WHAT'S NEW IN ATLANTA NEUROSCIENCE

THURSDAY 11/03/2022

6-8PM

Hosted by ACSfN

ENJOY LIGHT BITES AND DRINKS WHILE PREVIEWING THE BEST OF ATLANTA NEUROSCIENCE!

Located at **The Hatchery** in Emory Point

1578 Avenue Place
Suite 200
Atlanta Georgia 30329

Free 3hr parking available across the street (validation required at check-in)

SPEAKERS

Anita Devineni, Emory University
Sensory processing and behavioral flexibility in Drosophila

Chris Rodgers, Emory University
Learning by doing: distributed neural circuitry for perception and action

Alberto Stolfi, Georgia Tech
Tunicates: our closest invertebrate relatives

Shawn Dotson, Georgia State University
Exploring mechanisms of alimentary chemosensation and modulation

Jennifer Larimore, Agnes Scott College
Characterizing the effects of SCN1A mutations on CACNA1C expression

An Zhou, Morehouse School of Medicine
Epigenetic reprogramming of cortical neurons in response to brain ischemia

& POSTER PREVIEW SESSIONS!

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Thank you to the Hatchery for opening up their space for this event!

This event was organized by the **Atlanta Chapter of SfN.**
Learn more about us at https://acsfn.cbn.gsu.edu/

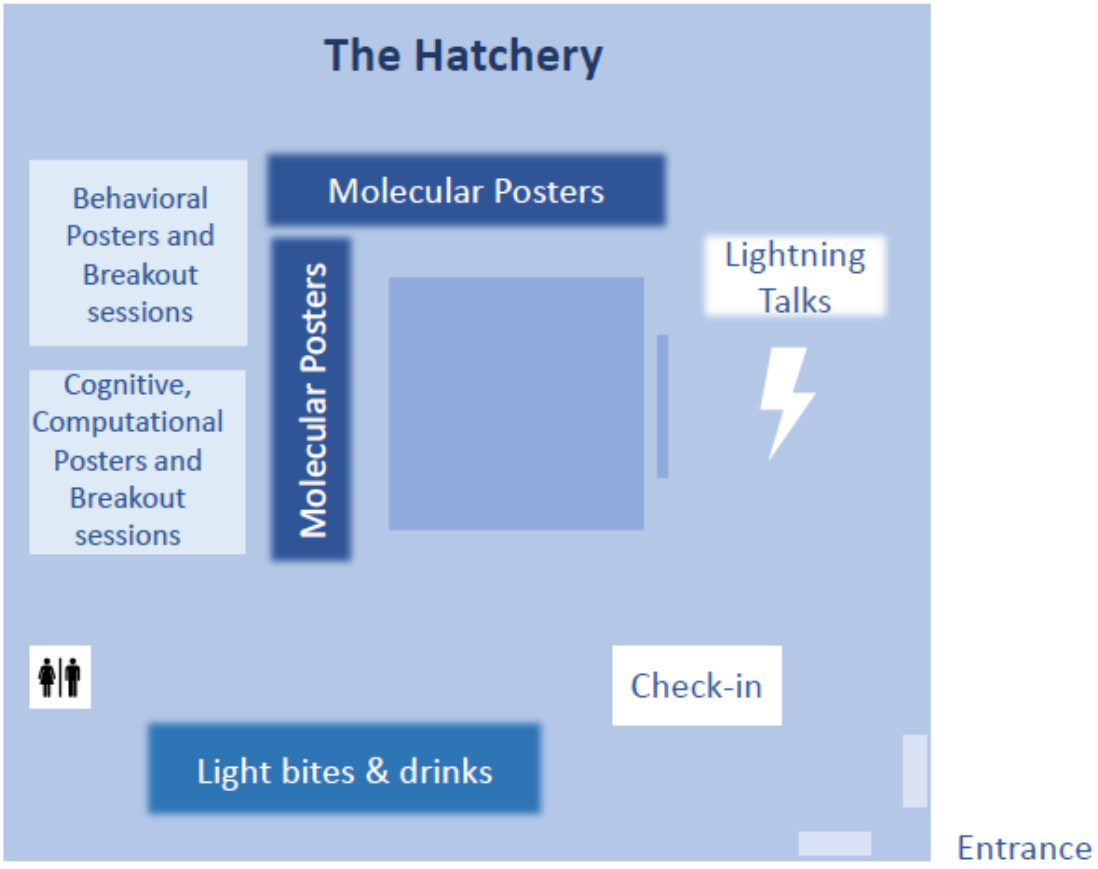
Our volunteers included: Angela Mabb, Kristen Frenzel, Jill Ward, Jennifer Walcott, Hannah Sturgeon, Erin Lottes, Tana Pottorf, Yahia Ali, and Claudia Espinosa among others!

Location and Parking Information

What's New '22 will take place in The Hatchery at Emory Point.

Address:
1578 Avenue Place
Suite 200
Atlanta Georgia 30329

Free 3hr parking is available across the street. Please bring your parking garage ticket to check-in for validation.



Schedule

6:00 pm **Welcome** by ACSfN President
Kristen Frenzel, PhD (Emory)

6:05 pm Lightning Talks
Anita Devineni, PhD (Emory)
Chris Rodgers, PhD (Emory)
Alberto Stolfi, PhD (Georgia Tech)

6:30 pm Poster session I and faculty group I breakout sessions

7:05 pm Lightning Talks
Shawn Dotson, PhD (GSU)
Jennifer Larimore, PhD (Agnes Scott)
An Zhou, PhD (Morehouse)

7:30 pm Poster session II and faculty group II breakout sessions

Poster Session I:

Molecular subtopic

Christine Bowen, Emory University: Kv1.3 potassium channels exhibit domain specific protein interactions in activated microglia

Introduction:
Alzheimer's Disease (AD) is characterized by progressive Aβ pathology and neuroinflammation. Disease-activated microglia in the brain, with potential contributions from peripheral T cells, promote neuroinflammation in AD. The Kv1.3 potassium channel is highly expressed on proinflammatory microglia and memory T cells. Blockade of Kv1.3 reduces Aβ pathology and decreases the proinflammatory phenotype of microglia. The molecular mechanisms regulated by Kv1.3 channels remain unexamined. Identifying proteins that interact with N and C terminal cytosolic domains of Kv1.3 channels will evaluate Kv1.3-regulated mechanisms and pathways.
Methods:
We utilized TurboID, a biotin ligase that biotinylates proteins within a 10nm proximity, fused to Kv1.3 and validated Kv1.3-TurboID fusion constructs in HEK Cells. We created three constructs, where TurboID was fused to the N terminus, C terminus, and a truncated Kv1.3, where the PDZ-binding domain is removed. We transduced these constructs into BV2 cells, a murine microglial cell line, and Jurkat T-cells, a human T-cell line, to determine potential immune interactors with Kv1.3. BV-2 and Jurkat T-cell stable cell lines were created and confirmed via qPCR and electrophysiology. Western Blot and Flow cytometry confirm TurboID biotinylates proteins. Mass spectrometry (MS) of biotinylated proteins was performed to identify proteins within proximity to Kv1.3.
Results:
BV2 biotinylated proteomes identified by MS revealed distinct N terminal and C terminal Kv1.3 interactors. Many Kv1.3 interactors overlap between the N and C terminus in the presence or absence of LPS inflammatory stimulation. The N terminus interacts with translation (e.g. Rpl10 and Eef1a1), plasma membrane proteins (e.g. Calr1 and Psma1), and mitochondrial tracking proteins (e.g. TIMM23), while the C terminus interacts with immune response proteins (e.g. Cd68, Tlr2, and Csf1). With the removal of the C terminal PDZ-binding domain, we observed reduced immune response and inflammatory proteins (e.g. Tmem106b, Larp1, and Gbp2) interacting with Kv1.3.
Conclusions:
Immune interactors with Kv1.3 likely depend on the C terminal PDZ domain while the primary function of the N terminus is protein processing and transport to the plasma membrane. Overall, this data identifies strong candidates for potential interactors with Kv1.3 and provides insight on how Kv1.3 influences microglial and leukocyte immune function in AD.

