in output layer weights and minimal changes in recurrent weights, unlike recurrent plasticity seen in the brain. This raises questions about whether this is due to improper gradient propagation or the true optimality of reservoirs.

We compare RSNNs trained using BPTT and EAs on temporal tasks. Our models include a hidden recurrent layer of leaky integrate-and-fire neurons with three types of inhibitory neurons and connectivity similar to mouse neocortex. EA training leads to substantial recurrent layer weight changes, suggesting that EAs capture genuine recurrent neural plasticity and can provide valuable insights into how changes in recurrent neural circuitry support learning.

Furthermore, the brain's spiking dynamics involve diverse excitatory (E) and inhibitory (I) neurons, yet their specific roles are not fully understood. We find that the inclusion of multiple interneuron classes in our models enhances temporal task performance. RSNNs with three types of inhibitory neurons (PValb, SST, and 5Htr3a) outperform those with a single inhibitory class, showing improved excitation regulation and smoother phase transitions. These findings demonstrate that the functional diversity of neuron types supports computations over time.

Theme I: Techniques

Re-analyzing the Null Space Hypothesis for Preparatory Activity in the Motor Cortex

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Abstract

Recent research in motor control studies has revealed that muscle activity reflects neural activity originating from neurons within the premotor and motor cortices. Despite this correlation, neurons in these areas also exhibit significant actity in the time period before a movement begins, a phenomenon known as “preparatory activity.” An important conundrum is therefore: why does neural activity during the preparatory period not directly elicit movement? Many hypotheses, focusing on single-neuron responses, have been proposed to address this phenomenon. In contrast, recent studies, such as Matthew Kaufman’s study on cortical activity in the null space, have described population activity occurring within an output-potent or output-null subspace. As a further explanation, neural subspaces such as output potent and output null subspaces refer to different factors within a neural network that do or do not influence the output, and in this case, the muscle activity. Although output null factors do not directly affect the output, they do influence other factors that have an affect on the output. In comparison, output potent factors have a directly causal effect on the output of a neural network. Given the novelty of this hypothesis, further analysis is necessary to better understand the mechanisms involved in motor preparation and muscle readouts. In this study, we compared different dimension-reduction techniques, such as principal component analysis (PCA) and slice tensor component analysis (sliceTCA) on muscle and neural activity matrices used in previous studies. We then employed principal linear regression, comparing the mean-square error to the number of dimensions we used. The main aim of this study was to understand how changing the number of dimensions for each matrix contributes to the muscle readout results.

Theme E: Motor Systems

Influence of First-Generation Status on Student Metacognition and Academic Performance in Undergraduate Biology Education

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Abstract

First-generation (FG) college students are less prepared for what to expect in college coursework and may struggle with academic performance and confidence. Alignment of student confidence with performance reflects metacognition, or awareness of what one knows. This investigation aims to elucidate whether FG students exhibit different metacognitive patterns of confidence in their knowledge relative to non-FG students. Previous studies analyzed confidence levels using pre- and post-exam surveys of overall exam performance, revealing lower confidence and academic performance for FG students. Our novel study evaluates confidence on individual exam questions categorized by Bloom's taxonomy to investigate the impact of FG status on metacognition, confidence, and academic performance in undergraduate neuroscience education. The research sample includes FG and non-FG undergraduate students (49% FG) enrolled in an introductory neuropharmacology class. Students self-reported confidence levels following each of fifty multiple-choice exam questions, graded for accuracy and stratified by levels of Bloom's taxonomy. Metacognition was evaluated as the absolute difference between accuracy and confidence, termed "Judgment Inaccuracy" (JI). Ordinal logistic regression analysis compared the relationship between confidence and accuracy, and independent t-tests compared FG and non-FG confidence, accuracy, and JI per Bloom's levels. Initial findings demonstrated strong association between confidence and accuracy, independent of Bloom's level and FG status ($p < 0.0001$). Analysis indicated no significant differences between FG and non-FG students in accuracy, confidence, and JI across all levels of Bloom's taxonomy. Future studies will consider additional demographic comparisons including gender and ethnicity with a homogenized distribution of exam questions across Bloom's taxonomy.

Putative neural mechanism underlying morphological changes induced by a 5-alpha reductase inhibitor in the pond snail

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Abstract

Despite the presence of steroidal androgen genes in gastropod molluscs, the direct effects of such androgens remain unclear. Dutasteride (DUT), a dual inhibitor of 5α-reductase types I and II, blocks the conversion of testosterone to 5α-dihydrotestosterone, and is used therapeutically to mitigate conditions linked to high testosterone levels in humans. Prior observations in Biomphalaria found that developmental DUT exposure altered the shape of the snail from a helical shell to a unique banana-shaped shell. Studies in our lab in the closely related gastropod Helisoma trivolvis successfully replicated this phenotype, and we further show that DUT exposure during a critical window of 48-72 hours post-deposition consistently induced the banana-shaped shell morphology (92.3%), with significant differences in hatch rates between DUT-treated and control groups (14.3% in DUT, 95.2% in control).

Changes in shell morphology could be because of altered expression of developmental markers or altered movement due to differential neural inputs in the developing embryo. To determine alterations in developmental markers, we treated snail embryos to varying concentrations of dorsomorphin, an inhibitor of decapentaplegic (dpp) shown to affect shell coiling. Only at the lowest dose, was the banana-shaped coiling observed. We found that immunohistochemical stains for catecholaminergic cells (dopamine, serotonin) in the developing embryo show differential expression between controls and DUT treated animals, especially in the areas of the foot. We suggest a putative neural mechanism for DUT action on shape changes in the snail embryo - with modified catecholaminergic innervation leading to altered movement, resulting in the morphological change.

Theme A: Development

Development and Validation of a Novel Fine Motor Task for Preclinical Analysis of Dexterity with Implications for Neurodegenerative Disorders

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Abstract

Alzheimer's disease (AD), affecting 1 in 9 older adults in the US, often goes undetected by primary care providers (PCPs), highlighting the need for better diagnostic tools. A brief motor test assessing anticipatory dexterity has shown promise in predicting AD progression. Prior studies indicate that such motor tests can predict AD progression and are sensitive to brain amyloid and hippocampal atrophy. This research aims to develop and validate a rat version of the motor test to uncover the mechanisms linking motor performance to preclinical AD.

Here, we trained 3-month-old male Fisher CDF rats (n=6) to reach for a sugar pellet from 1 of 3 increasingly difficult bowls for 10 minutes with 3 trials per bowl over 9 days. The average rate (%) of performance was found to be positively correlated with increasing failures as bowl difficulty increased ($R2 = 0.75$) and negatively correlated with decreasing successes ($R2 = 0.6$). There was a significant difference in total reaches per day ($p = 0.009$), and failures increased with bowl difficulty. Thus, we created a rodent fine motor reaching task that requires multiple strategies and stages with increasing difficulty.

Future research will study this task using mutant TgF344-AD rats that are genetically modified to have AD pathology. This work aims to create a preclinical model to explore the link between motor test performance and AD brain pathology.

Theme E: Motor Systems

Lesion-Induced Synaptic Plasticity of the Crossed Temporodentate and Septodentate Pathways in Intact versus Ovariectomized Female Rats

Kierra Marshall, Jordan Benson and Julio J. Ramirez

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Abstract

Alzheimer's disease (AD) affects almost seven million people in the United States with women comprising two-thirds of the disease population. AD is a progressive neurodegenerative disease without a cure, causing memory loss and mental dysfunction. The entorhinal cortex (EC) and hippocampus are particularly targeted in AD. Higher prevalence in women may relate to menopause-induced estrogen/progesterone loss, which may have neuroprotective functions under normal conditions. This study in female rats explored the neurophysiological correlates of sprouting in the crossed temporodentate pathway (CTD) after unilateral EC lesion (UECx), as well as the anatomical outcome of lesion-induced sprouting of the acetylcholinesterase-containing septodentate pathway. Estrous cycles of female rats were recorded by lavages on two operation days: day of craniotomy/entorhinal surgery and day of electrophysiological recording. The female rats were divided into four groups: sham-ovariectomized intact (with ovaries) or ovariectomized (OVx), AND right craniotomy or right UECx. Following a 12-day survival postlesion, rats underwent electrophysiological analysis of paired-pulse responses (conditioning pulse followed by test pulse) to examine the amplitude and slope of the CTD response, indicative of CTD sprouting after EC injury. We observed a lesion-dependent increase in optical density (i.e., significant septodentate sprouting) in the lateral and medial outer molecular layer in the ventral dentate gyrus. Electrophysiology results indicated an inhibitory effect of the homotypic, CTD-CTD paired-pulse stimulation in OVx-UECx rats. Slope and amplitude test-pulse analyses showed significant CTD-response declines in IPIs of 300-500 ms. Based on our findings, future explorations of lesion-induced septodentate and CTD sprouting in female rats are warranted.

Theme C: Neurodegenerative Disorders and Injury

Roots of relapse: Investigating the role of motivation and stress in resistance to diet-based interventions for compulsive overeating

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*Co-presenters

Abstract

Our food environment is abundant in calorie dense foods with high percentages of fats and sugars. Their palatability and availability often perpetuate overconsumption and disordered eating. Compulsive overeating is difficult to curb with diet-based approaches due to high rates of relapse, and this resistance to diet-based treatments may be attributable to altered motivation to consume palatable and less palatable foods. Our lab uses operant tasks to assess the reinforcing properties of palatable foods and their impact on eating behavior. Previously, we found that three-day palatable food access reliably induced overeating and led to undereating of a less palatable chow in mice fed on a fixed ratio one (FR1) schedule. We are now investigating the effect of three-day palatable food access on the subsequent motivation to earn chow using a resetting progressive ratio task. As before, mice overate the palatable food and then underate the chow, and our initial analyses suggest they also exhibited decreased motivation to earn chow. Stress is associated with relapse to addictive behaviors including compulsive overeating. Previous studies from other groups have examined stress-induced reinstatement of food-seeking behavior; however, few have done so in mice. Thus, we trained food-restricted mice to earn palatable food on a FR1 (20-s timeout) schedule. Then, the mice underwent extinction training followed by the administration of yohimbine, an anxiogenic drug. We expect yohimbine-induced stress to reinstate compulsive food-seeking behavior. Together, these two studies will increase our understanding of diet relapse and aid in the development of effective treatments for compulsive overeating.

Theme G: Motivation and Emotion

The Y-Maze and Radial Arm Maze Demonstrate Differences in Rat Spatial Working Memory Performance after Bilateral Entorhinal Cortex Lesions

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Abstract

The entorhinal cortex (EC) is among the first brain regions to show deterioration in Alzheimer's disease, a neurodegenerative disease characterized by significant memory loss. This study explores spatial working memory (SWM) assessed with either a Y-Maze or a radial arm maze (RAM) in rats with bilateral EC lesions. Male, Sprague-Dawley rats were assigned to an entorhinal-surgery or sham-operate group where they either received bilateral EC lesions or a craniotomy, respectively. The Y-Maze delayed alternation task measured the rats' egocentric/self-directed SWM performance. Their SWM was assessed using a Y-maze alternation task where performance was evaluated based on total and perseverative errors made in the task as well as days to criterion (DTC). The RAM task measured allocentric/cue-based SWM performance, which was evaluated based on arm re-entry and DTC. Brains were processed with a histological stain for acetylcholinesterase (AChE), which was used as a marker for lesion-induced, cholinergic, septodentate sprouting. Results from the Y-Maze and RAM testing revealed that rats provided with visual cues (allocentric RAM task) were able to behaviorally recover and complete the SWM task whereas the rats without cues (egocentric Y-maze task) failed to recover after six weeks of postoperative testing. Thus, the impact of bilateral EC lesions on rats' SWM performance and the potential contribution of axonal sprouting on behavioral recovery depended on the nature of the testing apparatus. The observed differences in the behavioral outcomes depending on the maze type indicate the importance of consideration of the behavioral task in assessing postlesion behavior.

Theme C: Neurodegenerative Disorders and Injury

Brain region volumes and socioenvironmental factors in the symptom severity of adult post-traumatic stress disorder in the AURORA cohort

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Background: Brain morphology of key neural threat structures is implicated in adult post-traumatic stress disorder (PTSD). However, the interplay between differences in brain morphology and socioenvironmental factors in adult PTSD symptom severity has not yet been fully characterized. This presents a significant gap given known associations between socioenvironmental factors and brain morphology. To address this knowledge gap, this study aims to assess the predictive value of early post-trauma brain region volumes for later PTSD symptom severity and explore how socioenvironmental factors might modulate these relationships.

Methods: We conducted secondary analyses on 293 participants with complete case data in the AURORA Study, a longitudinal multi-site assessment of post-traumatic neuropsychiatric sequelae. Participants completed an MRI scan to evaluate brain morphology at 2 weeks post-trauma and the Post-Traumatic Stress Disorder Checklist for DSM-5 to assess PTSD symptom severity at 6 months post-trauma. Socioenvironmental variables were self-reported at study enrollment. We conducted zero-inflated negative binomial regression to estimate associations between early brain region volume and later PTSD symptom severity, adjusting for race/ethnicity, sex, age, educational attainment, and socioeconomic status (SES). Interaction terms were used to examine effect modification by race/ethnicity, sex, and SES strata.

