The Society for Neuroscience Baton Rouge Chapter Presents:

Inaugural Neuroscience Symposium
Bringing Minds Together

Featuring:

Nicolas G. Bazan, M.D., Ph.D.

Boyd Professor
Ernest C. and Yvette C. Villere Chair
for the Study of Retinal Degeneration
Professor of Ophthalmology, Biochemistry
and Molecular Biology, and Neurology
Director, Neuroscience Center of Excellence,
Health Sciences Center, New Orleans, LA

"Uncovering principles to sustain neurons' long lives: signaling redundancy and resiliency at the onset of neurodegenerative disease."

Friday, March 8th, 2024
Pennington Biomedical Research Conference Center Baton Rouge, Louisiana

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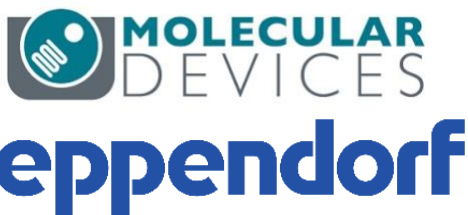
Friday, March 8th, 12:00 PM – 1:30 PM

Vendors, promos, prizes, and refreshments!
** For ALL attendees! **

Where: PBRC Conference Center, Building G

Who: Symposium attendees

Attending Vendors:

Prizes for Poster and Oral presentations
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All presentations from non-faculty are automatically entered. Three awards will be given at the closing ceremony.
 - Best oral presentation: $100 will be awarded for the best oral presentation by a non-faculty member (ex. Students and Post-Docs)
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CAMPUS MAP

Pennington Biomedical Research Center is unlocking the mysteries of why chronic diseases occur, who is at risk and how to improve human health across the lifespan. We are helping people to live *WELL* BEYOND THE EXPECTED.

KEY

BUILDINGS

- B Administration
- C Basic Science Laboratories No. 1
- D Clinical Research Building No. 2
  Pediatric Research Clinic - 1st floor
  Inpatient Unit - 2nd floor
- E Comparative Biology
- F Physical Plant
- G C.B. Pennington, Jr. Building & Conference Center
- G Population Science
- H Residential Lodge
- J Exercise Research
- K Gazebo
- L Basic Science Laboratories No. 2
- M Clinical Research Building No. 1
- N Biomedical Imaging Center
- P Central Storage & Utilities

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Conference site is Building G

Inaugural Neuroscience Symposium Schedule
March 8th, 2024
Pennington Biomedical Research Conference Center
6400 Perkins Road, Baton Rouge, LA 70808

8:30-9:00   **Registration /Breakfast**

9:00-10:30   Oral presentations I
Chair: Juhee Haam, Ph.D. Department of Biological Sciences, LSU, Baton Rouge

> **9:00-9:15** Ethan M. Anderson, Ph.D., CBS, LSU, Baton Rouge
> *"Heroin-Seeking Behavior and the Synaptic Proteome are Both Regulated by Phospholipase Cgamma1 in the Nucleus Accumbens"*
> **9:15-9:30** Bhuvanasundaram, Ramakrishnan
> *"Cerebellar endocannabinoid signaling mediates the extinction of associative fear memory"*
> **9:30-9:45** Michael Salling, Ph.D., LSU Health Sciences Center, New Orleans
> *"Adolescent alcohol consumption selectively affects prefrontal cortex projections to the mediodorsal thalamus"*
> **9:45-10:00** Laura Kaiser, Pennington Biomedical Research Center, Baton Rouge
> *"Preoptic area leptin receptor (POA-Lepr) neurons mediate temperature-dependent food intake adaptations via intersection with the melanocortin pathway."*
> **10:00-10:15** Yanlin He, Ph.D., Pennington Biomedical Research Center
> *"27-Hydroxycholesterol acts on estrogen receptor α expressed by POMC neurons in the arcuate nucleus to modulate feeding behavior"*
> **10:15-10:30** Carol Upchurch, LSU Health Sciences Center, New Orleans
> *"Persistent Silencing of PV+ Inhibitory Interneurons Results from Proximity to a Subcritical Hopf Bifurcation"*

10:30-10:50   Break/Vendor Show/Posters

10:50-10:55   Welcome from Chapter President: Alexander Murashov, MD, PhD
10:55-11:00   Opening Remarks: Dr. Oliver Garden, Dean and Kenneth Burns Endowed Chair, LSU School of Veterinary Medicine.
11:00-12:00   Keynote Address: Nicolas G. Bazan, MD, Ph.D., Boyd Professor, Director, Neuroscience Center of Excellence, Health Sciences Center, New Orleans, LA
"Uncovering principles to sustain neurons' long lives: signaling redundancy and resiliency at the onset of neurodegenerative disease."

12:00-13:30   Lunch/Vendor Show/Posters

13:30-15:00   Oral Presentations II
Chair: Arend W. A. Van Gemmert, Ph.D., College of Human Sciences & Education, LSU, Baton Rouge

> **13:30-13:45** Chloe Kindell, Louisiana State University, Baton Rouge

"Hidden Markov Modelling of Viewing Behaviors Reveals Discrete "Encoding States" During Visuospatial Memory Formation"
13:45-14:00 Alexander Lawriw, Louisiana State University, Baton Rouge
"Are representations in the hippocampus organized by the emotional content of stimuli? A multivariate analysis of intracranial electrode recordings"
14:00-14:15 Brandon Eich, Louisiana State University, Baton Rouge
"Influence on Attention and Working Memory During Visual Search with Cluttered Displays and Varied Target Prevalence"
14:15-14:30 Hanane Ramzaoui, Louisiana State University, Baton Rouge
"Effects of search priority on working memory-guided search for real objects: Evidence from eye-movements"
14:30-14:45 Felicia Chaisson, Louisiana State University, Baton Rouge
"Acute anxiety reduces behavioral and electrophysiological measures of semantic processing during memory formation"
14:45-15:00 Brianna Cairney, Louisiana State University, Baton Rouge
"Meaningful Co-Speech Gestures Enhance Associative Memory Formation, But Only When the Listener Expects Them To Be Meaningful"

15:00-16:00   **Poster Presentations with appetizers and beverages.**

16:00-16:15   **Closing Remarks and Awards from Chapter President:**
                Alex Murashov, M.D., Ph.D.

Keynote Presentation

Uncovering principles to sustain neurons' long lives: signaling redundancy and resiliency at the onset of neurodegenerative disease

Nicolas G. Bazan, M.D., Ph.D. Boyd Professor and Director, Neuroscience Center of Excellence, School of Medicine, LSU Health New Orleans, LA 70122, USA; and Foreign Adjunct Professor of Neuroscience Karolinska Institutet, Stockholm, Sweden.