Erin Lottes, Georgia State University: CCT and the TORC1 pathway function to shape dendritic arbors

Developing neurons rely on three major forms of proteostatic regulation – protein synthesis, maintenance, and degradation – to grow and maintain a dendritic arbor. In Drosophila melanogaster, larval multidendritic (md) neurons develop to form a variety of arbor shapes, ranging from simple class I (CI) to complex class IV (CIV) neurons, each dependent on carefully balanced proteostatic processes. One such process is protein maintenance, which is carried out by chaperones that ensure proper conformation of other proteins. While chaperones are particularly important to maintaining neurons, they have been under-studied in dendrites. Chaperonin-containing tailless complex polypeptide-1 (CCT) is an ATP-dependent chaperonin comprised of eight subunits which come together to form a double-ringed complex. CCT is thought to fold anywhere from 1-15% of the cellular proteome. Two of its most notable clients are actin and tubulin - major cytoskeletal components essential to the development and maintenance of dendritic arbors. Using live confocal imaging of larval md neurons, we have found that knockdown of CCT results in significant decreases in arbor complexity in CIV neurons, appearing at approximately 72 hours after egg lay. Two-channel live imaging of CCT loss-of-function (LOF) CIV neurons has revealed an underlying significant reduction in MTs, but not in F-actin. Though stability of MTs is compromised, polarity of MTs is unchanged in CCT LOF conditions.
CCT has recently been shown to fold components of the TOR (Target of Rapamycin) complex 1 (TORC1). TORC1 regulates S6 kinase, and we have found that S6K LOF and overexpression results in CIV dendritic arbor complexity reduction and enhancement, respectively. Preliminary studies of Cullin1 (Cul1), a component of the SCF E3 ubiquitin ligase, reveal that Cul1 LOF results in dendritic hypertrophy and increase in phosphorylated S6K signal, opposite to the hypotrophy and decrease in phosphorylated S6K seen in CCT LOF. Cul1 has been previously linked to negative regulation of TORC1 through inhibition of Akt. Altogether, our work suggests CCT operates as a part of a regulatory network spanning protein synthesis, maintenance, and degradation that collectively cooperate to regulate dendritic growth and elaboration.

Ruth Nelson, Emory University: Assessing the effect of systemic inflammation on the astrocyte proteome using in vivo proximity labeling

Background
Astrocytes are critical to the CNS during homeostasis and neurodegenerative disease as they perform a myriad of functions including maintenance of the blood brain barrier and aiding microglia in mediating the inflammatory response. Emerging in-vivo proteomic labeling approaches using proximity labeling provide exciting opportunities to resolve proteomic signatures of glia using mass spectrometry (MS)-based approaches, overcoming several limitations of isolation-based and transcriptomics strategies. The objective of this study is to apply a novel method called cell type-specific in-vivo biotinylation of proteins (CIBOP) to label and characterize the proteomes of astrocytes under homeostatic states and in response to systemic inflammatory challenge.
Methods
CIBOP employs a Cre-lox transgenic approach to selectively express biotin ligase TurboID in astrocytes via the Aldh1L1 promoter. Mice heterozygous for Aldh1L1-Cre-ert2 and Rosa26TurboID (astro-CIBOP), and controls (Cre-only), received Tamoxifen injections followed by 3 weeks of recombination and biotin supplementation for additional 2 weeks. Half the cohort received daily lipopolysaccharide (LPS) injections (intra-peritoneal, 10mg/dose/animal x 5d) during the first week of biotinylation to induce a robust neuroinflammatory response. Astrocyte-derived biotinylated proteins were enriched from whole-brain homogenates by streptavidin bead affinity-capture for MS. Immunfluorescence microscopy (IF) and biochemical studies were performed to confirm astrocyte-specific proteomic biotinylation and CSF was collected for detect astrocyte-derived CSF biomarkers.
Results
Western blot analysis confirmed robust biotinylation of the cellular proteome of astro-CIBOP mice under homeostatic and neuroinflammatory conditions compared to their respective controls. IF confirmed that biotin signal (using streptavidin) colocalizes with astrocytic markers (Gfap and Ndrg2) with preferential labeling of astrocyte end-feet around blood vessels. Further, to validate that the astro-CIBOP technique was exclusively biotinylating astrocytic proteins we confirmed the lack of colocalization of biotin signal with microglia (Iba1) and neurons (Map2). CSF from astro-CIBOP mice, but not control mice, also revealed biotinylated CSF proteins. MS studies of biotinylaed proteins in the brain and CSF are underway.
Conclusions
We validate the CIBOP approach to label the proteome of astrocytes in their native state, under homeostatic and neuroinflammatory conditions, and demonstrate labeling of astrocyte-derived CSF proteins. Our ongoing MS studies will identify astrocyte specific proteomic changes driven by systemic LPS and lay the groundwork for application of CIBOP in neurodegenerative disease contexts.

Sydney Sunna, Emory University: Comparative proteomics of LPS-induced inflammation in different brain cell types captured by TurboID proximity labeling

Chronic neuroinflammation is central to the etiology of neurodegenerative disease, but there is currently a critical gap in our understanding of how inflammatory challenges impact distinct cellular proteomes. Proximity biotin ligase TurboID, coupled with Lipopolysaccharide (LPS) challenge and mass spectrometry, can purify distinct cellular proteomes from adult mice undergoing inflammatory challenges. Proximity biotin ligase TurboID, coupled with Lipopolysaccharide (LPS) challenge and mass spectrometry, can purify distinct cellular proteomes from adult mice undergoing inflammatory challenges. To test the hypothesis first, in vitro, we generated BV2 and N2A cell lines stably expressing TurboID containing a nuclear export sequence. We treated cells with 1µg/mL LPS and 200µM biotin for 48 hours and generated whole cell lysates (inputs) and streptavidin affinity-purification (AP) fractions (n=4/group) for label free quantitative MS (LFQ-MS). In vitro, TurboID biotinylated 60-65% of the entire proteome identified by LFQ-MS, with 1,754 proteins significantly enriched in the BV2 AP proteome and 2,011 proteins in the N2A AP proteome. Principal component analysis of the AP proteomes revealed that effect of LPS was robust on BV2 AP proteomes but minimal on N2A AP proteomes. Differentially expressed proteins by LPS treatment (LPS DEPs) were identified in both BV2 AP (>500 proteins) and N2A AP (>100 proteins) samples. K-means clustering of BV2 AP proteomes revealed 5 clusters of proteins, with cluster 1 (C1) representing LPS-driven proteomic changes shared between AP and input proteomes, and cluster 3 (C3) representing down-regulated changes in response to LPS. Gene set enrichment analysis showed C1 proteins correlating with peroxisome, phagosome, cytokine secretion and amoebiasis, and C3 proteins associated with terms involving cellular homeostasis. Protein interaction network analysis of N2A LPS DEPs identified clusters of proteins involved with proteasomal machinery identified by local network clustering. Next to investigate the effects of systemic LPS on neuronal proteomes, we have successfully directed TurboID to CamKIIa and PV interneurons in adult mice undergoing LPS challenge (I.P. inj. x4 days) and pharmacological ablation of microglia with PLX3397 chow (290 ppm, 5 wks.). Our quantitative imaging and immunoblotting results validate the efficacy of microglial ablation in WT mice (n=10, ~50% by Iba1 count), and confirm robust biotinylation of proteins in CamKIIa-Cre/TurboIDfl/- mice. Our in vitro studies confirm that TurboID biotinylation of proteins can capture unique biological responses of neurons and microglia to inflammatory challenge.