Results: Larger volume of the left thalamus ($\beta = 5.266$, $p = 0.002$, 95% CI: 1.903 to 8.629) and right thalamus ($\beta = 4.565$, $p = 0.007$, 95% CI: 1.249 to 7.881), as well as increased cortical surface area of both hemispheres ($p < 0.05$) were observed to be predictive of an absence of later PTSD symptom severity. Decreased cortical thickness of both hemispheres and decreased volume of the right thalamus ($p < 0.05$) were also predictive of increased PTSD symptom severity. Interaction analyses revealed sex-specific impacts of brain region volume, including decreased right amygdala volume predicted increased PTSD symptom severity in men ($\beta = -2.055$, $p = 0.010$, 95% CI: -3.622 to -0.488), but with a reduced effect in women (interaction $\beta = 1.816$, $p = 0.047$, 95% CI: 0.025 to 3.608).

Conclusion: These results suggest that early neuroanatomical structures post-trauma are linked to later PTSD symptom severity, with associations influenced by socioenvironmental factors. This highlights the importance of considering both biological and social dimensions in the understanding, diagnosis, and treatment of PTSD, and suggests that neuroanatomical features warrant further investigation as potential mechanisms in the pathogenesis of PTSD.

Theme G: Motivation and Emotion

Curiosity in Bloom: Examining Toddlers' Motivation to Explore Their Own Abilities

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Abstract

Children learn about and explore the world through play. Much like little scientists, when young children explore the world, they tease apart confounding variables, test hypotheses, and follow up on surprising findings (Schulz, 2012; Gopnik, 2012). However, it remains unclear if toddlers are similarly driven to explore their own abilities. This study adapts classic exploratory play paradigms (Schulz & Bonawitz, 2007) to investigate toddlers' intrinsic motivation to understand their competence.

In an ongoing pre-registered experiment, two-year-old toddlers (planned sample: N = 48) play Montessori practical life games with their parents. These toys were verified as developmentally appropriate and equally appealing in an independent norming experiment (N = 24 two-year-olds) and presented in pairs. For each pair, parents guided the toddler's hands with one toy, providing ambiguous information about the child's competence, and took turns playing with the other toy independently, providing unambiguous information. At the end of each pair, toddlers are asked to choose one toy to further explore independently.

We hypothesize that children will systematically choose toys for which they have received ambiguous information about their competence to further explore on their own. Preliminary pilot results show that toddlers chose the ambiguous toy to further explore first in 70% of the trials (N = 11 two-year-olds, 30 trials), suggesting that toddlers are intrinsically curious to learn about their own competence. This work aims to provide a deeper understanding of the drivers of early childhood curiosity and the processes of self-directed learning.

Theme A: Development

Influence of semaphorins on development, adult neuronal plasticity, and behavior

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Abstract

The axons and dendrites of the nervous system require specific instructions from several families of guidance molecules during development. This same set of cues sometimes maintain limited expression in adult neuronal tissues, likely working to balance maintenance and plasticity. To understand the molecular control of neurons in developmental and adult plasticity, we have turned to the cricket, Gryllus bimaculatus. Hemimetabolous crickets are separated from the holometabolous Drosophila by an estimated 130 million years of evolution. Additionally, crickets display an unusually robust injury-induced anatomical plasticity in their auditory systems. Semaphorins are thought to influence both developing neurons as well adult neuronal plasticity in a wide array of organisms. Transcriptomic and genomic resources have identified well-conserved isoforms of sema1, 2, and 5. We explored the different roles Sema candidates play in development, adult plasticity, and behavior using dsRNA knockdown. In embryos, we asked whether semaphorins were important to the development of the CNS and PNS, using immunohistochemistry to examine neuronal morphology across development. In the adult prothoracic ganglia, we asked whether the semaphorins might play an instructive role in the injury-induced auditory plasticity by backfilling auditory neurons and examining their morphologies in knockdown animals. And finally, we also explored the negative phonotaxis behavior in control and dsRNA-treated crickets, using DeepLabCut to quantify differences in turning behavior. Our findings indicate that changes in the expression levels of semaphorins are likely important to both developing and adult nervous systems.

Theme F: Integrative Physiology and Behavior

Investigating the role of phosphorylation in alpha-synuclein aggregation

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting nearly one million people in the US. The disease is characterized by the incremental loss of dopaminergic neurons in the substantia nigra, eventually leading to movement disorder symptoms (Jagadeesan, 2017). Alpha-synuclein protein accumulates into aggregates called Lewy bodies; understanding the factors leading to aggregation is essential for developing effective treatments for PD. Although the mechanisms that underlie alpha-synuclein aggregation are not clear, phosphorylation at serine-129 (S129) is likely involved in disease; 95% of alpha-synuclein in Lewy bodies is phosphorylated at this site (Fujiwara et al., 2002). Phosphorylation at S129, however, does not seem to be the only factor causing aggregation (Weston et al., 2021). Nearby sites tyrosine-125 or tyrosine-136 could be involved in a more complex combination of phosphorylation events necessary to drive aggregation. Phosphorylation at Y125 may regulate alpha-synuclein binding capacity (Schreurs et al., 2014) and inhibition of Y136 phosphorylation may increase its aggregation, suggesting a protective role (Sano et al., 2021).We are studying Y125 and Y136 in relation to S129 to understand how phosphorylation of these sites together may affect aggregation. We inject DNA encoding different forms of phosphomimetic and phospho-inhibited human alpha-synuclein tagged with GFP into zebrafish embryos. We use in vivo Fluorescence Recovery After Photobleaching (FRAP) in zebrafish larvae to measure protein mobility and study aggregation. These studies will help us to further understand the mechanisms underlying alpha-synuclein aggregation, which may ultimately allow for targeted treatments and improvements in care for millions of people.

Theme C: Neurodegenerative Disorders and Injury

Role of Estrogen in Socio-Cognitive Functioning and Neurodegeneration in a Sprague Dawley Model of Early-Onset Alzheimer's disease

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Abstract

Early-onset Alzheimer's disease (EOAD) is a neurodegenerative disease wherein symptom onset and diagnosis occur before age 65. Just as in other forms of AD, EOAD features neuropathological symptoms (e.g., amyloid-beta (Aβ) plaque accumulation) that may underlie cognitive deficits in areas such as spatial memory and social recognition. Additionally, apathy is one of the most common neuropsychiatric symptoms of this disease, often resulting in decreased social motivation. Estrogen is a neuroprotective sex-steroid hormone that has been found to reduce Aβ densities; thus, its decrease during menopause may contribute to EOAD symptomology in females. This study investigated the neuroprotective effects of estrogen on socio-cognitive functioning in a Sprague Dawley model of EOAD. Female rats received either a true or sham ovariectomy, followed by a hippocampal injection of Aβ42 or vehicle solution. Finally, animals received daily estradiol benzoate (EB) or cottonseed oil injections. This resulted in three experimental groups: Aβ plus cottonseed oil (unmitigated EOAD group), Aβ plus EB (estrogen replacement therapy in EOAD group), and vehicle plus cottonseed oil (healthy reference group). On the eleventh day post-surgery, rats were evaluated for spatial memory and social recognition. Brain tissue was subsequently evaluated for evidence of neurodegeneration. Our preliminary findings indicate elevated neurodegeneration and social recognition deficits in Aβ plus cottonseed oil animals, confirming the model's effectiveness in inducing elements of EOAD pathology and cognitive impairments. The neuroprotective effects of estrogen replacement therapy and social motivation are currently under further investigation.

Theme C: Neurodegenerative Disorders and Injury

The Role of Self-Construal in Prefrontal Activity During Emotional Suppression: An fNIRS Study

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Abstract

Culture mediates how individuals regulate their emotions. For example, greater levels of social anxiety in East Asian Americans compared to European Americans may be mediated by emotional attunement through both emotional regulation and sensitivity to others. Studies have also found East Asians to be greater in interdependent self-construal, leading to differential experiences of emotion and greater demands to control emotion for the sake of others. Although some research suggests interdependence predicts the ability to emotionally downregulate, most studies on cultural differences in emotion rely on self-report measures. We used functional near infrared spectroscopy (fNIRS) to examine cultural differences in emotional downregulation and determine localized brain areas associated with this process. Participants watched negatively-valenced emotional videos and were instructed to suppress their emotions or react normally. Their prefrontal hemodynamic activity was recorded and analyzed using fNIRS. Self-construal and social anxiety were assessed via Qualtrics. Participants showed PFC deactivation when emotionally suppressing compared to baseline, and activation when attending to emotional stimuli. Those higher in interdependence showed greater medial PFC (MPFC) deactivation, suggesting introspection-involved brain areas may be especially sensitive to self-construal during emotional suppression. Interdependence had a direct effect on fear of negative evaluation (FNE) social anxiety subscores, and those with greater FNE scores showed less MPFC deactivation during emotional suppression, suggesting that the relationship between culture and FNE is mediated by MPFC activity. Additional research into the relationships between culture, social anxiety, and MPFC deactivation during emotional suppression may be crucial for advancing and individualizing therapeutics for emotional dysregulation.

Theme G: Motivation and Emotion

Optimization of Cannabidiol's Efficacy and Safety in Mice

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Abstract

Cannabidiol (CBD) is a non-intoxicating phytocannabinoid with escalating popularity for the treatment of off-label conditions including anxiety and autism spectrum disorder (ASD). Pharmacological strategies that expand CBD's dose-efficacy range will improve its medicinal utility. We've demonstrated that the addition of cannabis-inspired terpenes leads to more pronounced prosocial effects and higher reliability in the BTBR mouse model of ASD. Therefore, we hypothesize that terpenes can enhance CBD's therapeutic efficacy by expanding its dose-efficacy relationship, and elevations to GABAergic and anandamide signaling, which together, restore the brain's excitatory:inhibitory (E:I) balance, underlie these effects. Local field potential recordings revealed that BTBR mice are deficient in GABAergic signaling and have a pronounced E:I imbalance compared to control C57BL/6J mice. Further, MALDI-TOF mass spectrometry confirmed that BTBR mice were also deficient in anandamide signaling, which was restored by acute inhalation of vaporized CBD oil. These effects were associated with reduced anxiety behavior on the elevated plus maze and improved social interaction in the 3-Chamber Test and were not dependent on estrogen fluctuations across the estrus cycle in either strain. In considering toxicological risk of administering CBD to children, we tested the impact of CBD vapor exposure at three 2-week developmental stages. Vaporized CBD in only the PND14-28 exposure group increased risk-taking behavior and impaired learning and memory on the Barnes Maze. Together, we find that CBD's therapeutic effects may be optimized by examining molecular and physiological targets that correlate to behavioral outcomes, but our findings should be considered cautionary for off-label CBD administration to children.

Theme A: Development

Sex and stress effects on the discriminative stimulus properties of cocaine in rats

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Abstract

Cocaine produces interoceptive effects that can be used as discriminative stimuli to direct operant behaviors. The effects of cocaine in other paradigms (e.g., IV self-administration) differ across the sexes and are sensitive to stress manipulations. Here, we trained male and female Long-Evans rats to discriminate the interoceptive effects of cocaine from saline in a two-lever operant task using food as a reinforcer. Across two training doses of cocaine, 5.6 mg/kg and 10 mg/kg, female subjects required fewer training sessions than male subjects to meet discrimination criteria. We then performed dose-response tests of the interoceptive effects of cocaine following acute exposure to four modalities of stress (restraint, yohimbine, wet bedding, or tilted cage) or control conditions. Surprisingly, we did not observe robust shifts in the responses to cocaine following acute stress exposure.

Theme F: Integrative Physiology and Behavior

A meta-analysis of transcriptomic alterations in viral encephalitis

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Abstract

Encephalitis, the inflammation of the brain parenchyma, is a significant neurological disorder with high morbidity and mortality worldwide. It can be caused by pathogenic infections, primarily viral, or by autoimmune responses, resulting in distinctive neurological symptoms. These symptoms likely arise, in part, from changes in gene expression within the brains of the patients. However, the research on this aspect has been restricted due to the intrinsic heterogeneity of the brain's cellular environment, the complexity of human neuroimmune interactions, and the limitations of animal models.

To address this gap, we conducted a meta-analysis of publicly available transcriptional profiling datasets from microarray and RNA-Seq technologies, to preliminarily identify a panel of consistently differentially expressed genes in viral encephalitis of mouse models. Six datasets were selected through an adapted PRISMA procedure: GSE30577 (rabies), GSE42264 (measles), GSE44331 (vesicular stomatitis virus), GSE51365 (gamma herpesvirus), GSE53784 (West Nile virus and Japanese encephalitis virus), and GSE91074 (Venezuelan equine encephalitis virus). Using R statistical programming, the data were fit to a random effects model using effect sizes (log2 fold changes) for each expressed gene from individual datasets and their according sampling variances.