We have been experimentally asking if there is a molecular logic that sustains neuronal survival as the brain is confronted with onset and/or progression of neurodegenerations, stroke or neurotrauma (TBI). We found that under imminent homeostasis disturbance, the brain activates the production of molecular guardians of cell integrity and function that includes Neuroprotection D1 and Elovanoids. We initially found that: Neuroprotectin D1 (NPD1) and neurotrophins (PEDF and BDNF) are agonists for the synthesis of NPD1 in retinal cells; 15-lipoxygenase-1 (15-LOX-1) is the enzyme that catalyzes its synthesis; it targets protein phosphatase 2A (PP2A) to regulate anti-/pro-apoptotic proteins during uncompensated oxidative stress (UOS); and it regulates proteostasis as well. We identified the transcription of pro-inflammatory genes as a target of NPD1 and demonstrated that the CA1 hippocampal area from short post-mortem, early-stage Alzheimer's disease (AD) patients displays a 25-fold loss of NPD1 as well as of the enzyme for the synthesis of this lipid mediator. More recently, we found a new mediator family, which we named elovanoids (ELVs), formed from very-long-chain omega-3 polyunsaturated fatty acids (FAs) (C32-34) synthesized by neuronal-specific ELOVL4. Mutations of the gene that encodes this enzyme cause, among other pathologies, vision loss, seizures, and mental retardation. Most known lipid mediators are derived from 18-22C length FA precursors, including prostaglandins. ELVs protect neurons by upregulating pro-survival and downregulating pro-apoptotic protein abundance. Additionally, ELVs enhance deacetylase Sirtuin 1 that modulates longevity signaling, E3 ubiquitin ligase (Iduna), and the transcriptional regulator Prohibitin-2. ELV synthesis pathways are downregulated in AD models and specific retinal cells of age-related macular degeneration (AMD) patients. Using LiP-MS, we also found that ELV-N34 selectively modulates TNXRD1 (from thioredoxin, an NADPH/FAD redox-effector that sustains homeostasis) underlying neuroprotection at the top of the UOS cascade. Overall, ELVs are resiliency epigenetic regulators of telomere integrity targeting DNA methylation; induce neuronal cell survival; counteract oligomeric amyloid-β peptideinduced cell damage; are neuroprotective after ischemic stroke and TBI; modulate transcriptome architecture; and downregulate senescence gene programming, autophagy, extracellular matrix remodeling, and inflammaging. A central theme is understanding early responses to UOS, neuroinflammation, and conditions that recapitulate neurodegenerative diseases to gain insight into endogenous protective mechanisms. Our common thread of concepts has included homeostatic regulation, necessary proteins, and genetic and epigenetic events in single-cell phenotypes, which are critical to our understanding of aging. Also, we actively explore systemic dysregulation of neural functions as a consequence of co-morbidities (eg diabetes, hypertension, obesity) at the onset and progression of neurodegenerative diseases. Our ongoing quest is a response to one major challenge to civilization: the growing incidence of the loss of sight and cognition as seen today with a rise in the occurrence of photoreceptor- and neuronal-survival failure, as reflected by AD and AMD. We envision potential therapeutic avenues for AD and other neurological disorders.

Oral Presentations

(in order of appearance)

Heroin-Seeking Behavior and the Synaptic Proteome are Both Regulated by Phospholipase Cgamma1 in the Nucleus Accumbens

Ethan M. Anderson, Ph.D.[1] , Makoto Taniguchi, Ph.D.[2], Stefano Berto, Ph.D.[2], Mohammad Shahid Mansuri, Ph.D.[3], TuKiet Lam, Ph.D.[4], Angus Nairn, Ph.D.[4], Kenneth Williams, Ph.D.[4], & Christopher Cowan, Ph.D.[2]

[1]Louisiana State University
[2]Medical University of South Carolina
[3]Yale University School of Medicine
[4]Yale University

Chronic opioid use leads to long-lasting increases in drug-seeking behavior; however, the causal molecular and cellular mechanisms responsible are not fully understood. One mechanism may involve the brain-derived neurotrophic factor (BDNF) signaling pathway through its activation of phospholipase Cgamma1 (PLCg1) in the nucleus accumbens (NAc). Since opioids increase NAc PLCg1 signaling, we hypothesized that reducing PLCg1 levels in the NAc would increase heroin-seeking behavior. In addition, since both opioids and PLCg1 signaling regulate drug-induced dendritic spine density and morphology, we hypothesized that a reduction of NAc PLCg1 levels would modulate the synaptic proteasomal changes that occur following heroin self administration. Methods: We infused a viral vector that reduces PLCg1 levels (AAVshPLCg1) or a control virus into the NAc of both male and female rats using stereotaxic surgery. Three weeks later we allowed the rats to self-administer heroin for at least 12 days. Following a 7-day abstinence period, we measured heroin seeking. In a separate experiment, we infused AAV-shPLCg1 or a control virus into the NAc, then we allowed rats to self-administer either heroin or saline for 12 days in a 2x2 design. After 7 days of abstinence, rats underwent drug-seeking conditions for 30mins. NAc tissue was then immediately harvested, enriched for synaptosomes, and proteins were quantified using high resolution multiplexed liquid chromatography mass-spectrometry. Results: We first found that reducing NAc PLCg1 led to an increase in heroin seeking. No obvious sex differences were observed. We then examined NAc synaptic proteasomal changes using mass-spectrometry (2x2 design: saline vs heroin and shPLCg1 vs control) and found significant changes in the levels of 223 proteins. Interestingly, a subset of these proteins was decreased in synaptosomes by heroin, then further decreased in the PLCg1 knockdown plus heroin group, suggesting potential causal changes that could explain how PLCg1 reduces drug-seeking behavior. Conclusions: These results show that endogenous NAc PLCg1 limits heroin seeking. These findings suggest that therapeutics targeting PLCg1 function might be helpful for treating relapse vulnerability in individuals suffering from opioid use disorder. In addition, PLCg1 either alone, or in combination with heroin, can alter the NAc synaptic proteome. Determining if these synaptic

changes are causal to behavior might reveal new therapeutic targets for treating substance use disorders.

Cerebellar endocannabinoid signaling mediates the extinction of associative fear memory

*Ramakrishnan Bhuvanasundaram[1,2], M. FAROOQ[1,2], S. LIU[1,2]

[1]Department of Cell Biology and Anatomy,
Louisiana State University Health Sciences Center, New Orleans, Louisiana.
[2]Southeast Louisiana VA Healthcare System, New Orleans, Louisiana.