Meghan Vogt, Georgia State University: Perigestational morphine exposure disrupts postnatal cell proliferation in the hippocampus of male and female rats

Every nineteen minutes, a baby is born addicted to opioids. Nationally, the rate of neonatal opioid withdrawal syndrome (NOWS) is 7.3 per 1000 births, with rates in some states as high as 53.5 per 1000 births. NOWS infants show neurodevelopmental impairment, have smaller brain volume, and thinner cortices than age-matched peers. Endogenous opioids and their receptors are highly expressed during brain development by neural progenitor cells, neurons, and glia, and they modulating cell proliferation, differentiation, and maturation. Thus, any disruption to the endogenous opioid system during brain development can have lasting consequences on brain cell populations. Our lab has developed a clinically relevant perigestational morphine exposure rat model to explore how exposure to an exogenous opioid during brain development affects cell proliferation, specifically in the dentate gyrus of the hippocampus, a brain region critical for learning and memory. Our data show that rats exposed to morphine have decreased expression of doublecortin, a microtubule-associated protein expressed by newly proliferated neurons, relative to total dentate gyrus area at postnatal days 7 and 14. These data suggest morphine exposure during brain development delays cell proliferation in the dentate gyrus of the hippocampus. Future studies will explore glia proliferation and extend analyses into postnatal day 21.

Dina Yakout, Georgia State University: Role for Arc turnover in Tauopathies

Tauopathies are a diverse group of neurodegenerative disorders characterized by the deposition of aggregates of the microtubule associated protein tau (MAPT) in the brain, which is the main component of neurofibrillary tangles (NFTs). Alzheimer's disease (AD) is the most common tauopathy. Understanding tau's physiological role in the cell is key to the development of effective therapeutic strategies for tauopathies. Tau's most well-known function in neurons is stabilizing microtubules. However, recent findings suggest that tau is localized at postsynaptic sites. Here, we find that WT-Tau but not P301L-Tau causes a reduction in Arc protein. This reduction requires the proteasome and the R2 region of the Tau MTBD. Surprisingly, Tau-dependent Arc degradation was not associated with Arc ubiquitination, lysosomal degradation, phosphorylation or acetylation. However, Tau-dependent degradation did depend on the endophilin binding domain of Arc. WT-Tau degradation of Arc was also found to selectively occur in hippocampal dendrites. Importantly, overexpression of WT-Tau led to abnormal targeting of synaptic GluA-1 containing AMPARs to the soma in hippocampal neurons. Our findings highlight a unique role of WT-Tau in spatially regulating Arc removal, with hints of Tau microtubule binding and Arc endocytic targeting in regulating synaptic function.

Behavioral subtopic

Bhoomi Desai, Georgia State University: Effects of constitutive Cx3cr1-Cre expression on microglial density and morphology in the developing mouse brain

Cx3cr1-Cre transgenic mice express Cre recombinase under the direction of the Cx3cr1 promoter, and this Cre/lox system is an extensively used tool for genetic manipulations in microglia. Recently, Sahasrabuddhe et.al, 2022 described the adverse effects of inducible Cx3cr1-Cre expression on microglia, which included a lower cell density, an activated phenotype, an upregulation of their phagocytic function, and DNA damage in the developing brain, suggesting a Cx3cr1-Cre toxicity specific to inducing expression in the early postnatal period. These unintended and non-specific effects of the Cx3cr1-driven Cre expression in microglia also rendered the animals more anxious in adulthood, suggesting an urgent need to validate this genetic tool further. However, the possible detrimental effects of constitutive expression of Cx3cr1-Cre (BAC-Cre) on microglia remain unknown. We hypothesize that due to its continuous expression and accumulation, from embryonic stages through adulthood, constitutive Cx3cr1-Cre expression will lead to an altered microglial density, morphology and phagocytic function as well. Here, we performed confocal imaging of immunolabelled microglia in the paraventricular nucleus (PVN) of the hypothalamus, the central nucleus of the amygdala (CeA), the parietal cortex (PC) and hippocampal subregions (CA1, CA3 and Dentate Gyrus) of Cx3cr1-Cre+ and Cx3cr1-Cre- littermates (postnatal days 7-9). Our preliminary data in the PVN reveal a slightly decreased volume of P2RY12+ microglia in Cx3cr1-Cre+ mice, which we are currently following-up with Sholl analysis to further delineate possible morphological changes. However, no apparent differences in the number of P2RY12+ or Iba1+ microglia have been found with constitutive Cre expression, and no change in the number or volume of CD68+ lysosomes. Analysis of microglial phagocytic cups, proliferation, and potential DNA damage in the developing PVN is ongoing, along with other brain regions and behavioral studies in adult mice. The results of these experiments will have important implications for the use of the Cx3cr1-driven Cre/lox system to study microglia during development, and they also highlight the need to perform the correct control experiments when using these genetic tools.

Morgan Gomez, Georgia State University: Early life pain alters the response to an immune challenge in adult male and female rats

Premature infants are more likely to be admitted to the Neonatal Intensive Care Unit (NICU) where they experience upwards of 10-18 painful procedures each day, often without anesthesia or analgesia. Preclinical and clinical studies have shown that neonatal pain disrupts normal CNS development in multiple ways that persist into adulthood. The present study explores the effects of neonatal injury on the response to an immune challenge in adulthood. Male and female rats were exposed to a short-term inflammatory insult induced by intraplantar administration of 1% carrageenan on the day of birth (P0). In adulthood (P60-P90), Thermicron iButtons were implanted to monitor core body temperature; 14 days later, lipopolysaccharide (LPS) was injected to elicit an immune response. Rats were sacrificed at one of 3 time points post-LPS: 24 hours, group peak fever, or 2 hours. Brain tissue was analyzed via immunohistochemistry for VGAT, VGLUT, Fos and prostaglandin receptor 3 within the hypothalamic median preoptic area (MnPO). A whole brain survey of Fos activation patterns was also conducted. LPS administration resulted in a significantly greater febrile response in males and females exposed to early life pain compared to controls. Immunohistological analysis revealed sex and treatment differences in cellular activation in several brain regions, but no differences in receptor expression in the MnPO. Together, these studies are consistent with clinical studies reporting children experiencing unresolved pain during the perinatal period show an increased severity of sickness behavior and altered immune signaling following exposure to a pathogen, and will provide a foundation for future studies examining the biological underpinnings.