We identified several hundreds of genes that were statistically significantly differentially expressed across all datasets at the false discovery rate (FDR) of < 0.05 after correction with the Benjamini-Hochberg method. These findings suggest that certain genes are consistently altered in viral encephalitis, potentially becoming targets for therapeutic intervention. Regardless, more focused follow-up studies on each virus family are necessary before definitive conclusions can be drawn.

Theme C: Neurodegenerative Disorders and Injury

Network Correlates of Aggression Experience and Observation

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Abstract

Aggression is modulated by prior experience and exposure. Long-standing studies have proposed that repeated experience or exposure to aggression may increase the propensity of individuals to respond aggressively to environmental triggers. Although key neural circuits controlling this increased propensity for aggression have been identified, the long-term effects of repeated aggression experience or exposure to the brain, and whether these carry over to new aggression contexts, remain unclear. Here, we look at excitatory and inhibitory activity changes in the Social Behavior Network (SBN), a macro-circuit of a dozen brain regions, ranging from the forebrain to the midbrain, which regulates social behavior. Using a custom fiber photometry strategy, we recorded excitatory and inhibitory activity from these regions across three groups: mice that received direct aggression experience, mice that observed aggression in other mice, and mice that received no social experience. Individuals from each group were pitted against tougher aggressors to identify carryover effects from aggression experience and/or observation. We found that experienced individuals frequently engaged with stronger aggressors, a behavior recapitulated by observers, while those with no experience showed less engagement and more avoidance. Moreover, aggressive behaviors in experienced and observer individuals were underpinned by a relative increase of excitatory activity over inhibitory activity in key hypothalamic and amygdala areas. Importantly, this bias of excitatory signaling emerged longitudinally from the moment these animals either acquired experience or exposure to aggression. Altogether, our findings suggest that repeated experience with and observation of aggression induces large-scale and longitudinal dis-inhibitory changes to brain activity. Such changes could support an increased propensity for aggressive behaviors.

Theme F: Integrative Physiology and Behavior

Frontal traumatic brain injury increases suboptimal impulsive choice in rats

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Abstract

Behavioral dysfunction following traumatic brain injury (TBI) presents a common yet understudied complication barring patients from full recovery. Choice impulsivity correlates strongly with the development and persistence of maladaptive behaviors; however, it has been overlooked as a behavior susceptible to disturbance in TBI. Impulsive decision-making is a strong preference for quickly delivered, smaller reinforcers over larger reinforcers delivered after a delay. The present study assessed a causal relationship between TBI and choice impulsivity in rats using a controlled cortical impact TBI model and operant behavioral testing. We used a TBI vs. sham experimental design to probe the effects of TBI on a delay discounting task (DDT). On the DDT we presented a choice between 1 pellet after a shorter delay (5s initially) or 2 pellets after 60s. The shorter delay was then increased every 2 sessions until it reached 60s. In a previous study, the DDT failed to show group differences in rodents despite robust evidence in humans suggesting otherwise. This study altered the parameters of the DDT which allowed us to successfully record group differences: rats demonstrated lower rates of longer delay choice post-TBI, confirming its correlates with deficits in impulse control. TBI rats, as expected, had higher rates of impulsive choice post-injury. Ongoing work to be presented in the poster includes testing a behavioral intervention aimed at encouraging self-controlled behavior through repeated exposure to delayed reinforcement. At this time in the study, we have mirrored human results and confirmed that TBI induces suboptimal impulsive choice in rats.

Theme C: Neurodegenerative Disorders and Injury

Decoding Drosophila's Visual Neuron Function Using Connectomics

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3. Princeton Neuroscience Institute

Abstract

FlyWire, the first neuronal wiring diagram of a whole adult brain [1], has enabled us to measure the connectivity of every neuron in the drosophila (fruit fly) brain. Nevertheless, the extent to which these wiring diagrams alone can advance our understanding of neural computation remains uncertain, as other biological details, including the dynamic characteristics of individual neurons, are still elusive [2]. In this study, we demonstrate that by conducting computational analyses of FlyWire connectome data and integrating it with existing experimental functional data, we can investigate the anatomical structure-function relationships of LC11 neurons involved in small object detection and short-term freezing behavior in response to small moving objects. The predicted structure-function relationships of LC11 neurons were examined using FlyWire by assessing the spatial organization of the primary columnar inputs to LC11 cells. Our findings revealed that nearly all columnar cell types that synapse with LC11 are excitatory, with lateral inhibition provided by non-columnar cells, primarily TmY15 and Li15. Connectomics helped us understand how the morphology of LC11 neurons explains their high sensitivity to only small moving objects.

Theme D: Sensory Systems

A high-throughput pipeline for precise pupil size measurement using deep learning in mice and humans

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Abstract

Pupillometry is a non-invasive method to study autonomic nervous system function. By measuring changes in pupil size, this technique provides insights into the dynamic interaction between sympathetic and parasympathetic systems. Additionally, pupillometry informs about an individual's behavioral state, including their levels of arousal, emotional responses, and cognitive engagement. Despite its importance in research and clinic, standardizing pupillometry across different laboratories has been challenging, primarily due to the absence of standardized computational analysis pipelines. The development of a fast, high-precision, and minimally supervised pupil analysis pipeline would facilitate both research and clinical applications. In this study, we compared the efficiency of several open-source Deep Learning packages, including DeepLabCut, to establish an optimal pipeline. Remarkably, our pipeline achieved exceptional precision, surpassing 95%, with training on only 0.01% of the video dataset and enabled robust and rapid pupil identification across diverse experimental conditions in large rodent populations. We also tested the applicability of our analysis pipeline in human pupil recordings. Similar to rodent results, analysis of human pupil data yielded precision rates exceeding 95%, supporting the reliability and accuracy of our method for human data. Additionally, we successfully applied our methodology to analyze pupil datasets originating from neurodevelopmental and neurodegenerative preclinical rodent models, supporting our method's versatility and applicability across varied research contexts. Lastly, by leveraging advanced high-performance computational (HPC) systems, we reduced data analysis time significantly, processing approximately 20 million mouse and human pupil images in just 10 hours. The novel deep learning-based high-throughput pupil analysis pipeline (DeepVision) offers a reproducible, fast, and high-precision method with minimal supervision, which can accelerate human and rodent pupil analysis in research and clinical settings and effectively standardize pupil analysis results across diverse laboratory settings, addressing reproducibility concerns.

Theme I: Techniques

Presynaptic homeostatic potentiation at the mouse neuromuscular junction

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Abstract

For animals to move, an action potential in a motor nerve must release sufficient acetylcholine (ACh) at the neuromuscular junction (NMJ) to produce a postsynaptic response that is sufficiently large to trigger an action potential in the muscle cell. If the acetylcholine receptors (AChRs) are partially blocked at the NMJ, the motor nerve responds by releasing more ACh to compensate for the deficit in postsynaptic response. This phenomenon is called presynaptic homeostatic potentiation (PHP). In previous work, we have provided evidence that the increase in ACh release during PHP is triggered by activation of acid-sensing ion channels (ASICs) in the NMJ. This implies that the proton concentration in the synaptic cleft increases during PHP and activates ASICs in the presynaptic nerve, resulting in increased ACh release. In this poster we present data showing PHP in response to the application of pharmacological antagonists of AChRs. We also describe preliminary efforts to measure the pH in the synaptic cleft using viral (AAV) expression of a pseudo-ratiometric probe, pHusion-Ex. Current data from our lab shows that the probe can detect pH in the synaptic cleft as we observed an increase in the ratio of seGFP to FusionRed fluorescence as the muscle was perfused with bathing solution buffered to various pH levels with 10mM HEPES.

Theme B: Neural Excitability, Synapses, and Glia

Computational Representation of Skin Pattern in Dwarf Cuttlefish

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Abstract

Dwarf cuttlefish (Sepia Bandensis) are coleoid cephalopods like squid and octopus. They are masters of camouflage. Cuttlefish take in their visual environment and generate an appropriate camouflage pattern. Motor neurons from the brain dynamically control pixels on their skin, called chromatophores. Through the expansion and contraction of hundreds of thousands of chromatophores, patterns are formed on the skin. Surprisingly, despite cuttlefish camouflage having evolved to fool predators and prey, it also fools our own human visual system. We are interested in how the cuttlefish brain accomplishes this feat. That is, what neural algorithms do dwarf cuttlefish use to process the visual world and generate an appropriate camouflage pattern?

Here we aim to determine a computational representation that allows us to distinguish skin patterns. Skin patterns range from textured images to less homogenous patterns. We therefore consider computational algorithms that quantify both textural components, and inhomogenous features. We compared representations from three models: a texture model, CLIP embedding which extracts object features, and the DISTS metric which captures both textural and object features.

Comparing representations with cosine similarity, we find texture statistics best distinguish skin patterns. Texture statistics also best matched the manual observations we identified. Furthermore, we find texture statistic representations cluster similar patterns in PC space.

This work supports the hypothesis that cuttlefish could be representing the visual world via texture statistics and using this representation to generate appropriate camouflage patterns.

Theme I: Techniques

Sex Chromosomes Affect Density of Rat Cerebellar Granule Cells

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Abstract

Using MRI scans, Corre et al., (2014) noted that the cerebellar vermis was a region affected both by sex chromosome complement and gonad in Four Core Genotypes mice. In FCG-like rats, we previously found that Purkinje cell density differs due to gonadal sex as well as across lobules in the cerebellar vermis. Here we examine granule cell density across vermal lobules to see if it differs either with gonadal sex or sex chromosomes using a five-group design. This design includes XX gonadal females (FXX, n = 9), XY females in which the Sry gene was disrupted so they developed ovaries (FXY, n = 7), XY gonadal males (MXY, n = 10), XX males in which the Sry gene had been inserted into an autosome so they developed testes instead of ovaries (MXX, n = 6), and XYTG gonadal males that had Sry genes both on the Y chromosome and also inserted into an autosome (MXYTG, n = 5). Cerebelli were cut at 40μm in the sagittal plane and stained with thionin. Between 3-6 images per vermal lobule, each spanning 330μm, were taken at 50x. Since granule cells are quite small, we measured the relative optical density (ROD) using FIJI to measure the density of the granule cell layer as well as the adjacent molecular cell layer on the same section. The largest possible ROI was marked out within each layer and the mean density of the two layers subtracted for each lobule. This procedure controlled for variation in staining or illumination. All measures were made blind to gonadal sex and genotype. An ANOVA having 5 groups x 11 lobules revealed significant effects of lobule, $F(10, 32) = 4.615$, $p < 0.001$, $\eta 2 = 0.034$, and a lobule by group interaction $F(40, 32) = 1.475$, $p < 0.05$, $\eta 2 = 0.044$, but no main effect of group. Posthoc Holm analysis (corrected for 231 comparisons) revealed significant differences across lobules within the MXY group that did not occur in other groups. Most differences were because MXY lobules 6a and 6b had a higher ROD than other lobules within the MXY group (lobules 1, 9, and 10). Subsequent analyses further revealed that the MXX group had lower ROD than did the MXY group in Lobule 6a, $F(1,16) = 4.613$, $p < 0.05$, $\eta 2 = 0.224$. This latter difference suggests that granule cell numbers differ between two of our male gonadal phenotypes and are influenced by their sex chromosome complement. Notably, lesions of Lobule 6a result in impaired sexual performance and other motor problems in male rats (Ortiz-Pulido et al., 2010). Thus, a rat FCG-like model and the mouse FCG model both show sex chromosome effects on cerebellar morphology.

Theme E: Motor Systems

Dorsal raphe to basolateral amygdala corticotropin-releasing factor circuit regulates cocaine-memory reconsolidation in rats

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Abstract

Retrieval can destabilize context-drug memory traces, requiring their reconsolidation into long-term memory for continued environmental stimulus control over drug-seeking. Disruption of labile cocaine memories or interference with their reconsolidation may be a viable therapeutic approach for relapse prevention. Corticotropin-releasing factor (CRF) in the basolateral amygdala (BLA) is critical for cocaine-memory reconsolidation, but its source is unknown. Here, we investigated the role of a dorsal raphe (DR)→BLA CRF circuit in cocaine-memory reconsolidation. Sprague-Dawley rats (n = 4-10/sex/group) were trained to lever press for cocaine infusions in a distinct environmental context then extinction trained in a different context. Rats then received a memory-retrieval session to destabilize cocaine memories and trigger reconsolidation. First, we examined the effects of chemogenetic DR→BLA CRF pathway inhibition on cocaine-memory strength, as indicated by lever pressing in the cocaine-predictive context at test, and Zif268 expression, a molecular event critical for cocaine-memory reconsolidation in the BLA. Next, we characterized the cell types of BLA-projecting DR neurons that were activated (i.e., c-Fos-positive) during reconsolidation. Chemogenetic DR→BLA CRF circuit inhibition during reconsolidation reduced cocaine-memory strength, as indicated by a cocaine-predictive context-, memory reactivation-, DREADD-, and DREADD agonist-dependent decrease in lever pressing in both sexes, and reduced Zif268 expression in DCZ-dependent manner (ps < 0.05). Multi-label immunohistochemistry assays revealed that the BLA-projecting DR cells activated during reconsolidation co-expressed CRF and vesicular glutamate transporter 3 (ps < 0.05). These findings suggest that the DR regulates cocaine-memory strength during reconsolidation, and this phenomenon may involve CRF and/or glutamate (co)transmission in the BLA.