Fear extinction is a type of inhibitory learning that is used as behavioral therapy for patients with fear-related psychological disorders (e.g., post-traumatic stress disorder). The role of the cerebellum in associative fear learning and memory has been explored to some extent. However, its contribution to fear extinction remains poorly understood. This study addresses how Purkinje cells (PCs) in the cerebellum are involved in fear extinction, and its cellular mechanisms. We tested this in mice using chemogenetics, pharmacology, and an enzyme assay, combined with the fear conditioning (FC) and extinction behavioral paradigms. Mice aged 55-90 days underwent FC training with 8 tone and foot shock pairings and one extinction session with 20 tones in a new context 24 hours later, followed by an extinction memory retention test ("recall") the next day using a few tones. First, we injected L7-Cre/Gi-DREADD mice with clozapine N-oxide (CNO) to selectively silence cerebellar Purkinje cells (PCs) 30 minutes before extinction training. The freezing response to tone during recall was significantly higher in the CNO-injected mice than in the saline-injected control group. The results indicate that blocking PCs impaired extinction learning and memory formation. Next, since activation of PCs evokes the release of endocannabinoids, we examined whether the endocannabinoid system in the cerebellum plays a crucial role in fear extinction. To examine this, we micro-infused CB1 receptor blocker (NESS) into lobules V/VI before extinction training. CB1 receptors are highly expressed in the cerebellum, and 2-AG binds to these receptors and suppresses synaptic transmission. Our preliminary results demonstrate that blocking CB1 receptors during extinction learning impaired extinction memory. 2-AG is released from PCs and degraded by monoacylglycerol lipase (MAGL). We had previously discovered that FC accelerates the degradation of 2-AG via MAGL in lobules V/VI of the cerebellar vermis and this is critical for fear memory consolidation. We therefore hypothesize that fear memory extinction would suppress MAGL activity to elevate tonic 2-AG signaling. Our MAGL assay results demonstrate that extinction training reduces MAGL activity in lobules V/VI in wild-type (WT) mice, relative to conditioned mice. Overall, our results suggest that PC activity in the cerebellum is required for fear extinction learning and memory, and this is mediated by cerebellar endocannabinoid signaling.

Adolescent alcohol consumption selectively affects prefrontal cortex projections to the mediodorsal thalamus

G. Y. Qian[1,2], H. Mejia-Gomez, M.S.[1], F. Maxwell, M.S.[1], M.C. Salling, PhD[1].

[1]Dept. of Cell Biology and Anatomy,
Louisiana State University Health Sciences Center, New Orleans, LA
[2]Tulane University School of Liberal Arts, New Orleans, LA

Excessive alcohol consumption is highly prevalent in adolescents and is known to lead to residual cognitive deficits and increased susceptibility to substance abuse disorders in adulthood. Imaging studies show that adolescent binge drinking can lead to dysfunction of the prefrontal cortex (PFC), a brain region essential to reward-seeking and higher order cognition. In our studies, we have shown that intermittent alcohol consumption in mice during adolescence alters drinking patterns and performance on working memory tasks in adulthood. This exposure additionally affects the intrinsic excitability of medial PFC pyramidal neurons when measured ex vivo using patch clamp electrophysiology. Through systematic isolation of PFC subpopulations with a retrograde viral strategy, we have found the excitability of PFC projections to the mediodorsal thalamus (MdT) are uniquely affected by early, but not late adolescent alcohol consumption in male and female mice and that these effects extend into adulthood. In a series of behavioral tasks, we have found that male and female mice that consumed alcohol during early adolescence have selective deficits in object-inplace memory, but not novel object recognition tasks, consistent with lesions of the medial PFC and/or MdT. The connectivity between the PFC and MdT may be a major locus of alcohol's known negative effects on cognitive control and may contribute to the challenges in treating the disorder.

Preoptic area leptin receptor (POA-Lepr) neurons mediate temperature-dependent food intake adaptations via intersection with the melanocortin pathway.

Laura Kaiser[1], Sean Swetledge[1], Nathan Lee[1], Michael Smith[1], Allie Peever[1], Sangho Yu[1], Christopher D. Morrison[1], Hans-Rudolf Berthoud[1], Heike Münzberg[1]

[1]Pennington Biomedical Research Center, Baton Rouge, LA

Ambient temperature is a robust modulator of food intake. However, the hypothalamic mechanisms by which ambient temperature influences food intake are not fully understood. Previous work from our lab has demonstrated that glutamatergic POALepr neurons are activated by warm ambient temperature, and chemogenetic activation of these neurons decreases energy

expenditure in a temperature dependent manner (Yu et al., 2016). Stimulation of POALepr neurons also suppresses food intake, suggesting that POA-Lepr neurons may also drive temperature dependent adjustments of food intake, even though the exact circuits to mediate POA-Lepr suppression of feeding remains unclear. The melanocortin energy-sensing pathway, involving the competing actions of Pro-opiomelanocortin (POMC) and Agouti-Related Protein (AgRP) at melanocortin-4 receptor (MC4R) expressing neurons, plays a central role in maintaining body weight homeostasis, however the relationship between this pathway and thermoregulatory POA circuits has not been fully explored. Here, we hypothesized that warm temperature-suppressed feeding is mediated by warm-activated glutamatergic POA-Lepr neurons that integrate into melanocortin circuitry. Methods & Results: We used a combination of synthetic and physiological POA-Lepr activation with chemogenetics or ambient temperature changes (30°C, 10°C), respectively, to test temperature-dependence of food intake suppression. We show that CNO suppressed food intake robustly at 10°C (when POA-Lepr are physiologically inactive) but was significantly blunted at 30°C (when POA-Lepr physiologically activated). Together these data support that glutamatergic POA-Lepr neurons mediate temperature-dependent FI. Furthermore, anterograde tracing with reporter-expressing AAV supported POA-Lepr innervation of key regions in the melanocortin pathway, such as the ventral dorsomedial hypothalamus, the arcuate nucleus, and the paraventricular nucleus. Similar to what is seen with MC4R activation (Keen-Rhinehart et al., 2007), POA-Lepr activation results in a profound suppression of FI during refeeding. Further, MC4R activation with melanotan-II (MTII) also showed temperature-dependent FI suppression, and combined MTII/CNO treatment has no additional effect on FI. These data indicate that POA-Lepr neurons may suppress FI via MC4R activation at warm ambient temperature, even though it remains unknown if this connection is direct or indirect. Conclusions: These hypothalamic circuits potentially represent novel targets for the modulation of appetite.

27-Hydroxycholesterol acts on estrogen receptor α expressed by POMC neurons in the arcuate nucleus to modulate feeding behavior

Bing Feng[1], Hui Ye[2], Pingwen Xu[2,*], and Yanlin He[1,*]

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Abstract: Oxysterols are metabolites of cholesterol that regulate cholesterol homeostasis. Among these, the most abundant oxysterol is 27-hydroxycholesterol (27HC), which can cross the blood-brain barrier. Since 27HC functions as an endogenous selective estrogen receptor

modulator, we hypothesize that 27HC binds to the estrogen receptor α (ERα) in the brain to regulate energy balance. **Method:** We combine electrophysiology, Cre-loxp conditional knock out animal models, BioDAQ feeding measurement, and whole animal physiology to test our hypothesis. **Results:** Supporting this view, we found that delivering 27HC to the brain reduced food intake and activated proopiomelanocortin neurons in the arcuate nucleus of the hypothalamus (POMC[ARH]) in an Erα-dependent manner. Additionally, we observed that inhibiting brain ERα, deleting ERα in POMC neurons, or chemogenetic inhibition of POMCARH neurons blocked the anorexigenic effects of 27HC. Mechanistically, we further revealed that 27HC stimulates POMCARH neurons by inhibiting the small conductance of the calcium-activated potassium (SK) channel. **Conclusions:** Taken together, our findings suggest that 27HC, through its interaction with ERα and modulation of the SK channel, inhibits food intake as a negative feedback mechanism against a surge in circulating cholesterol.