Hannah Harder, Georgia State University: Long term immune consequences of perigestational opioid exposure

Neonatal opioid withdrawal syndrome (NOWS) rates have quadrupled in the last decade. Preliminary evidence suggests that children born with NOWS have an increased risk of infection in childhood; however, confounding factors, including comorbid drug use, make identification of underlying mechanisms challenging.

Although animal models of perigestational opioid exposure (POE) can help resolve these difficulties, current animal models often utilize steady-state truncated dosing paradigms that fail to recapitulate the intermittent and prolonged use typical of human opioid users. Our lab has developed a novel clinically-relevant rodent model of POE utilizing surgically-implanted minipumps to provide intermittent morphine exposure before, during, and after pregnancy, allowing pups to be indirectly exposed to morphine throughout gestation and immediately following parturition. To assess the impact of POE on fever, adult male and female POE rats are given an immune challenge with lipopolysaccharide (LPS), and eight hours later, fever response, sickness behavior, and cytokine release are measured. Compared to controls, morphine-exposed males and females showed an increased fever response to LPS and altered peripheral cytokine levels, suggesting immunodysregulation. This novel rodent model provides an opportunity to study long-term immune deficits in a tractable way to investigate potential treatments to ameliorate immune dysregulation noted in NOWS infants.

Yunmiao Wang, Emory University: Wide-field Voltage Imaging of Fast Cortical Dynamics during Locomotion and Reaching in Mice

Population imaging of cortex-wide activities has shed light on the cortical dynamics and functional networks of motor control.To date, the majority of wide-field imaging studies utilize calcium indicators. The relatively slow kinetics of calcium sensors have left the investigation of fast cortex-wide dynamics at the time scale of limb kinematics an uncharted area. In order to better understand cortical activities of motor control with higher temporal resolution, we performed wide-field voltage imaging at 200 Hz with a novel genetically encoded voltage sensor, JEDI-1P. First, we demonstrated that JEDI-1P reliably follows responses of air-puff stimulation of up to 60 Hz in somatosensory cortex. Given that this finding establishes fast-frequency following of JEDI-1P in vivo, we then imaged mice performing a wheel running task as well as a reaching task cued for either right or left forelimb reach. In both tasks, we observed a global decrease in high-frequency power during sensory stimulation. For the wheel running task, animals showed an increase in beta band activity during reward consumption as they stopped running. During the reaching task, imaging data showed rich and fast temporal signals in the caudal forelimb area orchestrating this reaching task. Pending detailed analyses of this rich dataset on fast cortical dynamics with voltage imaging is expected to provide further insights on how sensorimotor information is processed for modulating locomotion and controlling dexterous movement.

Cognitive Subtopic

Dieter Jaeger, Emory University: Layer specific cortical processing of thalamic input in a cued left/right lick motor task in mice

Previous studies have established causally impactful participation of a thalamo-cortical loop involving anterolateral motor cortex (ALM) and ventromedial thalamus (VM) in the execution of lick decision making tasks with a delay period in mice. In our current studies we are expanding our knowledge of how this task is processed in mouse cortex through 1) retrograde anatomical tracing, 2) manipulating dendritic dynamics in ALM through optogenetic manipulations, 3) 2-photon (2p) imaging, and 4) wide-field cortical voltage imaging. Retrograde tracing shows a rich and distinct connectivity for different layers in ALM, with both VM and MD thalamic input projecting to layer 1. A particular interest in understanding VM input to layer 1 (L1) in ALM depends on the relative balance between direct activation of apical tufts of pyramidal cell dendrites and L1 inhibitory interneurons. Since previous work has specifically implicated GABA-B receptors in the suppression of apical dendritic calcium spikes we used the GABA-B blocker Baclofen applied locally to the surface of ALM during lick decision task execution to study the behavioral relevance of this mechanism. We found that this GABA-B block leads to an increased error rate of the mouse licking at the wrong side, which appears in a clustered manner, indicating perseveration. Dendritic activity imaged with Gcamp8m showed a side specific ramping prior to lick execution, indicating dendritic involvement in the task. Overall, a picture begins to emerge that apical dendritic processing is critical for the processing of VM input to ALM in cued lick decision making in mice. To determine cortical network integration in this task we used the novel genetically expressed voltage sensor JEDI for brain-wide imaging. We find that lick task processing is widely distributed across many cortical areas. Activity occurred in distinct spatial and temporal patterns, with sensory responses mixed with ramp components prior to lick initiation. These results indicate cortex-wide participation in task processing.

Computational Subtopic

Nathanael Cruzado, Georgia Institute of Technology: Bridging model and experiment with CLEO: a testbed for in-silico prototyping of complex neuroscience experiments

Recent advances in neuroscience methods enable exciting new kinds of experiments. One of these is closed-loop optogenetic control, which combines simultaneous photostimulation and electrode recording to precisely control mesoscale neural activity on the order of milliseconds. Experiments such as these often require significant effort and resources to implement, which can slow development, limit opportunities to optimize experimental parameters, and pose a barrier to adoption. A potential solution is simulating an experiment—creating an in-silico prototype or proof-of-concept—which can demonstrate feasibility or reveal promising experiment designs for a fraction of the cost. Moreover, a virtual experiment with inputs and outputs resembling data collected in the lab allows for the realism of a spiking neural network model to be more directly evaluated. However, a convenient tool does not exist integrating optogenetics, electrode recording, and flexible closed-loop processing with neural population simulations. Thus, we have developed and now present Closed Loop, Electrophysiology, and Optogenetics Simulator (CLEO)—a Python package built around the Brian 2 simulator enabling closed-loop control as well as the injection of recording and stimulation devices into spiking neural network simulations.

These three components are designed to bring a degree of experimental realism to simulations. The closed-loop processor updates stimulator devices in response to measurements after a specified delay reflecting compute latency. The electrode module can detect spikes probabilistically with distance or read out a spike-based LFP proxy at arbitrary locations in the simulation, allowing the simulation of recording techniques such as a shank-style array. Finally, the optogenetics module simulates optic fiber light propagation and Markov state opsin dynamics for easily injecting photocurrents into user-provided model neurons. Beyond closed-loop intervention, CLEOSim is also useful for simulating electrode recording and photostimulation in open-loop experiments.

We demonstrate CLEO's utility in establishing proof-of-concept in two closed-loop optogenetics case studies. In the first, we inhibit a sparse traveling wave upon detection in a somatosensory cortex model, and in the second, we clamp firing rates to manipulate plasticity in a visual cortex model.