Theme G: Motivation and Emotion

Encoding of light direction and object identity in the monkey inferior temporal cortex

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Abstract

Real world objects produce widely varying images depending on illumination direction. This makes object-recognition a challenging problem, the neural basis of which has received relatively little attention. Here, we performed wireless recordings from the inferotemporal(IT) cortex of the macaque (Macaca radiata, 1 male, aged 9 years) while the monkey fixated on images of 3-dimensional objects with varied lighting directions. In Experiment 1, we presented images of naturalistic objects lit at the same intensity but from different directions. In Experiment 2, we extend this to bas-relief objects with ambiguous structure (convex/concave).

Our findings: (1) In Experiment 1, multi-unit responses were strongly modulated by object identity and only weakly by light direction: 30% (38/128) of channels showed a main effect of only object identity, and 9% (46/128) of channels showed a main effect of only light direction. Modelling the neural response as a multiplicative/additive combination of object identity and light direction tuning confirmed this result; (2) Neural selectivity for object identity peaked slightly later than light direction tuning (latency: 127ms for object identity, 111ms for light direction); (3) Decoding analyses showed that object identity and lighting direction can be reliably extracted from neural responses, with a similar delay in peak decoding accuracy; (4) In Experiment 2, we observe that the light direction tuning curves for concave and convex objects are mirrored with respect to each other, suggesting a shape prior biasing lighting direction perception.

Overall, our results elucidate how light direction is encoded at the neural level to achieve invariant object representations.

Male NS-Pten Adult Knockout Mice Display Increased Density of Iba1-Positive Microglia of an Immature Morphology Throughout the Hippocampal Dentate Gyrus

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Abstract

Dysregulated hippocampal neurogenesis is a feature of temporal lobe epilepsy (TLE), marked by increased neuronal proliferation. The tumor suppressor gene phosphatase and tensin homolog deleted on chromosome 10 (Pten) regulates neuronal proliferation and its deletion is implicated in TLE. We have previously shown that conditional deletion of neuronal subset-specific (NS)-Pten in mice leads to an atypical increase in the number of proliferating cells in subregions of the dentate gyrus that are typically devoid of neurons but rich in glial cells, notably the Hilus and Molecular Layer. In this study, we hypothesized that NS-Pten knockout mice would exhibit increased numbers of microglia in these same dentate gyrus subregions. To test this hypothesis, we performed immunohistochemistry for Iba1, a marker for microglia, on 24 wild-type and 23 NS-Pten knockout mice aged 4 and 10 weeks (N=5-6/group). Our data demonstrate that male NS-Pten mice resulted in a 50% and 66% increase, respectively, in Iba1+ cell density in the dentate gyrus at 4 and 10 weeks of age. When parsed into dentate gyrus subfields, male NS-Pten knockout mice displayed significant increases in Iba1+ cell density in the Granule Cell Layer and Molecular Layer at both ages and in the Hilus at 10 weeks of age. Additional analyses of Iba1 morphology also indicate that male NS-Pten mice have increased number of immature microglia, characterized by a round, amoeboid morphology, and fewer mature microglia with ramified processes. Our results increase our understanding of how microglia may contribute to the spatial dysregulation of neurogenesis in NS-Pten mice.

Auditory cocaine conditioning induces neuroplasticity in the early auditory system and implicates the locus coeruleus in sound-cued control of behavior

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Abstract

Enhanced behavioral reactivity to drug-associated cues is a primary feature of addiction that contributes to relapse vulnerability, a primary therapeutic target in addiction treatment. Substantial evidence supports a central role for mesolimbic system plasticity in addiction but much less is known about the involvement of sensory systems. This study reports neuroplasticity events in sensory neural representations of drug-associated cues – a fresh perspective on how the heightened drug-associated response may be due to altered neural cue leading to relapse risk. In recent years, the centrality of sensory systems in learning and memory has emerged. Here, we focus on the auditory brainstem response (ABR) in rats to investigate if basic sensory processing can be affected by experience with sound cues paired with the rewarding effects of cocaine. We report a novel stimulus control that reveals neutral sound cues selectively conditioned with cocaine (auditory cocaine conditioning (AuCC)) to control free exploratory behavior. We also report sound-specific changes to auditory processing in early sound-evoked timing and magnitude ABR signals for sounds associated with cocaine compared to saline that persists for at least weeks. Importantly, all behavioral and neural assessments report activity without cocaine on board, so are interpreted to be driven by the cocaine-conditioned properties. The findings are consistent with an emerging hypothesis that drug-induced neural plasticity in sensory systems may underpin the altered reactivity to drug-cues in cocaine addiction and cue-induced relapse. This study demonstrates that auditory cocaine conditioning can lead to sound-specific neuroplasticity that may drive attention and behavior towards drug-associated cues.

Theme D: Sensory Systems

Exploring Immune Biomarkers in Ethanol Addiction Using Mice and Monkey Models

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Abstract

Drug exposure induces inflammation based on drug type and dosage, impacting the degree of an immune response. Previously published studies suggest that ethanol (EtOH) exposure through self-administration potentially establishes rewarding drug effects and addiction-like behaviors across multiple species, with a spectrum of low to high responding individuals. However, it is unknown what specific components of the immune system are the most influential in EtOH susceptibility. Therefore, this study compares peripheral biomarkers across multiple species (mice and monkeys) examining low and high responders to EtOH self-administration in order to examine the role of immune signaling. As both species exhibit similar addiction-like behaviors, it is hypothesized that similar immune indicators of previous alcohol exposure will be present in an immune signature across species. Mice were subjected to drinking in the dark (DID), a four day paradigm that exposes them to alcohol and provides an opportunity to binge, followed by ethanol conditioned place preference (eCPP), an eight day paradigm that establishes a reward-context association, a proxy to examine reward seeking behavior. Total protein was extracted from mice and monkey blood samples, and the presence of protein in blood serum was confirmed using the automated sandwich ELISA, Ella. Concentrations of specific immune proteins were then compared across species and correlated with their initial addiction-like behaviors. This data has the potential to identify biomarkers that are essential for the process of addiction, filling in the gap of knowledge linking the immune system to reward learning.

Theme H: Cognition

Head direction cell activity and spatial memory is disrupted during administration of NMDA-receptor antagonists

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Abstract

Head direction cells (HDCs) in the rat provide orientation information by firing only when the rat's head points in a specific direction in the horizontal plane. Disruptions of NMDA receptor activity are related to the deficits in spatial learning and memory associated with some neurodegenerative disorders, such as Alzheimer's Disease. In this study, we investigated the effects of NMDA-antagonists on the firing properties of HDCs and spatial memory using environmental orienting visual cues.

HDCs in the anterior dorsal thalamus (ADN) were recorded while rats were systemically administered 1) MK801 (a non-competitive NMDA antagonist; 0.05mg/kg), 2) CPP (a competitive NMDA antagonist; 0.1 mg/kg), or 3) saline. Following administration of an NMDA antagonist, rats were returned to a cylinder with a novel cue card on the wall, and HDCs recorded. After a 24-hour recovery period, rats were again recorded in the cylinder with the novel cue card rotated to determine whether it had gained control over the HDC.

Preliminary results show that HDCs are unstable within a recording session while under the effects of MK801. HDCs rotated their preferred firing direction up to 270deg during the session, as the animal locomoted around the cylinder. Note that HDCs did not show similar amounts of instability under any other conditions.

These results show that NMDA-receptor antagonists impair the animal's ability to use an environmental visual cue to orient by. In addition, the animal's spatial memory – the ability to learn to use the visual cue to orient to - was impaired.

Theme F: Integrative Physiology and Behavior

Neurobiological Effects of Antiepileptic Drugs in Rats with Age-related Spatial Memory Deficits

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Abstract

Electroencephalogram (EEG) recordings in rats and mice commonly display prominent 7-12 Hz oscillations known as sharp-wave discharges (SWDs) that are usually brief (1-2 s), terminate abruptly, most often occur along with vibrissa twitching during quiet wake, and increase in duration and number with age. Elevated neural activity within specific circuits of the hippocampal memory system has emerged as a prominent signature of poor cognitive outcome in aging, though it is unknown whether SWDs might contribute to hippocampal hyperactivity and associated spatial learning capacity in rodent models of normal cognitive aging. Pharmacological approaches to reducing excessive hippocampal activity, and thus restoring cognitive function in aged rats, has included administration of the antiepileptic drug levetiracetam (LEV). Here, we first examined whether SWDs are associated with cognitive outcome in a well-characterized rodent model of normal cognitive aging, Long-Evans (LE) rats. Spatial learning capacity was assessed using the Morris water maze, and aged rats that performed on par with Y were categorized as aged unimpaired (AU) while those that performed worse were considered aged impaired (AI). We collected electroencephalogram (EEG) data of all Y, AU, and AU animals for 24h and quantified SWD occurrence/duration. We found that SWDs were not associated with cognitive outcome ($p>0.05$), but aged rats (AU+AI), compared to Y, had significantly more SWDs ($p<0.037$). Time spent in SWDs did not significantly differ ($p>0.05$). These data indicate that SWDs are unlikely to account for cognitive deficits observed in aged rats with memory impairment. Next, we carried out a within-subject pharmacological approach, testing the efficacy of LEV at reducing SWD activity among aged AI rats, in comparison to another antiepileptic drug, ethosuximide (ETX), which unlike LEV, appears not to hold cognitive therapeutic potential. Three doses of each drug of each drug were administered in an ascending/descending order: 1.25, 10, and 50 mg/kg LEV; 25, 100, 200 mg/kg ETX; or saline control. EEGs were recorded for 3h following each injection, and SWDs were quantified. While LEV did not significantly reduce the number ($p>0.05$) or duration ($p>0.05$) of SWDs, ETX significantly reduced both the number ($p<0.0001$) or duration ($p<0.0001$) of SWDs. Given that these doses of LEV are within the range shown to be effective at improving cognition in AI rats, but were ineffective at reducing SWDs, further indicates that SWDs are not coupled to cognitive capacity among aged LE rats.

Theme H: Cognition

Chronic Mild Stress Produces Sex Differences in Spatial Learning and Memory and Synaptic Plasticity

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Abstract

Major depressive disorder is one of the most common mental disorders. The prevalence of depression among women is twice that of men. The development of depression is tightly linked with stress. Despite the higher prevalence among the female population, research examining the relation of stress and depression has exclusively focused on males. There are limited studies examining chronic mild stress (CMS) in both males and female rats. We used CMS to examine sex differences in weight, sucrose preference, Barnes maze, the novel location recognition (NLR) task and long-term potentiation (LTP) in a rat model. Our results show that CMS differentially affected weight in CMS groups. There was no significant difference in sucrose preference between control and CMS groups. For the Barnes maze, the CMS male group took longer to find the escape hole. The CMS male group consistently committed more errors throughout the assay. For search strategy, CMS males utilized random rather than serial strategy during later trials. In the NLR task, there were no differences in the discrimination index. Electrophysiological results show that CMS males had the largest reduction in LTP compared with control males, female control and CMS female groups. The results imply that sex differences exist between male and female rats exposed to CMS in both spatial learning assays and electrophysiological experiments. These results could further our understanding of why there is a difference in the prevalence of depression between females and males and help develop improved treatments for both sexes in the treatment of depression.

Theme F: Integrative Physiology and Behavior

Role of Estradiol in the Behavioral Effects of Cocaine in a Rodent Model of ADHD

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by atypical dopaminergic signaling in reward/reinforcement and attention pathways within the brain; these alterations may underlie the increased risk for substance use disorders in ADHD. A preliminary study found that female adolescent spontaneously hypertensive rats (SHRs), a rodent model of ADHD, were more sensitive to the effects of cocaine than male SHRs or Sprague-Dawley (SD) rats. The female sex steroid hormone estradiol has been found to modulate dopaminergic neuron firing rates as well as increase behavioral responses to cocaine in SD rats. Given that this hormone increases dramatically during puberty, the current study seeks to evaluate if estradiol is driving the enhanced responses to cocaine previously observed in adolescent female SHRs. Prior to puberty (i.e., 4 weeks of age), female SHRs were ovariectomized to eliminate the primary source of endogenous estradiol. These females then underwent a series of behavioral tests beginning one week post-surgery. Specifically, they were initially assessed for ADHD symptomatology and then subsequently examined for behavioral sensitization to repeated injections of 10 mg/kg (i.p.) cocaine. Our initial findings indicate that SHR females with a history of cocaine injections exhibited significantly greater locomotor responses to an acute cocaine injection compared to drug-naive females. This suggests that SHR females do not require peri-pubertal estradiol to show behavioral sensitization to cocaine. Ongoing studies are examining SD and SHR strains for the effects of estradiol availability on adult behavioral and neural responses to this drug.