Persistent Silencing of PV+ Inhibitory Interneurons Results from Proximity to a Subcritical Hopf Bifurcation

Carol Upchurch B.S. [1], Christopher Knowlton Ph.D[1], Simon Chamberland Ph.D, Carmen Canavier Ph. D[1]

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Background: Persistent activity in excitatory principal cells has been suggested as mechanism to maintain memory traces during working memory. Persistent interruption of firing in PV+ inhibitory interneurons has been demonstrated and suggested to be the inhibitory counterpart of persistent activity in excitatory neurons. Since an interruption in inhibitory interneuronal neuron firing disinhibits the excitatory principal cells, it could serve a similar function. The purpose of this study is to examine the mechanisms behind this extended interruption. **Methods:** We compare two models of PV+ inhibitory interneurons, from the medial entorhinal cortex and CA1 region of the hippocampus, that show a persistent interruption in firing. We analyze them using bifurcation theory. **Results:** The mechanism is similar. In CA1, an inhibitory synaptic potential applied to a repetitively firing interneuron removes inactivation from rapidly activating, slowly inactivating potassium current KV1, bringing the membrane potential to a temporary equilibrium above the spike threshold during repetitive firing. After the stimulus has faded, KV1 continues to de-inactivate slowly until KV1 is sufficiently weak that repetitive firing can be reestablished. Using the inactivation variable as a bifurcation parameter shows the initial stimulus collapses the limit cycle for repetitive firing onto a co-existing stable fixed point corresponding to depolarization block. As this variable decays, the trajectory crosses a supercritical Hopf bifurcation following the curve of unstable fixed points until it spirals out into repetitive firing.

In an alternative model describing entorhinal cortical PV+ interneurons, similar behavior is achieved without a slowly activating/inactivating gated current. When the baseline current is close enough to a Hopf bifurcation, the fixed point is weakly repelling, taking hundreds of milliseconds to resume firing after an interruption. **Conclusions:** We show that the mechanism of persistent interruption in multiple models results from proximity to a Hopf bifurcation and demonstrate how the slower gating kinetics of Kv1 in the CA1 interneurons makes them more resistant to noise.

Hidden Markov Modelling of Viewing Behaviors Reveals Discrete "Encoding States" During Visuospatial Memory Formation

Chloe A. Kindell1 & Heather D. Lucas [1]

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Visuospatial memories can include information about item details, inter-item relations, and/or relations that involve the bounds of the display space. Item and relational encoding rely on distinct neurocognitive processes, but little is known about how learners balance these encoding goals from moment to moment. We used hidden Markov models to examine whether eye movements made during intentional study can be parsed into discrete "encoding states" that emphasize different types of information. Participants (n=60) studied visual displays containing six abstract items for 16 seconds each in preparation for either a spatial reconstruction task or an item recognition task. Each gaze transition ("visit") made to one of the display items during study was an observation in the model, and two variables—number of fixations made during the visit and mean fixation duration— served as emissions. Based on measures of model fit, we identified three states, one of which was consistent with item encoding and one with relational encoding. Task type (spatial versus item) interacted with state probabilities, with more time spent in the item state during the item versus the relational task and vice versa. In both tasks, memory errors were associated with insufficient time spent in the item state, particularly toward the beginning of a trial. Multistate modeling of eye movements is a promising avenue for memory research that can be easily extended in to map gaze-defined encoding states onto concurrently obtained neural data.

Are representations in the hippocampus organized by the emotional content of stimuli? A multivariate analysis of intracranial electrode recordings

Alexander Lawriw[1] (alawri1@lsu.edu) and Dr. Christopher R. Cox[1] (chriscox@lsu.edu)

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Although long understood to be sparse, episodic, and not organized around the similarity of stimuli or events, recent work suggests that representations in the hippocampus may have important structure. Within-category stimulus correlations among patterns of activity measured with fMRI from subfield CA1 can be significantly larger than between-category correlations (Schapiro et al., 2018; Nature Commun.) and some individual variability in rapid category learning can be explained by white matter integrity in the trisynaptic and monosynaptic hippocampal pathways (Schlichting et al., 2021; Hippocampus). We examined spike rates and local field potentials (LFPs) recorded by intracranial electrodes implanted in the hippocampus, amygdala, anterior cingulate cortex, and prefrontal cortex of 14 epileptic patients while they viewed and evaluated faces expressing positive, negative, or neutral affect. Using regularized logistic regression (elastic net), we attempted to discriminate patterns of activity associated with positive and negative faces within the hippocampus and spanning the four regions with electrodes. After exhaustive computational experimentation, modeling trial-level spike rates as well as the time-varying spectral power of the LFPs, it was not possible to discriminate positive from negative faces in this dataset. However, these null results do not provide tacit support for the conventional view. Instead, we situate these important null findings in a hypothesis space that considers the importance of time for how category structure may influence the hippocampus. In doing so, we discuss the limitations of intracranial recordings (our dataset, and the modality in general) for addressing questions of neurocognitive representation in the brain.

Influence on Attention and Working Memory During Visual Search with Cluttered Displays and Varied Target Prevalence

Brandon Eich, M.A., Melissa Beck, PhD

Dept. of Psychology, Louisiana State University, Baton Rouge, LA

The **purpose** of the study was to determine how the attention used to examine complex displays alters participants' ability to find a target when under the influence of varied target prevalence. Target prevalence influences the way participants perceive items in a display and quit searching. These changes have direct implications for searches with very low target prevalence (i.e., TSA & radiological screenings for cancer). **Methods:** Fifty-four individuals participated in the study. The data was collected with an eye-tracker and display pc where participants searched for the

presence of a target on a map. Average accuracy (i.e., missed targets & false alarms), response time, and fixation duration were used as quantitative measures of how participants were being influenced by a display's complexity. Low and high clutter maps were used with low (10%) and high (90%) target prevalence to influence participants' attention and working memory use. **Results:** Display complexity made participants more likely to say items were distractors, leading to missed targets, while low target prevalence made participants more likely to quit search before finding a target. **Conclusions:** Eye-tracking revealed that increased display complexity led to more distractor decisions regardless of prevalence level, suggesting increased display complexity makes participants more likely to perceive items as distractors. However, participants' expectations about whether a target is present or absent dictates when they will quit search, quitting search earlier if they expect a target to be absent. Thus, display complexity appears to influence working memory use while target prevalence more strongly influences attention use more strongly during search.