The package is accompanied by detailed online documentation including user-friendly tutorials, found at the links below:

Documentation: https://cleosim.readthedocs.io

Code Repository: https://github.com/Sensory-Information-Processing-Lab/cleo

Mykhailo Fomenko, Georgia State University: Dynamics of a high spike-frequency bursting in a Central Pattern Generator

Life-supporting rhythmic motor functions like heartbeating in invertebrates and breathing in vertebrates require an indefatigable generation of a robust rhythm by oscillatory circuits, Central Pattern Generators (CPGs). CPGs are adjusted by neuromodulation to meet environmental challenges. Leech heartbeating is controlled by a CPG based on two pairs of mutually inhibiting interneurons (HNs) forming half-center oscillators (HN-HCO). Neuromodulation navigates HN-HCOs between dysfunctional regimes by reducing Na + /K + pump current, I pump , and increasing h-current, I h , in a coordinated fashion, while naïve manipulation of I pump or I h leads to either seizure-like or asymmetric HCO bursting. Here, we report that this comodulation leads the HCO model through a domain where two functional bursting patterns coexist; and HCO can be switched between them by a current pulse. While cycle periods of the patterns are roughly the same, one of them has two-times higher spike frequency. Continuous operation of CPGs requires intracellular Na + concentration ([Na +] i) to remain in a functional range by having checks and balances on the Na + fluxes on the cycle-to-cycle basis of bursting. We suggest that a high spike-frequency bursting regime requires dynamic interaction of I pump and persistent Na + current, I P . I P is a low voltage-activated inward current that initiates and supports the bursting phase. It does not inactivate and is the major source of Na + influx. I pump is an outward current activated by [Na +] i and is the main source of Na + efflux. Both currents are active and counteract each other between and during bursts. We apply a combination of electrophysiology, computational modeling, and dynamic clamp to investigate the role of I pump and I P in HN neurons. By introducing with dynamic clamp additional I pump and I P into the dynamics of a living synaptically isolated HN neuron, we show that their joint increase produces transition into a new high spike frequency bursting regime with a larger amplitude of the membrane potential oscillations. Further increase of I pump speeds up the HN rhythm by shortening burst duration and interburst interval. [Na +] i , which reflects the intensity of the spiking during bursts, endows the Na + /K + pump current with a pivotal role in sculpting bursting patterns. We show that the dynamic interaction of I pump and I P offers a mechanism for the robust generation and flexible control of the functional bursting patterns. We suggest that this new regime provides effective control over rhythmic motor programs with faster output to the rest of the CPG network.

Developmental Subtopic

Andrew Worthy, Emory University: V1 Interneurons Expressing Foxp2 are a Highly Heterogeneous Clade

V1 interneurons are the largest group of ipsilaterally-projecting ventral, inhibitory interneurons. V1s are defined by embryonic expression of the transcription factor (TF) Engrailed-1 (En1) and are subdivided into four clades by TF expression: MafA, Pou6f2, Foxp2, and Sp8. The largest V1 clade expresses Foxp2. Here, we use intersectional genetics and a dual-conditional GFP reporter mouse to lineage-label this group and investigate its diversity. We first used en1-cre::foxp2-flpo mice to reveal more Foxp2-V1s than previously detected with antibody staining of Foxp2 on postnatal day 5 (P5). In the lower lumbar cord, we found 5 groups of Foxp2-V1s divisible by location (lateral or medial), neurogenesis, and P5 expression of the TFs Foxp2, Foxp4, OTP, and Zfhx3. Next, we used en1-flpo::foxp2-IRES-Cre mice. This model labeled similar Foxp2-V1s, but additionally revealed a dorsomedial cluster of cells that may transiently express Foxp2 during development. We suggest that differences in Cre- and FlpO-recombination efficiency combined with short-lived target gene expression best explains the slight differences between the models. The largest Foxp2-V1 subgroup (60%) expresses OTP at P5 and is clustered beside the lateral motor column (LMC). This group of cells is especially enriched with VGLUT1 synapses which suggests they are involved in proprioceptive pathways like reciprocal inhibitory circuits. Recently, long projecting spinal interneurons were found to express Zfhx3. We detected Zfhx3 expression in a subset of Foxp2-V1s (20%) that also all co-expressed OTP at P5. Our investigations reveal that the Foxp2 clade of V1s includes a variety of interneurons prominently consisting of an OTP-expressing subgroup that is involved in proprioceptive pathways and may include a subpopulation of long-projecting interneurons. The high density of Foxp2-V1s near the LMC and the many synapses they make with LMC motoneurons suggests a close relationship with limb control.

Poster Session II:

Molecular Subtopic

Carly Lancaster, Emory University: A conserved RNA binding protein regulates RNAs critical for neurodevelopment

Inherited forms of intellectual disability (ID) are common in the general population and have been linked to lesions in >700 genes. Emerging evidence suggests that this diverse group of genes converge on a limited set of neurodevelopmental pathways, including those that rely on RNA binding proteins (RBPs) to guide spatiotemporal patterns of neuronal mRNA trafficking and translation. Our labs co-discovered a monogenic form of ID caused by loss-of-function mutations in the ubiquitously expressed RBP ZC3H14. Studies exploiting the conserved ZC3H14 ortholog in Drosophila, Nab2, reveal that Nab2 localizes to neuronal nuclei and cytoplasmic ribonucleoprotein granules and is required specifically within brain neurons for olfactory memory and proper patterns of axon projection. At a molecular level, Nab2 can act as a translational repressor in conjunction with the Fragile-X mental retardation protein homolog Fmr1 and shares target RNAs with the Fmr1-interacting RBP Ataxin-2. However, neuronal signaling pathways regulated by Nab2, as well as mechanisms that elevate ZC3H14/Nab2 function in neurons relative to other cell types, remain elusive. We will present evidence that Nab2 controls neuronal expression of a well-conserved growth cone guidance factor, the guanine-nucleotide exchange factor (GEF) Trio, whose vertebrate homolog TRIO acts through the F-actin regulatory GTPases RHO and RAC to guide axon projection. Nab2 controls Trio levels in the fly brain by modulating an intron-retention event within the 5' UTR of trio mRNA isoforms, and this mechanism appears to be dependent on N6-methyladenosine (m6A) deposition on the trio pre-mRNA. Data will be presented on the role of m6A and Nab2 in controlling Trio splicing and expression, along with Nab2-Trio coregulation of axonal development in the CNS. Given that human TRIO is mutated in a dominant form of ID, this potential link between Nab2 and Trio in Drosophila could suggest that Nab2/ZC3H14 and Trio/TRIO act in a conserved ID pathway required to pattern neuronal processes in the developing nervous system.

Young Lin, Emory University: Split-TurboID Proximity Labeling to Identify Kv1.3 Channel Interactors in Mammalian Cells