Theme G: Motivation and Emotion

Functional microstructure of value tuning in primate orbitofrontal cortex

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Abstract

The orbitofrontal cortex (OFC) is crucial for encoding value information about stimuli to guide decision-making. Despite this, its functional microstructure remains poorly understood compared to well-characterized sensory regions like the visual cortex. For example, value encoding OFC neurons can be tuned positively (firing rate increases with value) or negatively (firing rate decreases with value). Here we investigated whether neurons exhibiting these different value tuning properties exist in anatomically distinct patches of OFC. To address this issue, we performed high density neuropixel recordings to monitor the activities of hundreds of simultaneously recorded OFC neurons in monkeys performing a value-based choice task. We report evidence of functionally distinct parcelations of positive and negative value encoding neurons within the OFC. Specifically, we found that ensembles of positively and negatively tuned value neurons occupy non-overlapping patches within the OFC.This result challenges prior reports of salt and pepper value tuning within the OFC and suggest a deeper functional microarchitecture than previously appreciated.

Theme H: Cognition

Comprehensive Analysis of Solution Optimized Fentanyl and its Analogs in the Human μ-Opioid Receptor

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Abstract

Opioids are widely administered to treat acute and chronic pain; however, the abuse of prescription and illicit opioids is a major health crisis in the United States. The current concern is that the clinical efficacy of these drugs is limited by the capacity to develop tolerance and addiction. Yet, opioids are continued to be prescribed for their unrivaled ability to moderate severe pain. Fentanyl and its analogs are capable of binding at different receptor sites, which enables different receptor conformations and production of negative side effects. This study aims to fill the gap in the understanding of how known flexible opioid ligands, like fentanyl and its analogs, are arranged in solution to bind tightly into the human μ-opioid receptor (hMOR) and why fentanyl has different physiological effects. Therefore, we hypothesize fentanyl and its analogs will stabilize different conformations of the receptor in solution, such that the overall binding energy of the hMOR-ligand complex is optimized. Solution phase structures were optimized using the ωB97X-D density functional with the 6-31++G** basis set, and entropies were generated for each structure. DLPNO-CCSD(T)/cc-pVnZ (n=D,T,Q) model chemistry with a complete basis set extrapolation resulted in accurate relative Gibbs free energies at the DLPNO-CCSD(T)/CBS/SMD//ωB97X-D/6-31++G**/SMD level of theory. All structures were computed using the SMD implicit solvation model at 310.15 K to simulate biological conditions. Results of this study will illustrate how fentanyl and its derivatives are arranged in solution and their ability to stabilize the receptor in different conformations unique from pain modulation pathways. Future work includes employing Quantum Mechanics/Molecular Mechanics (QM/MM) to combine traditional methods of Molecular Dynamics simulations with highly accurate quantum calculations for specific parameters set in the binding pocket of the hMOR.

Theme I: Techniques

The Limits of Vision Language Models Through the Lens of the Binding Problem

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Abstract

Recent work has documented striking heterogeneity in the performance of state 2 of-the-art vision language models such as GPT-4v and the DALL-E text-to-image models. These models are able to describe and generate an incredibly diverse array of complex, naturalistic images, yet they exhibit surprising failures on basic multi-object reasoning tasks – such as counting, localization, and simple forms of visual analogy – that humans perform with near perfect accuracy. To better understand this puzzling pattern of successes and failures, we draw on theoretical accounts from cognitive science that postulate a fundamental trade-off between representational flexibility (i.e., the use of compositional representations to promote generalization) and channel capacity (i.e., the number of entities that can be represented at any one time). This trade-off gives rise to the classic binding problem, leading to severe constraints on the ability to rapidly process multi-object scenes, and necessitating the use of serial processing to prevent interference. Drawing on this perspective, we hypothesize that VLMs, under pressure for generalization, also learn structured representations, but lack the serial processing mechanisms to effectively use these to process and generate multi-object scenes, resulting in severe capacity constraints similar to those observed when humans are forced to rely on rapid, parallel visual processing. We test this hypothesis through a combination of classic cognitive tasks and novel benchmarks. Our results provide a unique perspective on VLMs, informed by work in cognitive science, suggesting that their capacity for generalization paradoxically gives rise to many of their most notable limitations, possibly for the same reasons humans exhibit a similar profile of competencies and limitations.

Theme H: Cognition

Cortico-striatal representation of decision variables across cognitive demand

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Abstract

Evidence accumulation is vital for decision-making and a fundamental cognitive operation involving the dorsomedial striatum (DMS) and the anterior cingulate cortex (ACC). Bolkan et al. (2022) revealed that inhibiting DMS pathways elicited opposing effects on decisions only in tasks requiring evidence accumulation, suggesting task-dependent interactions between DMS and ACC. However, how these structures represent decision variables like evidence and choice across tasks with distinct cognitive demands remains unknown. We performed unilateral Neuropixels recordings across cortex and striatum in mice performing a virtual reality-based accumulation of evidence task, where visuo-tactile cues were transiently presented on each side of a virtual T-maze. Mice were rewarded for turning to the side with more cues. Mice also performed a sensory-guided ("no-distractors") virtual task, where cues appeared only on one side without the need for evidence accumulation. This enabled us to decode how decision variables are represented in cortical and striatal populations across tasks. In both tasks, a subset of ACC and DMS neurons predicted upcoming decisions by encoding evidence levels toward decisions or binarized choice. Decoding accuracy of cumulative evidence was comparable from both brain regions, although evidence information rose earlier in DMS in contralateral choice trials. Similarly, binary choice information rose earlier in DMS, but with more information from ACC as mice progressed the maze before turning. There was no significant difference in evidence decoding across tasks. These findings suggest that decision information might be routed from striatum to cortex, which in turn can broadcast binary choice to subcortical areas for motor execution.

Theme E: Motor Systems

Tracking Developmental Changes in Spatial Orientation Using Organization of Open Field Behavior in The 5xFAD Mice Model

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Abstract

Wandering behavior or becoming lost in familiar environment is frequently observed during the progression of Alzheimer's Disease (AD) and can be extremely dangerous. The accumulation of amyloid-beta peptide has been implicated in the neuropathology and cognitive deficits associated with AD. This study investigated changes in spatial orientation in a 5xFAD mouse model of AD that is associated with development of severe amyloid pathology. Movement was recorded under dark and light conditions as each mouse was placed on a round table with a small plastic tab attached to the edge. Noldus (video tracking software) was used to digitize the position of the mouse on the open field during the 20-minute session. This data was collected longitudinally when the mice were three, six, nine, and twelve months old. The resulting x- y-coordinates were segmented into stops and progressions. Significant group differences were observed in the topographic and kinematic characteristics of open field organization. These observations are consistent with impaired spatial orientation in the 5xFAD mice. This study furthers the understanding of impaired behavior in individuals suffering from AD. The persistence of the disruption in the organization of open field behavior observed in the 5xFAD mouse model establishes a foundation to evaluate the long-term efficacy of novel therapeutic interventions.

Theme H: Cognition

Effects of chronic vagus nerve stimulation in aging

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Abstract

Cognitive decline adversely affects activities of daily living and overall quality of life. This decline is mediated in part via age-related changes in excitatory/inhibitory (E/I) signaling in the brain, as well as increases in inflammation. Electrical vagus nerve stimulation (VNS), an FDA-approved treatment for epilepsy, shows promise in enhancing neuroplasticity and reducing inflammation, suggesting that it may counteract age-related cognitive deficits. The goal of this research is to address several potential beneficial effects of VNS in aging: first, to investigate whether VNS can remediate age-related impairments in cognitive tasks mediated by the hippocampus and prefrontal cortex (PFC), second, to determine if VNS can attenuate age-associated E/I dysregulation and impaired synaptic function in the hippocampus and PFC, and third, to determine how VNS affects peripheral and brain markers of inflammation in aged rats. Aged male and female FBN rats (24 mo.) were surgically implanted with a cuff electrode around the left vagus nerve and received daily 1-hour sessions of VNS to enhance cortical plasticity and various forms of learning (100 stimulus trains/session at 30Hz, 700 μA, 120 μs biphasic pulse width, 0.8 s train duration), or a sham control procedure, for at least 30 sessions. Preliminary data indicate that this VNS regimen significantly improves working memory performance in aged rats and significantly alters the profile of cytokine expression in aging. These findings, along with published data across species, suggest that VNS may serve as a promising intervention to mitigate cognitive decline and improve overall brain health in the aging population.

Theme H: Cognition

Quantitative Trait Locus Analysis to Identify genes associated with four parameters of locomotive controlled activities in Drosophila simulans, Drosophila sechellia, and their interspecies lines

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Abstract

Two sister species of Drosophila, simulans and sechellia, exhibit different 24-hour circadian-controlled locomotive activities influenced by external stimuli like light and internal mechanisms such as genes and neural networks. We hypothesized that by analyzing the varying locomotive phenotypes of these lines, combined with gene sequencing, we could identify the genetic loci associated with the targeted locomotion phenotype traits using quantitative trait locus (QTL) analysis. QTL is a statistical method that links phenotypic and genotypic data to explain the genetic basis of variation in complex traits (Miles and Wayne, 2008).We sequenced the DNA from over 100 interspecies lines and used a Drosophila Activity Monitor (DAM) to gather data on the circadian-controlled locomotive activity of each line. We characterized four parameters of the rhythmic locomotion profiles: day activity, night activity, day anticipation, and night anticipation. Our data was processed using hundreds of different genetic markers for the smoothing process, preparing it for QTL analysis. Our preliminary QTL analysis revealed promising peaks. We plan to screen more lines to increase the statistical power of our data and determine if those peaks are statistically significant.

Theme E: Motor Systems

A novel behavioral measure of long-term memory for naturalistic social content

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Abstract

How do individuals differ in their ability to remember information about other people? Existing measures of long-term memory performance use simple stimuli such as words or images. This approach offers tight stimulus control, but doesn't capture the abstract social information that humans encode about others in naturalistic experience, including information about personality, relationships, and mental states. To address this gap, we developed and validated a novel behavioral task for measuring long-term social memory from narrative movie stimuli. Participants (N = 72) watched the pilot episodes of either Friday Night Lights or Gossip Girl, which were chosen for their rich social content and character development. Both immediately after watching the episodes and following a 3-week delay, participants answered multiple choice probe questions assessing their memory for social information. Probes were separated into six categories based on the type of information they were designed to test, including "event-based" questions about specific events in the narrative (actions, statements, and mental states), and "abstract" questions for information not tied to a specific event (personality, relationships, and mental states). Performance with no delay was high (>90%), demonstrating consensus on correct answers to potentially subjective questions. Performance dropped significantly after the delay, with an interaction between question category and delay reflecting a larger decrease in memory for event-based versus abstract information. Delay performance ranged from 50 to 95% across participants with moderate split-half reliability, indicating the utility of this measure to capture individual differences. To compare our novel social memory measure to other tests of long-term memory performance, we included several additional measures in a subset of participants: 1) the Rey Auditory Verbal Learning Task, a standard test for verbal memory; 2) a face naming task; and 3) an image recognition task. Social memory performance was strongly correlated with face naming, and weakly with the RAVLT, suggesting convergent validity with other related measures. These results provide preliminary evidence that our social memory task captures reliable individual variance in long-term memory ability, providing a tool for future studies to assess memory in the social domain.

Theme H: Cognition

Midkine and Syndecan-4 Double Knockout by CRISPR May Alter Vascular Development in a Mouse Model of Supratentorial Ependymoma

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Abstract

Supratentorial Ependymoma (ST-EPN) is a lethal pediatric brain tumor without an effective non-surgical treatment. More than 60% of ST-EPN are caused by fusions between ZFTA and RELA genes. We used a genetically engineered mouse model of ST-EPN in which expression of Zfta-Rela fusion is conditionally controlled by CRE. Previous RNAseq experiments in this mouse model and in human ST-EPN brain tumors indicated that many genes are upregulated including MDK and SDC4. SDC4 is necessary for vascular endothelial cadherin and angiogenesis, and MDK is a secreted heparin binding growth factor that promotes angiogenesis and carcinogenesis. We targeted both Mdk and Sdc4 by somatic CRISPR in our mouse model. Cre recombinase mRNA, Cas9 mRNA with and without sgRNA targeting Mdk and Sdc4 were co-electroporated into radial glia at P0-P2. Brains were processed for immunohistochemistry at P21 and tumor vasculature and tumors were labeled by CD31 antibodies, tomato lectin, and Hoechst dye. Sections were imaged using an AxioZoom fluorescent microscope and ImageJ was utilized to analyze images. We found that tumors in Mdk-Sdc4 knockouts were generally smaller compared to controls. Furthermore, in smaller tumors vasculature was limited in double knockouts relative to controls. In larger tumors by contrast vascularization was extensive and complex in both controls and knockouts. We propose that Mdk and Sdc4 in early stages may affect tumor vasculature and reduce tumor growth, but as tumors grow additional pathways may cause comparable hyper-vascularization in both controls and knockouts. Further studies are necessary to confirm the effects on ST-EPN growth and neovascularization.