Effects of search priority on working memory-guided search for real objects: Evidence from eye-movements

Hanane Ramzaoui, Melissa Beck

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Working memory (WM) serves current goals while enabling future ones to be planned and maintained. This latter role of WM is crucial, as everyday activities require finding task-relevant objects in a timely manner and therefore prioritizing WM representations with respect to moment-by-moment task-relevance of items held in WM. How this level of priority could affect the different processes guiding search remains unanswered. Here, we compare current and prospective search template in a sequential search task. The current search template is the first target to be searched for, while the target to be searched for in a subsequent display is the prospective search template. On each trial, the participants thus perform two consecutive searches. Before the search display, a memory display indicate by a cue which target to look for in the subsequent search displays. Both target are presented before the first search array. Each array includes six colored objects arranged in a circle. In each trial, the objects share neither their main color nor their semantic category. Using an eye-tracker, reaction times were segmented into three behaviorally defined epochs: initiation time (first saccade latency), scanning time (elapsed time between the first saccade and the first fixation on the target) and verification time (elapsed time between fixation on the target and manual response). Search priority affects all three phases, resulting in shorter times for the first search than for the second search. This finding suggests that

search priority affects both the process of setting up the template and the process of matching a fixated object to an internal representation of the target. Specifically, the information that are currently relevant provides a quickly and precise template, enabling search to begin as soon as the array appears, as well as faster processing of the fixated object and therefore faster rejection of a distractor.

Acute anxiety reduces behavioral and electrophysiological measures of semantic processing during memory formation

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Acute anxiety can negatively impact memory, but the underlying mechanisms are not well understood. One theory is that anxiety interferes with goal-directed processes, which include the spontaneous use of meaning-based encoding strategies to enhance memory formation. To test this idea, across three experiments, we asked participants to view and attempt to recall two sets of neutral words, one of which was encoded in a stressful context using the threat-of-shock paradigm (threat blocks), and one of which was encoded without threat (safe blocks). In Experiments 1 and 2, significantly fewer words were recalled during threat than safe blocks. In addition, in both experiments free recall patterns following safe blocks showed higher levels of semantic organization relative to threat blocks, consistent with reduced semantic processing during study. Experiment 3 was similar to Experiments 1 and 2, except that ERPs were recorded during the study phases. Relative to safe blocks, words studied during threat blocks elicited larger N400 amplitudes, indicative of more difficult semantic access, as well as smaller amplitudes of a late frontal positivity associated with elaborative encoding. Overall, these results support the notion that threat disrupts memory encoding by interfering with participants' tendency or ability to implement effective encoding strategies.

Meaningful Co-Speech Gestures Enhance Associative Memory Formation, But Only When the Listener Expects Them To Be Meaningful

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Co-speech gestures can enhance memory for accompanying words, but their effects on memory for non-gestured associates are unclear. In three experiments, we provide ERP and behavioral evidence for a moderating role of expectations regarding gesture ambiguity. In Exp 1, participants watched videos of an actor reciting sentences that ended in unrelated verb-noun pairs (e.g., '…driving apple'). The verb in each pair ("driving") was accompanied by either a matching iconic gesture, a simple beat gesture, or no gesture. Relative to other trial types, iconic gestures enhanced memory for both the verbs and the associated nouns. In Exp 2, ERPs were recorded during study, and beat gestures were replaced with semantically ambiguous "nonsense" gestures. Here the memory benefits of iconic gestures were limited to the verbs and no longer extended to the nouns. ERPs elicited by the nouns suggested that the ambiguous gestures may have caused a global shift in attention toward the gestures and accompanying verbs and away from the paired nouns. Indeed, when the same set of iconic- and non-gestured word pairs were studied without the nonsense-gestured pairs (Exp 3), the associative memory benefits found in Exp 1 were restored. Moreover, under these circumstances, nouns preceded by iconic-gestured verbs elicited larger N700 amplitudes relative to those preceded by non-gestured verbs, suggesting enhanced associative imagery. Overall, this work suggests that iconic gestures enhance associative memory primarily when the listener expects them to be consistently meaningful and unambiguous.

Poster Presentations

#	Title	Authors
1	Central amygdala GABA neurons are involved in reward context discrimination.	Rana Fallah-Safa and Olalekan M. Ogundele
2	The faciliatory role of rhyme during implicit and explicit word learning	Tengwen Fan, M.S., Will Decker, Jacob P. Momsen, Eileen Haebig, and Julie M. Schneider.
3	Oxytocin receptor-expressing neurons in anteroventral periventricular nucleus regulate pupretrieval	Armita Abdollahi Govar, Kaustubh Sharma, Bandana Ghimire, Katsuhiko Nishimori, Elizabeth Hammock, and Ryoichi Teruyama
4	Functional convergence of bilateral auditory tectothalamic pathways	Tolulope T. Adeyelu, Olalekan M. Ogundele, and Charles C. Lee
5	The Armadillo as a Model for Leprosy Nerve Function Impairment: Preventative and Therapeutic Interventions	Maria Teresa Pena, Ramanuj Lahiri, Gigi J. Ebenezer, Stephen W. Wheat, John Figarola, Richard W. Truman and Linda B. Adams
6	Stretch times of acute opposing ankle muscles: Stretch less to sway less	Taylor M. Gauss, Rhys M. Lormand, Matthew A. Yeomans, Jan M. Hondzinski
7	Interconnection of adipose tissue and CNS to modulate energy metabolism	Swetledge S, Mohammed M, Williams J, Kaiser L, and Münzberg H
8	Astrocytes neuroprotective phenotype induced by Maresin1 'in vitro'	Tonya Chaney, E. Tendayi Mpofu, and Jorgelina M. Calandria
9	CFTR interactions in neurons, and implication in synaptic transmission	Brandon Leviskas and Evanna Gleason
10	Effect of Chronic Stress and sleep deprivation on long -term memory	Atharva A. Dingankar, Jacob Carrigan, and Juhee Haam
11	Recurrent ethanol treatment does not produce a cumulative effect on plasma leptin levels in rats	Arline Y. Narez, Victoria M. Fuentes, Mahad T. Ahmed, and David H. McDougal
12	"Assessing the Therapeutic Potential of Ketamine in Alzheimer's Disease in a mouse model"	Zeynab Nourozi, William N. Sitterson, John A. Kara, Pilip Saint Martin, Yan Zermeno, Charles C. Lee.
13	Effects of Temporoammonic Pathway Hyperpolarization on Delta Oscillations and Memory Consolidation	Suman Gunin and Juhee Haam
14	Feature or Memory: Influences on Visual Search in Varying Levels of Clutter	Tom Tomshe, Amanda van Lamsweerde, Brandon Eich, and Melissa R. Beck
15	Regulation of oxytocin neurons by oxytocin receptor expressing neurons in the perinuclear zone of the hypothalamus	B. Ghimire, A. Govar, and R. Teruyama
16	Reward-oriented spatial learning outcomes in acute stress is sex-linked	Ajn Vats and Olalekan M. Ogundele
17	Unraveling the potential circuitry of BNST, CeA, and DRN triad on the neural regulation of positive and aversive stimuli	Ignitius E. Lim and Olalekan M. Ogundele
18	Emotional stress decreases endocannabinoid signaling in cerebellar cortex	Mohamed Sayed, Jessica Fawcett-Patel, Muhammad Farooq, and Siqiong June Liu
19	Maresin-1 turns Astrocytes and Microglial cells into anti-inflammatory effectors	E. Tendayi Mpogu, Tonya Chaney, and Jorgelina M. Calandria
20	Dopaminergic Neurons Regulate Aging and Reproduction in Drosophila	Nathan Le, Chunlai Wu, and Xiaolin Tian