Background: Kv1.3 potassium channels expressed by immune cells have emerged as promising therapeutic targets for several neurological diseases. Kv1.3 is a tetramer of four alpha subunits (Kcna3) which co-assemble with auxiliary beta subunits (Kvβ2). Based on Kv1.3 domain topology, we suspect Kv1.3 channels interact with key signaling pathways which impact cellular function and gene regulation. However, the exact role Kv1.3 plays in such signaling pathways is unclear. To identify proteins that interact with Kv1.3 channels assembled in the cell membrane as a tetrameric complex, we employed proximity labeling using the split-TurboID approach. When fused with the protein of interest, the biotin ligase TurboID biotinylates proteins within a 10nm radius, allowing us to map interacting proteins. Split-TurboID consists of two inactive fragments that can be fused to proteins of interest. TurboID only becomes functionally active when the fused proteins interact in close proximity, leading to biotinylation of interacting proteins.
Methods: We created constructs by fusing split-TurboID components to the C- and N- terminuses of mouse Kcna3 (Kv1.3) and Kvβ2 with a flexible linker. We then transfected HEK-293 cells with either the split constructs or a combination of the split constructs. We used electrophysiology and flow cytometry to evaluate the presence and activity of Kv1.3 on the surface and western blot to evaluate the presence of biotinylated proteins using Kcna3/Kcna3, Kcna3/Kvβ2 and Kvβ2/ Kvβ2 combinations.
Results: All Kv1.3 fusion constructs resulted in formation of functional channels on the surface, as measured by flow cytometry and electrophysiology. We observed slightly slower inactivation kinetics with N-term Kv1.3 fusions. Transfection with only one component of the split-TurboID resulted in no biotinylation, while co-transfection of Kv1.3/Kv1.3 and Kv1.3/Kvβ2 combinations resulted in robust biotinylation of proteins. Specifically, the highest biotinylation occurred in the Kv1.3/Kvβ2 combinations, suggesting functional channels recruit several proteins that co-assemble or interact with the Kv1.3 channel complex.[YL1] [BC2] Mass spectrometry studies of these biotinylated proteins are underway.
Conclusions: The Kv1.3-split-TurboID approach provides a unique opportunity to interrogate Kv1.3 channel interactomes. Our ongoing work extending this approach to immune cells that express Kv1.3 channels, such as microglia and lymphocytes, will identify novel immune mechanisms regulated by Kv1.3 channels.

Ruochuan Liu, Georgia State University: Identification of Neuronal E3 ubiquitin ligase substrates for TRIAD3A using Orthogonal Ubiquitin Transfer (OUT)

Protein ubiquitination (UB) is a posttranslational modification that is mediated by E1-E2-E3 enzymatic cascades. Ubiquitination regulates key pathways of neuronal cell biology that include signal transduction, protein degradation, DNA repair, inflammation, neural development, and synaptic plasticity. The way in which ubiquitin is transferred to a substrate is dependent on the type of E3 ligase catalytic domain. E3 UB ligases also specify the targets, timing, and subcellular location of protein ubiquitination reactions. Mutations in the E3 Ub ligase RNF216/TRIAD3 have been identified in Gordon Holmes syndrome (GHS), a rare disorder associated with hypothalamic dysfunction, dementia, and neurodegeneration. Although GHS causative mutations have been shown to decrease ubiquitination of RNF216/TRIAD3 targets, a knowledge gap remains on the molecular mechanisms that drive the development of GHS due to challenges to identify E3 ligase substrates in neurons. Here, we use an innovative platform known as "orthogonal ubiquitin transfer (OUT)" to identify new substrates for RNF216/TRIAD3A, which takes advantage of an exogenous UB transfer cascade constituted by xE1-xE2-xE3 to exclusively deliver an engineered xUB to its substrate proteins. Purifying xUB-conjugated proteins from neural cells and identifying them by proteomics would generate the substrate profile for RNF216/TRIAD3.

Jordan Owyoung, Emory University: The role of the sympathetic nervous system in improving skeletal muscle quality with exercise

Myopathies are neuromuscular diseases that affect the muscle and result in muscle weakness from dysfunctional muscle fibers. They affect hundreds of thousands of people a year and can cost millions of dollars per patient. Exercise is currently the only therapeutic that partially restores motor function in patients with myopathies; however, how exercise improves locomotive function remains largely unknown. Research shows that exercise influences sympathetic nervous system (SNS) activity. β2-adrenergic receptors (B2ARs) are the main receptors of the SNS and play a role in muscle protein synthesis. Furthermore, aerobic exercise has been shown to increase B2AR (Adrb2) expression.

I hypothesize that aerobic exercise modulates skeletal muscle metabolic health and function via sympathetic nervous system signaling. I will test my hypothesis in two ways. First, I will evaluate whether exercise can improve skeletal muscle function in mice with an ablated sympathetic system and in mice with a tamoxifen-induced homozygous knockout of Adrb2 in skeletal muscles. For each of the treatments, I will exercise a subset of mice. I hypothesize that a functional SNS is required for exercise to improve skeletal muscle function and therefore expect that exercise will not improve skeletal muscle function in either the sympathectomized or Adrb2-/- mice. Next, I will evaluate whether B2ARs are required for exercise to influence skeletal muscle health. I will use my Adrb2-/- mice and exercise a subset. Because B2ARs are essential for SNS signaling in the skeletal muscle, I hypothesize that exercise will not improve skeletal muscle health in Adrb2-/- mice.

Behavioral Subtopic

Erica Cross, Georgia State University: Winning increases tonic and phasic DA release in the NAc while losing increases phasic DA release but reduces overall DA tone in the NAc in Syrian hamsters

Social interactions are highly salient regardless of their valence (i.e., whether they are rewarding or aversive). Social stress is one of the most salient stressors across taxa, but it is less clear how winning versus losing an agonistic encounter might impact the rewarding or aversive properties of these interactions. Recent data suggest that the mesolimbic dopamine system (MDS), which includes the ventral tegmental area (VTA) and its dopamine (DA) projections to the nucleus accumbens (NAc) encodes reward as well as aversion based on activity of specific subregions in the MDS. Axonal projections from the VTA into the NAc core release dopamine in a phasic manner, with sharp spikes functioning as a salience cue, “stamping in” important information associated with intense stimuli so that individuals can appropriately respond to future stimuli of any valence. Release of DA in the NAc shell occurs in a tonic manner with changes occurring over a longer time scale than in the core. We have begun to test the hypothesis that the NAc core encodes the intensity or salience of social stimuli while the NAc shell encodes the valence, whether it is rewarding or aversive. In male and female Syrian hamsters, we are measuring DA release in the NAc during social interactions using in vivo amperometry. We have obtained DA measurements in the NAc core and shell in awake, behaving hamsters during socially rewarding interactions wherein the subject “wins” (i.e., becomes dominant over a nonaggressive intruder) and during aversive interactions wherein the subject “loses” (i.e., is defeated by to a larger, resident aggressor). In support of the hypothesis, we found that similar bursting occurred in the NAc core during social interactions, suggesting that agonistic encounters are associated with similar DA activity regardless of outcome. By contrast, tonic DA in the NAc shell was found to be higher in the rewarding social context and lower in the aversive social context. Baselines recorded before and after social sessions indicate that these DA changes are tied to the social experiences, and spiking in the NAc core is time-locked to attacks. Electrodes outside the NAc (anatomical controls) did not show the same trends, suggesting that the signals recorded in the core and shell are specific to DA efflux in those NAc subregions. In these experiments, winning (rewarding) is salient (spiking in core) and has positive valence (tonic increase in shell), whereas losing (aversive) is salient (spiking in core) but has a negative valence (tonic decrease in shell), indicating that that NAc subregions (core v shell) and their characteristic DA release (phasic v tonic) are encoding valence and salience, respectively.