Neural Basis for Concurrent Visual Perception and Visual Working Memory Processing

Khayla Santiago, Fanta Jatta, Chunyue Teng

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Abstract

Successful goal-directed behavior requires the delicate balance between managing task-relevant information stored in working memory and the continuous processing of incoming sensory input. The current study investigates the role of neural oscillations in supporting concurrent visual perception and visual working memory. We recorded electroencephalogram (EEG) while healthy human participants performed a task that requires simultaneous engagement of working memory and perceptual processing. Participants were instructed to maintain a specific orientation in mind while also observing another orientation patch on the screen. After a variable inter-stimulus-interval (ISI), they were prompted to compare a test probe against either the memorized orientation or the visually monitored orientation. Critically, we manipulated the duration of the ISI: 500-1500 ms with a 20 ms step, resulting in a total of 50 ISIs. Response time (RT) and accuracy were analyzed separately for each task. Visual inspection of the time courses revealed notable fluctuations in both RT and accuracy. We performed Fast Fourier transform of the data to extract spectral power and phase angle across different frequencies, and the analysis identified increased power within the theta and low-alpha frequencies for both the perceptual and memory tasks. Importantly, the two representations fluctuated at different phase angles at those identified frequencies, indicating a distinct rhythmic alternation in attentional sampling between external and internal visual representations. Together, these results demonstrate the rhythmic nature of attentional shifts between internal and external visual representations, and further highlight the functional relevance of neural oscillations in segregating visual representations of different sources.

Theme H: Cognition

Exploring the therapeutic potential of strategies that upregulate sAPPα and reduce beta-amyloid

Santiago Serrano, Owen Richards, Daniel J. O'Leary, Karen D. Parfitt

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Abstract

Alzheimer's Disease (AD) is a neurodegenerative disorder affecting one in nine Americans over the age of 65. It is linked to the accumulation of beta-amyloid (Aβ) proteins and reduced secretion of amyloid precursor protein alpha (sAPPα). The FDA-approved drug acitretin has been shown to enhance cognitive function, reduce Aβ levels, and increase the secretion of sAPPα. We have observed that acitretin treatment of an AD mouse model, 5XFAD mice, reverses deficits in hippocampal LTP, a cellular process underlying learning and memory. In previous studies, we and others have reported that sAPPα , as well as a tripeptide portion of sAPPα (RER), rescues LTP deficits in APP/PS1 mice. Our ongoing work aims to evaluate the therapeutic effects of acitretin in reversing spatial learning deficits and suppressing Aβ formation. In addition, we aim to identify the binding site of sAPPα using the RER tripeptide derivative; this will be achieved by synthesizing RER with an N-terminus suitable for click chemistry. Further understanding of the molecular actions of sAPPα may enhance the development of targeted therapies for AD.

Theme C: Neurodegenerative Disorders and Injury

Restraint stress and cocaine cross-sensitization: influence of adrenergic signaling in male rats

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Abstract

Sensitization is the process through which repeated exposure to cocaine increases the locomotor response produced. This effect can be modulated by administration of adrenergic receptor antagonists and stress. Cross-sensitization is the process through which repeated exposure to another stimulus increases the locomotor response to cocaine. To test the interaction of these systems, we conducted a seven-day cocaine sensitization protocol in male Long-Evans rats. We first determined the animals' locomotor responses to cocaine challenge (10 mg/kg). Then, for the next seven days, we exposed the subjects to either 1) cocaine (10 mg/kg), two hours of restraint stress, or home cage control 2) with or without administration of the alpha-2 adrenergic receptor agonist clonidine in a 3x2 between-subjects design. We then repeated the locomotor challenge to determine levels of sensitization and cross-sensitization effects.

Theme F: Integrative Physiology and Behavior

Vicarious Trial and Errors (VTEs) Represent Deliberation

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Abstract

When faced with multiple options, imagining the possible future outcomes deliberatively plays a role in the evaluation and subsequent choice amongst those outcomes. Rodents are thought to engage in the imagination of future outcomes through 'vicarious trial and error' (VTE), an overt process characterized by pauses in running accompanied by head swivels. Deliberating between future outcomes requires the subject to know the possible outcomes/options, thus there will be little deliberation when options are new. In contrast, if the subject already knows with a high degree of certainty what the best possible outcome is, there is little need to deliberate. Thus, we hypothesize a delay between the introduction of a new environment and the peak in VTE frequency, followed by a decline in VTEs as rats learn whether the new environment will lead to a better outcome. To test this hypothesis, we used a transitive inference (TI) task using rats. In TI, there is a hierarchy of elements (A>B>C>D>E) that subjects must learn by appropriately responding to the relative value of presented pairs. However, subjects are only trained on overlapping pairs and pairs are added serially starting with A-B & B-C then adding C-D followed by D-E. The introduction of new pairs requires the introduction of new arms - a change in the environment. Rats' learning rates, performance, and VTE counts are measured as new environments are added. We see a delay before observing an increase in VTE events after the change in environment, reaffirming the characterization of VTEs as deliberation.

Theme H: Cognition

Rhythmic Endogenous Attention Sampling Under Spatial Uncertainty

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Abstract

The rhythmic theory of attention proposes that attention operates in rhythmic cycles at the theta band (4–8 Hz), reflecting alternating states of external sampling and internal processing. While previous studies tested the theory using bottom-up attention cues, this project investigates whether the same applies to endogenous, voluntary attention, and how spatial uncertainty affects the rhythmic process.

Participants performed a spatial attention task where they fixated in the center while monitoring two peripheral gratings. A brief dot cloud of blue and red dots served as an endogenous spatial cue. The color dominance indicates where a target would appear with 80% validity, while spatial uncertainty was introduced by varying the blue-to-red ratio. The target would appear after the cue, with a cue-target interval (CTI) randomly selected from 300 to 1100 ms, representing a near-threshold orientation change on either of the gratings. Participants were required to indicate the target location and then rate their confidence about the cue's content.

We found an endogenous attention effect; compared to the uncued condition, people displayed better detection performance for targets at the cued condition, while this effect attenuated with increasing spatial uncertainty. Importantly, preliminary results showed that detection accuracy fluctuated as a function of the CTI at the theta band. We further predict that when the spatial uncertainty increases, the rhythmic attentional sampling will accelerate to alternate between locations in a rapid manner.

The study advances our understanding of how the brain allocates attention under uncertainty, with implications for underlying neural mechanisms.

Theme H: Cognition

Benign Taste Experience Enhances Aversion Memory Persistence and Plasticity Markers in Gustatory Cortex

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Abstract

Both humans and animals learn to reliably avoid or seek foods based on experience. For example, through associative learning, animals learn to avoid tastes that have been previously paired with negative consequences. In a laboratory setting, this is known as conditioned taste aversion (CTA). This learning experience, however, can also be influenced by prior experiences. For example, taste experience with sour and salty tastes (TE) enhances CTA to novel sucrose 24 hours later (Flores, 2016). Benign taste experiences are ubiquitous in the everyday lives of humans and animals, so it is important to understand its influence on learning in the long term. Here, we investigate the behavioral and neural impacts of benign taste experience on long term memory retention and persistence. We expected that rats who had TE would better retain their aversion at 1 week and 2 weeks post CTA than rats who had only had water experience which is what we found after 2 weeks. To address the strength of memory persistence, we tested all rats at 24 hours and then either 1 week later or 2 weeks later. We expect that rats in the TE group will have stronger memory persistence. Preliminarily, we have seen evidence of memory persistence between test 1 and 2. In addition, we aim to study the underlying neural plasticity involved in the effect of TE. We will use immunohistochemistry to locate cells expressing Npas4, a protein known to be involved in synaptic plasticity, in gustatory cortex (GC).

Theme D: Sensory Systems

Do Silver Nanoparticles Disrupt Synapse Structure in Rat Brain?

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Abstract

Silver nanoparticles (AgNPs) are incorporated in products including toys, cosmetics, and surgical tools due to their unique antimicrobial properties. During the manufacturing process and usage, AgNPs are released into the environment resulting in the exposure of animals. When mammals are orally exposed, AgNPs bioaccumulate and persist within the brain. We previously found that AgNP exposure disrupts F-actin structure and induces neurite collapse in cultured neural cells and promotes the formation of tau protein aggregates in rat brain. Cytoskeletal structure is key to synaptic morphology. Because synapses require highly specific structure and organization to function, disruptions of these critical proteins could lead to dysfunction in neural pathways and circuitry. Thus, the objective of this study was to determine if AgNP exposure disrupts synapse structure by quantifying synaptic protein expression and colocalization of pre- and post-synaptic terminals. Through immunohistochemical experiments, we labeled the pre-synaptic proteins bassoon, vesicular glutamate transporter, or vesicular GABA transporter and the post-synaptic proteins gephryn or post-synaptic density protein-95. To quantify expression and colocalization of synaptic proteins, images taken with confocal microscopy were analyzed using SynBot in ImageJ. Because AgNP exposure impairs critical structural and organizational proteins in both cell culture and rat brain, we anticipate that oral AgNP exposure will disrupt the close apposition of pre- and post-synaptic terminals in the rat brain. If the expected disruption in synaptic morphology occurs, chronic low-level environmental exposure to AgNPs could lead to neurodevelopmental or neurodegenerative disorders. Therefore, our work could guide regulation of AgNP usage and disposal in manufacturing.

Theme B: Neural Excitability, Synapses, and Glia

A novel rat model of sudden social withdrawal (experienced universally during the COVID pandemic) offers inclusive opportunities for behavioral and neurophysiological investigation by early-stage college students that are experimentally accessible and diverse

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Abstract

The experience (shared by all during the COVID pandemic) of a sudden withdrawal from social interaction has effects upon cognitive/mental health in ways that are not yet fully understood. A novel rat model was developed to reflect the behavioral and neurophysiological changes incurred by sudden removal of high social enrichment during adolescence. For 5 weeks, juvenile rats were pair-housed in larger cages with multiple toys and underwent extra handling & 20-min playdates with 13 same sex rats. Afterwards, baseline scores were obtained for rearing, grooming, nose poking in a hole-board, time in the center of an open field, arm entry in an elevated plus maze, arm alternation in a T-maze, and novel object/place exploration (Trial 1). For the following 4 weeks, Control rats continued to experience high social enrichment, whereas Experimental rats were transitioned to standard enrichment with smaller cages, minimal handling, and no playdates. Behaviors were re-evaluated (Trial 2). Levels of norepinephrine (NE), serotonin (5-HT), and dopamine (DA) in post-mortem tissue from structures of cortico-basal ganglia-thalamic circuits were analyzed. Results from student projects demonstrate that response to reduction of social enrichment is markedly influenced by Sex. For example (Figure 1), reduction of high social enrichment decreased time spent in open arms by males, but not by females. Reduction of high enrichment increased NE levels in the hypothalamus and 5-HT levels in the dorsal striatum in males, but decreased the levels in females. This novel model offers an experimental paradigm with numerous advantages: wide-ranging usefulness for behavioral and/or neurophysiological projects; utilization of inexpensive and experimentally accessible methodology appropriate for first/second year students; application to topics directly relatable to students of all backgrounds; and potential to obtain results with translational value for better understanding of how psychiatric conditions are impacted by sudden social deprivation.

Theme J: History, Education, and Society

The role of sleep in age-related cognitive decline: A search for cellular and molecular substrates

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Abstract

Accumulating evidence indicates that age-related changes in sleep quality and quantity contribute to increased risk of Alzheimer's disease and cognitive impairment later in life. At present, however, our ability to identify the cellular and molecular mechanisms that link sleep and age-related cognitive decline are limited in large part by the lack of animal models that reliably recapitulate relationships observed in humans. Given the long lifespan in humans, a valid preclinical model would also facilitate longitudinal study designs that examine whether sleep earlier in life affects cognitive outcome later in life, and moreover, would offer a means to identify interventions aimed at slowing, stopping, or even preventing age-related cognitive decline. To that end, we focused on Fisher 344 rats, which are the most widely used rat strain in aging research, are provided by the National Institute on Aging (NIA) as a resource to facilitate aging research. Here we tested young (~6 months; N = 8 males, 10 females) and aged (~23 months; N = 11 males, 10 females) rats in a hippocampus-dependent version of the Morris water maze. Spatial memory capacity was assessed by means of a learning index (LI) score, which was calculated as the weighted average proximity to the hidden escape location across probe trials. We observed that, on average, young rats performed significantly better than aged rats ($p<0.0001$), where only two aged rats performed within the range of young. These data suggest that F344 rats may be particularly well-suited to assess cognitive impairment. Young male and female rat LI scores did not significantly differ ($p=0.86$), nor did LI scores between aged male and female rats ($p=0.23$). Next, we recorded EEGs and EMGs from these rats to assess sleep quantity (both REM and NREM) and quality. These analyses are ongoing. Together these data will allow us to determine whether Fisher 344 rats may be a useful model to examine the neurobiological basis connecting sleep and cognitive outcome later in life.