21	Identifying the Cognitive and Neural Mechanisms of Spatial Reasoning	Beck, M. R., Moen, K. C., Saltzmann, S. M., Burleigh, L. M., Butler, L. G., Ramanujam, J., Cohen, A. S., & Greening, S.G., Lucas H. D., Eich, B.J., Tomshe, T., and Ramzaoui, H.
22	Cell Type Specific Signatures Of Social-Stress Escalated Alcohol Consumption In The Paraventricilar Thalamus	E. Dore, E. Blaze , E. Garcia, F. Paliarin, N. Salem, A.W. Warden1, R.D. Mayfield, and R. Maiya
23	Untargeted Lipidomics Reveals Elovanoid-Mediated Suppression of Oxidized Phospholipids in Ischemic Stroke Model	Christopher J. Van Leeuwen, Rasangi M. Perera, Jeff X. Ji, Ludmila Belayev, and Nicolas G. Bazan
24	Inhibition of Lipid Peroxidation by Elovanoid Precursor: A Comprehensive Untargeted Lipidomic Approach	Rasangi M. Perera, Jorgelina Calandria, and Nicolas G. Bazan
25	ELV-N34 or RvD6-isomer counteracts damaging astrocyte phenotypes protecting the brain from Omicron BA.5-mediated long COVID	Jorgelina M. Calandria, Surjyadipta Bhattacharjee, Haydee E. P. Bazan, Nicholas Maness, and Nicolas Bazan
26	Neuroinflammation and Neurodegeneration in Adipor1-/- and Mfrprd6 Mice Linked to Fatty Acid Elongases 2 and 4 Downregulation	Kautzmann, M-A, Mukherjee, P., and Bazan, N.G.
27	Cell heterogeneity in limbal/corneal cells relevant to nerve regeneration defined using Single and Spatial Cell transcriptomics	Abhilash Ponnath, Surjyadipta Bhattacharjee, William Gordon, Haydee Bazan, and Nicolas Bazan
28	Analysis of Elovanoids Mechanism of Protection in Ischemic Stroke Using a Single-cell Multiome Approach	Jeff Ji, Surjyadipta Bhattacharjee, Sam Baum, Ludmila Belayev, and Nicolas G Bazan
29	A multiomic analysis reveals robust neuroprotection conferred by Elovanoid 34:6 and precursor Free Fatty Acid 34:6 following experimental traumatic brain injury	Samuel E. Baum, Ludmila Belayev, Andre Obenaus, Surjyadipta Bhattacharjee, Jeff Ji, Brian Giles, Alina Mohiuddin, Nicolas G. Bazan
30	Spatially resolved transcriptomics uncover differential gene expression mechanisms in age-related macular degeneration	Warner Moore, Surjyadipta Bhattacharjee, Marie-Audrey I. Kautzmann, and Nicolas G. Bazan
31	Elovanoids are Neural Resiliency Epigenomic Regulators Targeting Histone Modifications, DNA Methylation, Tau Phosphorylation, Telomere Integrity, Senescence Programming, and Dendrite Integrity	Surjyadipta Bhattacharjee, Pranab K. Mukherjee, and Nicolas G. Bazan
32	The Influence of Native Language on Motion Event Encoding: An ERP Study	Stephanie L. Lopez, Tengwen Fan, Marcus L. Forest, and Julie M. Schneider
33	Identification of Possible Early Gene Markers of Alzheimer's Disease By 2-Month APP Knock-In Mouse Model in Defined Cell Clusters	Brian Giles, Surjyadipta Bhattacharjee, Jeff Ji, Marianne Schultzberg, and Nicolas G Bazan
34	Enhanced Neurobehavioral Rehabilitation and Increased Homeostatic Gene Expression Following Experimental Ischemic Stroke with Combined NPD1 and RvD1 Therapy	Alina Mohiuddin, Jeff Ji, Ludmila Belayev, and Nicolas G. Bazan
35	From Stem cell to GABAergic Vs Dopaminergic differentiation	Keerthika Yalakaturi and Eduardo Martinez-Ceballos
36	Impact of Sex and Diet on Gut Microbiota and Cognitive Function in Sprague-Dawley	Yu I, Solch-Ottaiano RJ, Prats MM, Prus NM, and Maraganore DM

Central amygdala GABA neurons are involved in reward context discrimination.

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Amygdala projections are involved in diverse neural circuits that govern complex adaptive behavioral response. Notably, the role of the cortico-amygdala pathway and amygdala projections to the hypothalamus in conditioned fear learning, and social interaction behavior have been ascertained. However, how CeA projections to midbrain regions that drives reward-aversion learning, contributes to the determination of weight of positive valanced contexts – e.g., reward – is still poorly understood. The current study deploys cre-lox recombination and chemogenetic modulation methods to target CeA GABA neurons in a conditioned place preference test where mice made a ranked choice between two positively valanced contexts (sucrose and sucrose/alcohol). In the learning phase, mice were exposed to sucrose in two contexts that differ in spatial location, visual cues, tactile cue, and odor (vinegar or none). Each mouse preferred one context to the other while obtaining the sucrose reward. As such, in the conditioning phase mice choose between sucrose on the preferred side, and sucrose/alcohol on the non-preferred side. Results of the baseline testing phase showed that mice preferred the sucrose, compared with sucrose/alcohol. However, selective excitation of CeA GABA neurons during the conditioning phase attenuates the ranked choice between the two types of reward. Consequently, the propensity for exploring contexts containing sucrose or sucrose alcohol were comparable with CeA GABA stimulation. We conclude that activation of CeA GABA neurons during the conditioning phase of reward-choice and context discrimination tasks attenuates discrimination outcomes.

keywords: CPP, Learning, CeA, GABA, Contexts, Circuits.