Behnoush Dadkhah, Georgia State University: Oxytocin Receptor Expressing Neurons in the Lateral Septum Regulate Social Behavior in Mice

The neuropeptide oxytocin (OXT) and the oxytocin receptor (OXTR) regulate social behaviors and communication in mammals, including humans. One brain region that contains abundant levels of OXTR is the forebrain lateral septum (LS), an area known to play an important role in social behaviors like aggression. To investigate the behavioral role of the OXTR system in the LS, we deleted OXTR – expressing neurons in the LS using viral delivery of a Cre-dependent activated caspase cell-death construct in OXTR-Cre male and female mice, using their wildtype (Cre-) littermates as controls, and assessed their social, sexual, and aggressive behaviors. In males, lesioning LS OXTR-expressing cells increased communicative behavior (urine marking) in the presence of a caged male, without altering their investigatory behavior. Additionally, males with significant deletion of LS OXTR cells increased their copulatory behavior toward females (decreased latency to mount and intromit; greater proportion of males ejaculating) but decreased their aggressive behavior towards other males, compared to control males. Removing LS OXTR-expressing neurons in females also increased their copulatory performance, as evidenced by increased mounting by males, but without effects on other social behaviors. Our results indicate that OXTR neurons in the LS may normally suppress both male and female pro-social (copulatory) behavior. This, in turn, suggests that OXT may not act in all brain regions to increase prosocial tendencies and argues, instead, for separate and circuit-specific functions of OXT/OXTR systems.

Kevin Donaldson, Georgia State University: Chronic activation of primary cold nociceptors causes increased sensitivity to subsequent cold challenge

Organisms encounter constantly changing sensory stimuli requiring timescale-specific processing to ensure proper growth, development, and survival. The predictive qualities of many stimuli are encoded via inherent neuronal circuitry, but some are modified through exposure. While experience-dependent plasticity has been previously studied in a variety of modalities and sensory systems, little is known about thermal sensation, specifically cold. Drosophila larvae predominantly respond to acute noxious cold (≤10°C) with a full body contraction (CT) behavior requiring activation of Class III multidendritic neurons (CIIIs) by cold stimuli. Injury-induced cold sensitization via UV damage leads to behavioral plasticity such that CT responses are diminished, while body rolling behavior, which is normally associated with noxious heat, mechanical or chemical stimulation mediated by Class IV neurons (CIVs), begins to emerge. These data reveal that cold nociceptive circuitry exhibits injury-induced behavioral plasticity, however, whether this plasticity holds true in a non-injury model involving activity dependent plasticity through accumulated cold experience remains unknown. Here, we sought to determine the existence and extent of cold-evoked behavioral plasticity as a result of prior cold experience under non-damage conditions and to explore the potential cellular mechanisms underlying changes in behavior. Drosophila larvae were reared under noxious cold temperature (10° C) for various durations prior to being selected at the 3rd instar stage for behavioral testing during acute cold challenge at noxious and innocuous temperatures. In a set of parallel experiments, chronic “fictive cold” was achieved by targeted optogenetic stimulation of CIII neurons using the GAL4/UAS system to selectively express the light-gated cation channel, ChETA. In this condition, larvae were reared sans cold at room temperature (23°C) while being exposed to repeated blue light stimulation in a custom built, high-throughput device. We find that prior cold experience causes cold-evoked behavioral plasticity, exhibited by increased magnitude of CT behavior as well as the appearance of additional CIV-related behaviors such as C-bending, a precursor to rolling. These changes in behavioral responses were mirrored in “fictive” cold reared larvae, indicating that chronic activation of primary nociceptors is sufficient to induce behavioral sensitization and shifts. Together, these data demonstrate that the cold nociceptive system is capable of experience-dependent plasticity in non-injury conditions and that this change is neuronally driven.

Satya Iyer, Georgia State University: Taste buds treated with AAV vectors encoding PYY and exendin-4 impact upon taste perception and body mass accumulation in mice.

The availability of high-calorie foods is likely a causative factor for high rates of obesity and metabolic disorders, which have been linked to food intake dysregulation. Several gut peptides have been implicated in feeding modulation and body mass accumulation. For example, glucagon peptide-like 1 (GLP-1) and peptide tyrosine-tyrosine (PYY) have been shown to mediate satiety and reduce food intake. While systemic administration of such peptides has been explored as a therapy for metabolic disease, the effects of these hormones on taste signaling should also be considered given the importance of taste to feeding decisions. Peptide signaling systems are present in taste buds and oral GLP-1 and PYY signaling has been shown to influence taste responsiveness and feeding. Indeed, we previously demonstrated that genetic knockout of PYY in mice can impact on taste responsiveness and feeding and that viral overexpression of PYY in the salivary glands of these mice can rescue responsiveness. The present work uses AAV-mediated salivary overexpression of both GLP-1 receptor agonist exendin 4 and PYY to explore the impact of the presence of these peptides on taste and body-mass accumulation in wild-type mice with intact peptide signaling systems. Results showed a significant effect of peptide expression on responsiveness to multiple taste qualities. Overexpression of both peptides in saliva resulted in substantial reduction in body mass accumulation. These findings show taste modulation by salivary expression of peptides in wild-type mice and impacts on body mass accumulation and suggest the taste bud as a promising substrate for food intake modulation.

Lisa Meyer-Baese, Emory University: Cortical networks relating to arousal are spatiotemporally coupled to neural activity and hemodynamics

Even in the absence of specific sensory input or a behavioral task, the brain produces structured patterns of activity. This organized activity has been shown to be modulated by changes in arousal. Here, wide-field voltage imaging was used to establish the relationship between cortical network activity and arousal in spontaneously behaving head-fixed mice expressing voltage sensitive fluorescent proteins (VSFP). Video recordings were used to parse out the contribution of arousal by measuring changes in pupil diameter whilst tracking spontaneous orofacial movements. Changes in pupil diameter were strongly coupled to global voltage cortical signals but not global hemodynamics, with low frequency (<1Hz) having the highest coherence. In addition, we found bilateral correspondence between the spatiotemporal patterns of both changes in voltage and hemodynamics which was localized to medial sensory-motor and secondary sensory/auditory cortices. Correlations in these areas were found to be driven by periods of orofacial movements. These observations demonstrate a consistent contribution of both arousal and orofacial motion to changes in cortical activity in distinct spatial patterns and frequency bands.

Chris Searles, Georgia State University: Perigestational Opioid Exposure Alters Alcohol Consumption in Adolescent Male and Female Rats

Every fifteen minutes, a baby is born in the US experiencing neonatal opioid withdrawal syndrome (NOWS). NIDA reports that since 2004, the rate of NOWS has increased 7-fold. Clinical studies have established intrauterine exposure to drugs of abuse as a risk factor for adverse health outcomes in adult life, including the propensity for future illicit drug use. Despite extensive knowledge about common mechanisms of action in the neural circuitry that drives opioid and alcohol reward, there is little data on the risks that those born with NOWS incur with alcohol use later in life. Here, we investigate the impact of perigestational opioid exposure (POE) on the mesolimbic reward system of male and female Sprague Dawley rats at postnatal and adolescent ages. Our lab has developed a clinically relevant model for morphine exposure spanning pre-conception to the first week of life. Using this model, we found that POE increased alcohol consumption in female rats under noncontingent conditions. POE also reduced latency and impulsive action to earn alcohol rewards during operant conditioning sessions. Increased alcohol-seeking behaviors also extend to relapse testing scenarios without differences in relapse potential, possibly indicating long-term enhanced reward task focus or memory.

Cognitive Subtopic

Dawn Jensen, Georgia State University: Epigenetic Regulation of Adolescent Grey Matter Maturation and Cognitive Development

Introduction

Adolescence is the second most critical phase of neurodevelopment, a period of brain maturation marked by many changes including non-linear decreases in grey matter volume and cognitive development. While animal studies have shown that there are large-scale epigenomic changes happening during phases of heightened synaptogenesis, there is currently little or no information regarding what role methylation plays in the development of human brain structures past fetal development.