Alzheimer’s disease associated pulmonary changes in humans and the AppNL-G-F mouse model

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease affecting cognition. Brain immune changes are a component of the disease, but immune dysfunction in secondary organs has also been reported. The amyloid precursor protein (APP) produces Aβ by using secretase enzymes and Aβ aggregates into plaques. This neural role of APP is well explored but relatively unclear in secondary organs like lungs where we previously observed robust APP expression in the epithelium. Based on this expression pattern, we hypothesized that lung APP expression/metabolism leads to Aβ production and epithelial dysfunction as a peripheral characteristic of disease. Lungs were collected from 8/9-month male and female C57BL/6 wild type and AppNL-G-F mice and human normal and AD subjects and were used to perform immunohistochemistry and western blotting. Both sexes of AppNL-G-F mice showed no differences in Aβ immunoreactivity, APP levels, or APP immunoreactivity compared to wild type. However, human AD lungs showed a dramatic increase in APP and Aβ immunoreactivities compared to normal controls. Next, we examined claudin-4, an epithelial tight-junction marker, which showed reduced immunoreactivity in both sexes of AppNL-G-F mice and AD subjects compared to their respective controls. To the best of our knowledge, we are the first to report increased APP levels, Aβ immunoreactivity, and reduced tight-junction integrity in particularly human AD male lungs. These data suggests that organs, including lungs, are affected by AD. Further characterization of AppNL-G-F mouse model lungs is needed to confirm their relevance for studying this peripheral aspect of AD.

Theme C: Neurodegenerative Disorders and Injury

Effects of Liraglutide on STZ-Treated Aged C57 Mice

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Abstract

Recent studies have shown that the anti-diabetic drug, liraglutide (LIR), can reduce age-related deficits in rodent models of Alzheimer's disease (AD) and age-related cognitive decline. The aim of the present study was to see if LIR treatments could reduce deficits in aged C57 mice that were given intracerebroventricular injections of the potent toxin, streptozotocin (STZ), which is used to model sporadic AD. STZ is a toxin derived from the bacteria Streptomyces achromogenes that can produce vascular dysfunction within mammalian models, likely through inducing endothelial dysfunction. In our study, aged (17-19-month-old) C57 mice received either bilateral intracerebroventricular injections of STZ or citrate buffer solution (CBS) vehicle and were subsequently treated with either LIR or Hank's buffered saline solution, intraperitoneally, once a day for 36 days. Mice were evaluated on three behavioral tests: passive avoidance, open-field, and novel object recognition tasks. Following behavior assessments, various organs, including the brain, pancreas, heart, spleen, liver, kidneys, and lungs were extracted, weighed, and processed for Western blot analyses to assess inflammatory markers, including TNF-alpha, SOD-1, and IL-6. Our findings suggest that LIR had only modest effects on the behavioral performance of the mice and this correlated with the changes observed in the biochemical profiles of the mice. These results suggest that the modest effects of LIR in the aged and STZ-treated C57 mice indicate that earlier interventions with LIR treatment might be needed in order to optimize its therapeutic effects.

Theme C: Neurodegenerative Disorders and Injury

Investigating the effects of environmental enrichment on morphine-induced withdrawal symptoms and anxiety-like behavior

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Abstract

Opioid Use Disorder (OUD) is a significant global health issue, affecting over 16 million individuals worldwide, including 2.1 million in the United States (Dydyk, 2024). Despite available treatments, relapse rates remain alarmingly high, exceeding 50% (Lee, 2022). Previous research suggests that environmental enrichment (EE) can reduce drug cravings and the risk of relapse (Galaj, 2019). This study investigates the impact of EE on opioid withdrawal symptoms and anxiety-like behaviors, which are critical factors in relapse. We hypothesized that EE would significantly alleviate these symptoms. To test this, we induced opioid dependence in 16 Sprague Dawley rats through twice-daily escalating doses of morphine over ten days, starting at 2.5 mg/kg and doubling every two days until reaching 40 mg/kg. This was followed by a five-day withdrawal phase. The rats were housed in either standard cages (n=8) or enriched environments (n=8) equipped with stimuli such as running wheels, chew toys, tunnels, and hammocks. We assessed withdrawal symptoms as well as anxiety-like behaviors using the Elevated Plus Maze and Light-Dark Box tests. Contrary to our initial hypotheses, we found no significant differences between the standard and EE groups in terms of withdrawal symptoms or anxiety-like behaviors. These results highlight the complexity of OUD and suggest that EE alone may not significantly influence withdrawal or anxiety symptoms. Further research with refined protocols and larger sample sizes is necessary. Given the ongoing opioid crisis, these findings underscore the urgent need for innovative interventions to improve addiction recovery outcomes.

Theme G: Motivation and Emotion

Identifying peripheral immune response signature dependent on Parkinson's Disease progression

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Abstract

Disrupted immune function is a significant component of Parkinson's disease (PD) and inflammatory cytokines in the blood may serve as biomarkers to identify early PD. However, there is significant variability in circulating cytokine levels due to circadian rhythm, diet, and environmental exposures. Stimulation-based assays may be more sensitive to underlying immune dysfunction, potentially allowing us to observe immune deficits in patients prior to the development of motor symptoms in PD. To investigate this, peripheral blood mononuclear cells were collected from healthy controls, early and moderate PD, and prodromal PD individuals with REM sleep behavior disorder who are likely to convert to PD. Monocytes and T-cells were isolated, plated, and treated with vehicle or a stimulation paradigm (interferon gamma for monocytes, CD3/CD28 beads for T cells) for 72 hours to assess stimulation-based responses rather than baseline differences. Flow cytometry was used to analyze monocyte and T-cell subtypes, activation, mitochondrial health, and lysosomal activity. The cultured media was analyzed for cytokine secretion using Meso Scale Discovery assay. We observed that later stages of PD are associated with a more proinflammatory monocyte composition, and T-cells from later stage PD patients showed lower fractions of functional mitochondria after stimulation. Prodromal PD cells exhibited higher stimulation-dependent secretion of TNF, IL-1β, and IL-8 relative to early and moderate PD, as well as a distinct signature of immune activation relative to healthy controls. These findings reflect observable immune dysfunction based on PD progression, indicating potential in blood stimulation-based assays as biomarkers for early PD identification.

Theme C: Neurodegenerative Disorders and Injury

Impact of reduced gut bacteria on neurodegeneration in a Drosophila model of human tauopathy

Melissa Tribley, Mihira Karnik**,** Owen Kamer**,** Pooja Jakkampudi**,** Srivatsa Bellamkonda**,** Joseph Figura**,** Oyunsuvd Bat-Erdene**,** Matthias Hirst**,** Lindsay Gray**,** Kelly Lohr

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Abstract

Deposition of the microtubule-associated protein tau is a hallmark pathology of the family of neurodegenerative diseases known as tauopathies, including Alzheimer's disease, frontotemporal dementia, and chronic traumatic encephalopathy. Ongoing work on mechanisms of tau-mediated neurodegeneration suggest that genetic contributions interact with peripheral or environmental factors to contribute to disease onset and severity. Recently, the gut microbiota has emerged as a potential modifier of brain function in human, rodent, and invertebrate models via changes to neurotransmitter levels and systemic inflammation. We have previously shown that Drosophila expressing human tau in neurons show reduced gut motility and an increased bacterial load compared to control animals. Further, tau transgenic flies show activation of the innate immune system as shown by antimicrobial peptide expression. To expand upon these studies, we have grown control and tau transgenic flies in an environment with limited bacterial exposure and show enhanced neurodegenerative outcomes. Taken together, these data suggest that tau transgenic flies have an innate deficit in gut function and that manipulation of the gut microbiota is capable of altering neuronal health in this Drosophila model of human tauopathy.

Theme C: Neurodegenerative Disorders and Injury

Differential immune responses may contribute to varying outcomes between a single, severe TBI and a mild, repeated TBI

Daniel Tulchinskiy, Jorge A. Garcia, Kamden Kuklinski, Doyinsola Ogunshola, Maria Jose Orozco Fuentes, Dr. Rebecca Delventhal

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Abstract

Traumatic brain injuries (TBIs) occur when external forces damage the brain, commonly resulting in hospitalization, long-term disability, and death. This neurological disorder accounts for nearly 30% of deaths due to injury in the US. The features of injury that lead to worse outcomes are difficult to discern in the human population due to varying demographics and injury types. To eliminate these confounding variables, we used Drosophila melanogaster as a model organism to study the short- and long-term outcomes of mild, repeated TBI (multi-day, MD) compared to a single, severe TBI (single-day, SD). We discovered that the outcomes of the two patterns of TBI differed. We found that flies given a MD TBI showed lower acute mortality (within 48 hours), but the surviving flies displayed a shorter lifespan than flies given a SD TBI. Likewise, flies given a MD TBI exhibited worse long-term locomotor ability. We hypothesized that different immune responses to MD versus SD TBI may mediate differences in short- and long-term outcomes and found evidence of prolonged immune gene expression in MD TBI several weeks post-TBI. To determine if the differences in immune response were causal, we examined flies with mutations in key immune genes and measured their effects in the two injury paradigms. Specifically, we measured acute mortality and lifespan of Imd and Toll mutant flies post-MD and SD TBI. We found that short- and long-term survival in both injury conditions worsened when Imd was absent, suggesting that the Imd immune signaling is likely protective against short- and long-term outcomes from both MD and SD TBI. Interestingly, mutants lacking Toll immune signaling displayed opposite responses to each injury type: worse survival after SD TBI, but better survival after MD TBI. The Toll mutants also displayed increased lifespan following MD TBI, relative to wild type controls, suggesting that Toll signaling is detrimental for both short- and long-term outcomes from a MD TBI. Cell-type specific knockdowns of Imd and Toll signaling suggest that immune signaling in glial cells plays a larger role than in neurons in affecting the outcomes of TBI. Understanding differences in cellular immune responses, and the timing of these responses, to different types of TBI could enable the development of tailored treatments, and ultimately improve outcomes.

Theme C: Neurodegenerative Disorders and Injury

Fear Memory Engrams in the Dorsal Hippocampus During Fear Learning and Fear Generalization: Implications for Vulnerability to Post-Traumatic Stress Disorder

Aasrita Tulluri, Lola Fay Papanikolaou, Molly M. McAnespie, Hussain K. Asgarali, L. Hazel Edwards, Sofia Cañuelas del Valle, Alexander Stratmann, Prajit Chatterjee, Adam Daki, Monica Mackey, Zain Ahmad, & Stephanie L. Grella

Loyola University Chicago

Abstract

The lifetime prevalence of Post-Traumatic Stress Disorder (PTSD) is 7.8% in the U.S. Currently, it is unknown why specific subsets of individuals are more vulnerable to developing PTSD. For instance, women are more likely to develop PTSD1. A hallmark symptom of PTSD is fear generalization, where acquired fear responses to a particular stimulus or context are transferred to other stimuli and contexts. This may stem from memory-updating impairments involving a failure to remap trauma-related memory traces in the presence of novel information (e.g., safety signals), and the persistent recall of these traces in the presence of non-trauma-related contexts / stimuli. Here, we assessed these potential remapping deficits at the engram level in wildtype male and female c57BL/6 mice. The stability and flexibility of fear-related memory traces in the hippocampus were examined using a viral-based neuronal tagging strategy (Tet Tag system) combined with immunohistochemistry and fluorescent confocal microscopy. We also examined whether fear generalization or remapping deficits could be predicted using a behavioral pre-screening method associated with the acoustic startle reflex where mice were parsed into susceptible and resilient populations based on their response to a startle stimulus delivered acoustically.