The faciliatory role of rhyme during implicit and explicit word learning

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Purpose: Strong word learning skills are contingent upon effective prediction and retrieval. Rhyme increases the predictability of phrases individuals hear (Read et al., 2014) and enhances recall from working memory (Chow et al., 2016) by heightening phonological sensitivity. Whether rhyme aids word learning remains unknown. **Methods:** Fifty-seven adults completed an exposure and recall word learning task where they were taught 15 nonwords as their EEG was recorded. Participants were randomly assigned to either a rhyme or no rhyme condition, where the nonword rhymed or did not rhyme with an earlier word in the sentence during the exposure phase. They were then tested on their recall of nonwords. **Results:** Binomial general linear mixed effects modeling (GLMER) indicated that individuals in the rhyme condition (M=73.5%, SD=44.1%) were significantly more likely to accurately identify a target word in the recall test compared to the no rhyme condition (M=54.7%; SD=49.8%; B=1.23, SE=0.50, p=0.01). We next conducted two GLMERs to identify how amplitude of the MMN (150- 300 msec) and N400 (350-450 msec) interacted with learning condition to predict binomial accuracy across post-test trials. A significant interaction between condition and MMN amplitude was observed over frontal and central electrodes, as was a significant interaction between condition and N400 amplitude over frontal and occipital sites (ps< 0.05). A larger MMN and N400 was predictive of correct recognition of the nonword for individuals in the rhyme condition. **Conclusions:** Our results suggest that rhyme may facilitate both explicit and implicit correlates of word learning in adults.

Oxytocin receptor-expressing neurons in anteroventral periventricular nucleus regulate pupretrieval.

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Mother-infant bonding is crucial for the survival and development of offspring. The oxytocin system has an essential role in mother-infant bonding. Oxytocin modulates maternal behavior by binding to oxytocin receptors (OXTRs) in various parts of the brain. Previously, we showed that OXTR is expressed in the anteroventral periventricular nucleus (AVPV) of females, but not in males, using OXTR reporter (OXTR-Venus) mice. This finding suggests that OXTR neurons in the AVPV are involved in the expression of female-specific behaviors. The present study was conducted to investigate if OXTR cells in the AVPV are involved in the regulation of maternal behaviors. The total number of the OXTR-Venus cells was significantly greater in postpartum dams (1371 ± 89 cells) than in virgin females (644 ± 23 cells, $p<0.0001$). Since dopaminergic neurons in the AVPV are involved in the regulation of maternal behaviors, immunocytochemistry of tyrosine hydroxylase (TH) antibody was performed on brain slices from OXTR-Venus mice. Only ~25% of OXTR-Venus cells were TH+ in postpartum dams and virgin females, although the number of TH+-OXTR-Venus cells in postpartum dams was significantly higher (339 ± 41) than in virgin females (198 ± 7 cells, $p=0.0004$). To assess if activity of the OXTR cells is involved in expression of maternal behaviors, the Designer-Receptors Exclusively Activated by Designer Drugs (DREADDs) technique was used. A Cre-recombinasedependent adeno-associated virus vector containing inhibitory DREADD (hM4D(Gi)) or control DREADD (DIO) was injected into the AVPV of OXTR-Cre mice. A series of maternal behavior tests were conducted on the postpartum day one: first without Clozapine-N-Oxide (CNO: a ligand for the DREADD) and subsequently with i.p. injection of CNO. None of hM4D(Gi) dams retrieved any pups following the CNO injection. The CNO injection did not affect the ability of DIO dams to retrieve pups. After the CNO injection, hM4D(Gi) dams spent significantly less time ($915.3 \pm 285.9s$) crouching over pups compared to themselves without CNO (1993.5 ± 86.08 s, $p=0.008$). The effect of CNO was not observed in the time spent inside the nest, pup-directed licking, selfgrooming, eating, or drinking behaviors in hM4D(Gi) or DIO dams. These findings demonstrate that OXTR cells in the AVPV are involved in the expression of specific maternal behaviors namely pup retrieval and crouching over pups.

Poster #4

Functional convergence of bilateral auditory tectothalamic pathways

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Ascending information in the central auditory system is conveyed eventually by pathways from the auditory midbrain (inferior colliculus: IC) to the auditory thalamus (medial geniculate body: MGB). These tectothalamic pathways are composed of both excitatory and inhibitory projection neurons, which transfer and modulate this incoming auditory stream. Although the role of the ipsilateral auditory tectothalamic pathways in this process has been intensively investigated, the contribution from the contralateral tectothalamic pathways has been largely ignored. Here we employed a cre-lox approach to examine the neuroanatomical and physiological properties of the contralateral tectothalamic pathways in auditory processing. Floxed viral tracers expressing either mCherry or EYFP were injected bilaterally into each IC of VGLUT2-Cre or VGAT-Cre transgenic mice. The resultant bilateral terminal fields were then examined in the MGB. In addition, we assessed the functional impact of these projections, by utilizing an optogenetic approach to express halorhodopsin using floxed viral vectors in the Cre-transgenic animals and then recording physiologically from the MGB to acoustic stimuli. From our studies, we found that the MGB terminal fields from bilateral IC tectothalamic projections overlapped on a gross level. On a finer scale, terminal puncta were often closely apposed near presumed cell bodies, suggesting single-cell convergence of these inputs. Physiologically, optogenetic inhibition of contralateral tectothalamic pathways affected the responsiveness and spiking characteristics of MGB neurons to sound stimulation. Together, these data demonstrate a significant role for the contralateral tectothalamic pathways in the bilateral integration of the auditory scene.

Poster #5

The Armadillo as a Model for Leprosy Nerve Function Impairment: Preventative and Therapeutic Interventions

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Mycobacterium leprae infection of peripheral nerves and the subsequent nerve function impairment (NFI), especially in response to reactional episodes, are hallmarks of leprosy. Improved treatments for M. *leprae*-induced nerve injury are needed, as most if not all of the disability and stigma associated with leprosy arises from the direct or indirect effects of NFI. Nine-banded armadillos (*Dasypus novemcinctus*), like humans, exhibit the full clinical spectrum of leprosy and extensive involvement of the peripheral nerves. The **purpose** of this study was to evaluate state-of-the-art technology to compare nerve function between uninfected and M. leprae-infected armadillos. **Methods and Results:** Motor nerve conduction velocity (MNCV) and compound muscle action potential (cMAP), which measure changes in the rate of impulse conduction velocity and amplitude, revealed a progression of impairment that was directly correlated with the duration of *M. leprae* infection and enabled development of an objective nerve impairment scoring system. Ultrasonography accompanied by color Doppler imaging detected enlargement of the *M. leprae*-infected nerves and increased vascularity, possibly due to inflammation. Assessment of epidermal nerve fiber density (ENFD), which shows a length-dependent innervation in armadillos that is similar to humans, identified small fiber degeneration early after *M. leprae* infection. Staining for neuromuscular junction (NMJ) integrity, which is an indicator of signal transduction efficiency into skeletal muscle, discerned a markedly lower number and structural integrity of NMJ in *M. leprae*-infected armadillo footpads. These tools for assessing nerve injury were used to monitor the effects of intervention therapy. Two potential neuro-protective drugs, ethoxyquin (EQ) and 4-aminopyridine (4-AP), were tested for their ability to ameliorate peripheral nerve injury in *M. leprae*-infected armadillos. 4-AP treatment improved MNCV, cMAP, and EFND compared to untreated animals, while EQ had less effect. **Conclusions:** These results support the armadillo as a model for *M. leprae*-induced peripheral nerve injury that can provide insights toward the understanding of NFI progression and contribute to the preclinical investigation of the safety and efficacy of neuro-preventive and neuro-therapeutic interventions for leprosy.