Here we analyze the dynamic methylation networks and their modulating effect on human adolescent brain reorganization. To do this, we used longitudinal data collected during the Developmental Chronnecto-Genomics (Dev-CoG) to expand our model of normal brain development. The Dev-CoG project recruited 200 subjects aged 9 -14 years for a multi-modal longitudinal study, collecting structural MRI (sMRI), DNA methyla-tion (DNAm), and cognitive data at three time points.

Methods

A difference map to represent the changes over time was created for each measure (DNAm, sMRI, and cognitive scores) by subtracting time point 1 from time point 2 (deltaT1) and time point 2 from time point 3 (deltaT2).

Three analyses were done on these measures, one multivariate (MANCOVA) to capture as many sub-jects as possible, one repeated measures linear mixed effects regression to capture effects over time, and one multi-level mediation analysis to explore the indirect effects of the brain between methylation and cognition.

Results

The multivariate analysis revealed that multiple CpGs had relationships with all the spatial maps of GM volume change and with several of the measures of cognition. The repeated measures analysis highlighted networks of GM changes that were related to changes in methylation of several of the CpGs. These same net-works were also related to increases in executive function as well as decreases in episodic memory. The me-diation analysis also showed these same regions of GM volume change to be mediating the relationship be-tween several of the CPGs and the changes in executive function.

Conclusion

These analyses give a first look into the varied relationships between the dynamic changes of DNAm and their connections to GM volume changes and cognitive development in adolescence.

Computational Subtopic

Kyle Johnsen, Georgia Institute of Technology: CLOCTools: A library of tools for closed-loop neuroscience

Closed-loop control enables scientists to adapt stimulation based on measured activity to drive a system towards a target. In neuroscience, the ability of closed-loop experiments to reduce variability and decouple connected systems has proven to be valuable. However, despite the promise of enabling stronger inference from experimental measurements, it remains challenging to implement fast, real-time feedback control. To address this obstacle, we are releasing CLOCTools, an open-source software collection designed to accelerate the use of closed-loop optogenetic control (CLOC). CLOCTools is designed to assist neuroscientists in online estimation, decoding, and control by providing fast, cross-platform C++ libraries implementing core algorithms and various support tools. These libraries and tools include: ldsCtrlEst, which features linear dynamical systems; hmm, which implements system identification and decoding algorithms for Hidden Markov Models (HMMs); wrapper modules, which implement ldsCtrlEst and hmm in the Real-Time eXperimental Interface (RTXI) system in tandem with Tucker-Davis Technologies (TDT) electrophysiology data acquisition; support tools for profiling new algorithms; and tools for multi-language compatibility in the form of Python and MATLAB interfaces. CLOCTools thus provides a unified set of tools for developing and deploying powerful new closed-loop stimulation approaches for deciphering the function of complex neural circuits. CLOCTools: documentation: https://cloctools.github.io/ repositories: https://github.com/CLOCTools

Jack Taylor, Georgia State University: Principal component and network analyses reveal relationships between sex, social status, oxytocin receptor, vasopressin V1a receptor, and serotonin 1A receptor densities across the social decision-making network

The social decision-making network (SDMN) has been a useful concept for examining the roles of interconnected nodes in the expression of social behavior. In order to understand these brain networks, it is necessary to describe the relationships between nodes and to relate connections and patterns within the network to distinct social behavioral states, such as sex or dominance status. In this study, we used graph theory network analysis (NA) and principal component analysis (PCA) to analyze oxytocin (OTR), vasopressin (V1a), and serotonin 5HT1a receptor binding data from 14 regions across the SDMN with the purpose of elucidating novel receptor expression networks and relationships. To investigate differences based on sex and social status (dominant, subordinate, nonsocial control) we extracted PCA scores and performed 2(sex) x 3(social status) ANOVAs using these data as dependent variables. Three PCA components accounted for nearly 50% of the variance. Component 1 was dominated by positive loadings from OTR nodes and V1a nodes within the mesolimbic dopamine system. Component 2 was more heterogenous, and was marked by strong loadings from V1a and 5HT1a in the AH and the MPOA. Males loaded significantly more highly than females on this component. Component 3 was dominated by V1a nodes, particularly those within the mesolimbic dopamine system. Our NA revealed similar and complementary results. OTR nodes represented 60% of the top 25% of nodes.

The three most central nodes were OTR in the paraventricular nucleus, the bed nucleus of the stria terminalis, and the medial prefrontal cortex (mPFC). Despite the high centrality of the mPFC with regard to OTR expression, the nodes representing V1a and 5HT1a in the mPFC were among the least central. The NA between males and females showed similar patterns of centrality among nodes. Notable differences include OTR in the anterior hypothalamus, which was the ninth-most central node for females, but 22nd for males, and OTR in the medial preoptic area, which was the 12th-most central node for females, but 25th for males. Node centralities were largely similar between dominants and subordinates. Notable exceptions were V1a in the central amygdala, which was the 35th-most central node for dominants, but was 21st for subordinates. These data show that, in Syrian hamsters, OTR expression in nodes in the SDMN are tightly coupled, and V1a and 5HT1a expression in these nodes differ between males and females but not between hamsters with differing dominance statuses. Supported by R01MH122622 and R01MH110212 to HEA and KLH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or GSU.

Nerve Repair Subtopic

Tina Tian, Emory University: Neuronal activity-based therapies do not enhance sympathetic axonal regeneration

Introduction: Axonal injuries are common and lead to a loss of motor, sensory, and autonomic functions that lead to lifelong disabilities. Enhancing axon regeneration is important for the development of novel therapeutics to complement surgical repair, such as nerve transfers for hand reanimations after spinal cord injury. However, the regenerative capacity of post-ganglionic sympathetic axons and their functional recovery has rarely been studied. Sympathetic innervation plays a major role in muscle strength and thermoregulation. The objective of this study is to study the regenerative capacity of sympathetic axons in the sciatic nerve after injury following neuronal activity-based treatments.

Methods: A conditioning lesion (CL) paradigm and a bioluminescent optogenetics approach were used to stimulate the whole nerve or sympathetic axons, respectively. To study sympathetic regeneration, I performed immunohistochemistry on sciatic nerve sections and utilized retrograde tracing techniques.

Results: My results suggest that the elongation of sympathetic axons is not enhanced with a conditioning lesion or electrical stimulation. Additionally, selective activation of sympathetic axons with bioluminescence decreases the number of sympathetic axons that have reached 5 mm of growth from the injury site 2 weeks after transection and repair of the sciatic nerve. Thus, activity-based therapies neither enhance sympathetic axonal elongation nor increase the number of sympathetic neurons participating in regeneration.

Conclusions: My preliminary data indicate that neuronal activity-based therapies that have previously been shown to enhance regeneration of motor and sensory axons may be detrimental to sympathetic axon regrowth. This data will have implications for activity-based therapeutic methods, such as electrical stimulation which has reached clinical populations, that can potentially be used to complement nerve repair surgeries.

Future Directions: I will further investigate the effects of neuronal stimulation on functional sympathetic recovery. Additionally, I plan to alter the traditional electrical stimulation paradigm to stimulate sympathetic neurons more effectively.

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