Theme H: Cognition

Investigating the Link Between Social Reward Sensitivity and Social Media Addiction

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Princeton University

Abstract

With over 5 billion people using social media, it is clear that social media is becoming an important part of daily life around the world. Although social media can have a positive effect on someone's ability to connect socially through various online platforms, there is also evidence that social media can have a serious impact on (and be impacted by) mental health in ways that are unclear. The very feature of social media that signals social support, praise or validation - the social media rewards, such as likes, shares or comments - could itself be potentially harmful through reward processing mechanisms that lead to addiction. Prior research has found that looking at social media posts with more likes results in increased activity in neural regions associated with reward processing, reinforcement, and addiction. Other studies have shown that heightened activity of these regions in response to task-based social reward in early adolescence predicts social media addiction and depression in late adolescence. In order to test this connection directly from social media behavior in adults, here we use participants' whole history of Twitter data to examine how their social media addiction relates to their "behavioral reward sensitivity", i.e. how participants' posting is reinforced by how many likes they receive . We predict that people with higher symptoms of social media addiction had higher levels of reward sensitivity upon starting their account, which then decreased with the number of years of social media use. Overall, this finding would suggest that initial high reward sensitivity is a potential cause of social media addiction later on, and would corroborate neural findings in adults using participants' real-world social media data.

The influence of age on the gut-brain axis following recovery from an intestinal insult

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Abstract

A growing body of evidence links dynamics in the intestine to behavior, thus highlighting an inter-organ connection referred to as the gut-brain axis. Mechanisms that establish the gut-brain axis are poorly understood, particularly as they pertain to behavioral changes that may be linked to advanced age. Here we evaluated behavioral changes and microglia morphology in multiple brain regions following recovery from an acute intestinal insult. Intestinal insults, from either enteric pathogens or non-specific mediators of inflammation, are a normal component of mammalian life and our overarching hypothesis was that age would play a role in behavioral and morphological outcomes after recovery from an intestinal insult. To model a non-specific intestinal insult we used the acute dextran sodium sulfate model (DSS) of colitis in young (8-week-old) and aged (60-week-old) male mice. DSS-treated mice were allowed to fully recover from the insult, but are hereafter referred to as DSS mice. Age-matched, control mice were used as comparisons. Sociability, evaluated by the three-chamber sociability apparatus, revealed no significant differences between groups. In contrast, the elevated plus maze revealed increased anxiety-like behaviors for DSS mice, regardless of age. We are currently evaluating microglia morphology in the amygdala, hypothalamus, and hippocampus in order to better understand the role of inflammation in this model. We hypothesize increased activated microglia in DSS mice compared to control mice, and the most activated microglia for aged DSS mice. This study was a collaboration between a neuroscience lab (Freeman Lab) and a mucosal immunology lab (Hammer Lab).

Theme F: Integrative Physiology and Behavior

Behavioral Tests for the Characterization of Zebrafish Acetylcholine Receptor Mutants

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Abstract

Nicotine-use behavior represents a major cause of preventable diseases worldwide. Studying genes that change the risk for nicotine-use could lead to the development of new nicotine-cessation treatment. Single nucleotide polymorphisms in genes of nicotinic acetylcholine receptor subunits alpha 3 (CHRNA3), alpha 5 (CHRNA5) and beta 4 (CHRNB4) have been linked to heavy smoking and early smoking onset in humans. In rodents Chrna3 and Chrna5 function is critical for nicotine avoidance behavior. Larval zebrafish represent an excellent model for studying gene function in behavior as genome modifications and behavioral tests can be performed with high efficiency. For studying the impact of chrna3 gene knock-out mutations in larval zebrafish we developed robust behavioral stimulus-response tests for sensitivity to light, temperature, chemical agents, and mechanoreceptor stimulation (tapping) using Daniovision (Noldus). Wild-type larval zebrafish attenuated quickly to repeated tapping and could partially recover within seconds. Bright light reduced the swimming activity. Mustard oil but not capsaicin increased movement activity and reduced attenuation to repeated tapping. Quick temperature changes triggered increased movement activity. Nicotine application (20 µM) resulted in stronger acute behavioral responses. Both the alpha3-beta4 nicotinic acetylcholine receptor antagonist SR16594 and chrna3 gene-knockout mutations weakened the attenuation and recovery in tapping experiments. Overall, the results indicate that the chrna3 gene could play a role in regulating responses to repeated and irritant stimulation in zebrafish. Moreover, the results will help to interpret the impact of chrna3 gene knockout mutations in zebrafish nicotine-seeking and avoidance assays.

Theme G: Motivation and Emotion

Exploring the Impact of Drug-Associated Memories in the Dentate Gyrus on Drug-Seeking Behavior

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Abstract

Addiction is characterized by a continual propensity to relapse. Relapse-prevention strategies aimed at reducing the likelihood and severity of relapse following abstinence, focus on reducing cravings that lead to drug-seeking. Factors precipitating drug-seeking include exposure to drug-related cues, to the drug itself, and to stress. We are interested in the contribution of drug-related memories in drug-seeking behaviors. Memories are thought to be stored as representations (engrams) in the hippocampus. Recent technological advances have given us the ability to genetically tag and manipulate memories in mice, such that we can reactivate them with light post-encoding. To investigate the role of these memories in promoting or protecting against relapse, we tagged dorsal dentate gyrus (dDG) cells involved in encoding a cocaine-related memory using a Tet-tag system to express ChR2 driven by the c-Fos promoter, in male and female c57BL/6 mice. Conditioned place preference (CPP) has been used to study the rewarding aspect of drugs and the reinstatement model has been specifically used to study relapse. We carried out multiple CPP experiments to assess whether a cocaine-tagged memory could be used in place of cocaine during conditioning and during reinstatement thus exploring whether conditioning or reinstatement could be primed via the memory of the drug in comparison to the drug itself. We also assessed whether these effects were additive.

Theme H: Cognition

Examination of how carbamazepine affects sleep in different light-controlled environments in Drosophila melanogaster

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Abstract

Carbamazepine (CBZ) is a commonly used medication to treat bipolar disorder and epileptic seizures in humans. CBZ has been found to promote wakefulness during the nighttime under standard 12 hr/12 hr light/dark (LD) conditions in the fruit fly Drosophila melanogaster. It is unknown why CBZ specifically affects sleep during the night. To address this, we conducted experiments in environmental conditions of total darkness (DD) and total light (LL). Both male and female flies exposed to CBZ in LD conditions followed the same pattern from previous studies, with decreased sleep only seen during the 12 hours of dark. However, in DD conditions, CBZ treatment in both male and female flies caused a decrease in sleep across the entire 24 hours. In females, this effect diminished gradually over successive days. It was also found that males exposed to CBZ had a lengthened circadian period in DD, resulting in a gradual right-shift in sleep/wake behavior. In LL, both sexes followed a similar sleeping pattern, where CBZ caused a slight decrease in sleep across the whole 24 hours. These differences suggest that the presence or lack of light is a significant factor in how CBZ functions to affect sleep. Future studies will be conducted to observe how CBZ interacts with sleep-promoting signals. Overall, these studies will acquire insight into the localization of the molecular and cellular pathways that CBZ acts through to influence sleep.

Delineating the Relationship Between Plasma Biomarkers and Brain Amyloid Pathology In Preclinical Alzheimer's Disease

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Abstract

Over six million Americans are diagnosed with Alzheimer's disease (AD). By 2050, this number is projected to nearly triple to 16 million. Mitigating this rise necessitates establishing quantifiable preclinical indicators present prior to symptom manifestation. Brain amyloid-beta (Aβ) burden - a hallmark of AD pathology - is a principal preclinical indicator. Unfortunately, accessing this diagnostic currently requires either an expensive PET scan or a highly invasive spinal tap procedure. Fluid biomarkers, measured through blood or saliva samples, proffer a more accessible alternative. Identifying which fluid biomarkers correlate most closely with brain Aβ levels can help establish vital preclinical AD indicators and contribute to early risk assessment. In this study, plasma samples were collected from a cohort of 69 cognitively normal adults (40 female, aged 60-86, average age 70) enrolled in the Biomarker Exploration in Aging, Cognition, and Neurodegeneration (BEACoN) study at the University of California, Irvine, and run on the Quanterix Simoa platform. Brain Aβ was measured with 18F-florbetapir-PET, using the mean SUVR of a cortical composite region as an indicator of global Aβ burden. Aβ positivity was defined as > 1.11 cortical composite SUVR. Relationships between individual biomarkers and Aβ-PET uptake were evaluated through linear regression analysis, and a Random Forest Classification machine learning model, which incorporated covariates like age, sex, and education, was created to determine which combination of plasma biomarkers best predicted Aβ status. We found that, while Aβ-PET does not correlate with cerebrovascular integrity markers like VEGF, TGFβ, and PDGF-BB, it does increase significantly with AD pathological markers like pTau-217 (R=0.425) and pTau-181 (R=0.262), and GFAP (R=0.554). Moreover, the latter exhibited above-chance accuracy in predicting Aβ status (AUC=0.68). In all, these results suggest that specific plasma biomarkers can be used in the future to reliably estimate one's brain amyloid levels and, by extension, their preliminary risk for developing AD.

Theme C: Neurodegenerative Disorders and Injury

Ketogenic Diet impact on Long-Term Potentiation in the Dorsal CA1 Hippocampal Region and Memory Behavior in Young and Adult Rodents

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Abstract

The ketogenic diet (KD) initially gained attention for treating epilepsy, though its effects on the neurological system remain unclear. We investigated the cognitive effects of KD on behavior and synaptic plasticity, employing hippocampal long-term potentiation (LTP) as a measure in young (2-8 weeks) and adult (7 months) mice. Two treatment methods were used: 1) a 3–4-week high lipid diet to increase ketone bodies in vivo, 2) bathing hippocampal slices in beta-hydroxybutyrate (BHB)-enriched artificial cerebrospinal fluid (ACSF) to achieve higher ketone concentrations than in vivo. Field electrophysiology experiments were conducted. In young animals, no statistically significant differences in LTP ($p>0.05$) were observed between KD and control diet groups. However, adult mice on the KD showed significantly increased LTP (181 ± 18%; $n=10$; $p<0.05$) compared to control diet animals. No difference in LTP ($p>0.05$) was noted between slices from young mice exposed to 7.5 mM BHB and 2.5 mM glucose for >2 hours compared to 0 mM BHB and 11 mM glucose controls. We are currently analyzing experiments with adult mice exposed to BHB-enriched ACSF. Behavioral Morris water maze experiments were also performed to test spatial memory in young and adult mice given 3-4 weeks of KD. No significant differences in time to platform or time in the correct quadrant ($p>0.05$) were found between young mice on the high-fat diet chow and controls. Overall, our data suggests the KD could have significant impact on neurological function such as LTP and memory behavior in adult mice, but not young mice.

Theme H: Cognition

Epigenetic Regulation Following Long-Term Sensitization Training in Aplysia californica

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Abstract

Epigenetic mechanisms play an important role in the regulation of neuronal gene expression. Specifically, we are investigating DNA methylation changes in the process of encoding and maintaining memories. Long-term sensitization in Aplysia californica is a type of painful memory measured by an increase in reflex responsiveness and associated with gene expression changes. We analyzed promoter methylation of ApEgr, ApCREB1, and ApCREB2, genes which encode transcription factors thought to be involved in memory maintenance. Sensitization was induced with four shocks on one side of the body. One day later, when the sensitization memory is strongly expressed, gDNA was isolated from trained and control pleural ganglia. Bisulfide treatment of gDNA was performed, followed by methylation-specific PCR at regions identified as potential CpG promoter sites. Across six control samples, the ApEgr and ApCREB2 sites were partially methylated, while ApCREB1 was fully unmethylated. Our data support promoter-specific methylation; however, we did not observe methylation changes produced by the specific training protocol that we utilized.

Theme B: Neural Excitability, Synapses, and Glia

Characterizing social deficits and potential prosocial effects of D-cycloserine in adolescent Df(h22q11)/+ mice, a model of 22q11.2 Deletion Syndrome

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Abstract

A typical 3Mb microdeletion within the 22q11.2 chromosome region results in 22q11.2 deletion syndrome (DS), which has been implicated in neurodevelopmental disorders, including schizophrenia and autism spectrum disorder (ASD). A wide array of behavioral phenotypes are present in 22q11.2DS; however, there has been limited assessment of social deficits in 22q11.2DS mouse models, especially in relation to developmental age and sex. The NMDA receptor (NMDAR) is involved in the pathophysiology of schizophrenia and ASD, and may represent a novel therapeutic target in 22q11.2DS. This study sought to characterize possible social deficits in Df(h22q11)/+ mice and determine the effects of a NMDAR partial agonist invention on several social measures. Specifically, four- to six-week old Df(h22q11)/+ (n=60, 30 males 30 females) and C57BL/6 WT control mice (n=60, 30 males 30 females) were injected for 7 days with D-cycloserine (30 mg/kg, i.p.) or saline. Following drug administration, social behaviors were assessed in a 3-chamber apparatus to assess social preference and interaction with a conspecific. Preliminary measures of locomotor activity and sociability showed no effect of D-cycloserine on social preference. However, comparison of genotype (22q11.2DS vs. B6) showed a trending difference on the amount of time spent sniffing the social cup containing the stimulus mouse (p=0.056). Additional measures of latency to approach and number of approaches toward the social stimulus will be analyzed. Overall, these data provide insight into the interplay between neurobiological mechanisms of 22q11.2DS and behavioral domains.

Theme A: Development