Poster #6

Stretch times of acute opposing ankle muscles: Stretch less to sway less

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Benefits of static stretching include improved flexibility and range of motion; however, the impact of static stretching on postural sway and proprioception remain unclear. We previously showed that acute stretching of opposing ankle muscles in 2-4 30 s bouts decreased sample entropy, thus automated control of sway, and increased center of pressure (COP) variability in the mediolateral (ML) direction compared to no stretch (NS) and/or non-opposing ankle muscle stretches. Interestingly, standing sway remained the same after stretching the non-opposing ankle muscles, despite different stretch times. The **purpose** of this study was to determine if postural sway would differ for various times of acute opposing ankle muscle stretches. **Methods:** Twelve young adults (4 F/8 M; Age 25 +/- 4.9 years) received NS or passive plantar- and dorsi-flexion stretching to discomfort for 2-4 bouts of 15, 30, or 45 s before performing 3 trials of static stance (barefoot participants stood as still as possible with eyes closed for 45 s on an ATMI force plate) and proprioception tasks (participants actively matched remembered ankle angles, measured by a handheld goniometer). **Results:** Repeated measures ANOVAs revealed increased M-L standard deviation (SD) and M-L displacement (D) in the 45 s condition compared to NS ($p < 0.05$). As with our previous outcomes, results revealed that lower M-L sample entropy after stretching compared to NS ($p < 0.001$), stretching did not influence proprioception or anteroposterior sway, and proprioception error negatively correlated with M-L SD and M-L D, especially in more flexible participants. **Conclusions:** A better ability to actively reproduce ankle positioning likely encourages an internal focus of attention on movement, known to increase postural sway. Moreover, while less automation of M-L sway occurs after stretching bouts as short as 15 s, it takes only 2-4 bouts of opposing muscle stretching for 45 s to increase postural sway displacement and its variability. We recommend use of less than 45 s bouts of stretching when prioritizing reduced postural sway.

Poster #7

Interconnection of adipose tissue and CNS to modulate energy metabolism

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Energy expenditure is important for homeostatic control (e.g body temperature, body weight) and requires communication between adipose tissue and the brain, such as spinal sensory/sympathetic interaction or humoral feedback (e.g. adipocyte-derived hormone leptin). We identified leptin receptor neurons in the preoptic area (POA-Lepr neurons) that receive sensory information about ambient temperature changes and selectively mediate warm-induced suppression of energy expenditure (EE) and food intake. POA-Lepr neurons are glutamatergic

and project directly (or indirectly via the dorsomedial hypothalamus) to the raphe pallidus (RPa) in the brainstem. Direct glutamatergic POA>RPa projections are against the dogmatic view that GABAergic warm-activated POA neurons suppress glutamatergic RPa neurons. We hypothesized: a) projection-specific activation of POA-Lepr projections to the RPa is sufficient to mimic chemogenetic activation of POA-Lepr to suppress EE and rectal temperature (Trec: -6°C). b) that stimulation of GABAergic RPa neurons is similarly sufficient to suppress EE and Trec.

First, we selectively stimulated POA-Lepr>RPa projections optogenetically and measured EE in metabolic cages or Trec in home cages. Compared to control animals this robustly suppressed EE and Trec (n=4), supporting the idea that glutamatergic POA-Lepr neurons would stimulate GABAergic interneurons in the RPa, and further suppress glutamatergic RPa neurons or alternatively act on spinal neurons. Second, to test if GABAergig RPa neurons overall suppress EE, we virally expressed ChR2 in the RPa of vGat-cre mice. In a first cohort of mice (n=7 ChR2 virus, n=2 control virus) we found surprisingly no effect on Trec, while EE was unexpectedly increased. Third, anatomical studies showed successful labeling of RPa neurons, but the very small RPa region is difficult to hit exclusively.

Our data confirm that glutamatergic POA-Lepr inputs to the RPa is able to suppress EE and body temperature. Yet, unexpectedly overall stimulation of GABAergic RPa neurons increased energy expenditure, which is inconsistent with the current dogma that activation of thermogenesis is mediated by glutamatergic, spinal projecting RPa neurons. Thus, these data collectively allow several avenues how glutamatergic input from POA-Lepr neurons may suppress energy expenditure. Anatomical studies are on the way to look for local vs. spinal projections of GABAergic RPa neurons.

Poster #8

Astrocytes neuroprotective phenotype induced by Maresin1 'in vitro'.

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Parkinson's disease (PD) is a neurodegenerative disorder that affects the dopaminergic neurons in the Substantia Nigra (SN). Astrocytes and microglia signaling play a key role in the maintenance and support of the neurons in the central nervous system. For this purpose, astrocytes change their phenotype, in some cases transforming themselves into reactive types with the subsequent release of cytokines and chemokines with the activation of NFkB/p65 transcription factor and β-Catenin. Compelling evidence shows a wide variety of astrocytic phenotypes with specific functions in each case. These phenotypes direct the defensive neuroprotective efforts to modulate neuroinflammation. Our overall hypothesis is that DHA derivative, Maresin 1, induces the

passage of astrocytes from chronic reactivity states found in PD to resolving reactivity. The **purpose** of this study was to test "in vitro", using rat astrocyte cultures, the conversion from chronic reactivity mediated by cytokines to neuroprotection by Maresin-1. **Methods:** primary rat astrocytes were exposed to 1) cytokines (TNF-α and IFN-γ) or α-synuclein performed fibrils to mimic Lewy body structures. NF-kB/p65 and β-catenin were detected in the nucleus by immunocytochemistry and Imaris software with spatial cellular recognition algorithms. **Results:** Nuclear content of NF-κB is increased in astrocytes exposed to TNFα and INFγ. The addition of Maresin 1 decreased the nuclear translocation of NF-κB induced by the cytokines. α-synuclein preformed fibrils also induced nuclear translocation of NF-κB and Maresin 1 decreased the transcription factor this activation. In no case Maresin 1 alone induced any effects. **Conclusions:** Maresin-1 showed anti-inflammatory pro-homeostatic properties by decreasing the activation (by nuclear translocation) of NF-kB. Maresin 1 was previously demonstrated to work via two receptors: LRG6 and RORα. In future work we will silence these two receptors and we test the translocation of NF-κB to the nuclei. These results suggest that Maresin-1 is a key signaling molecule that maintains homeostasis regulation and anti-inflammatory phenotypic status in astrocytes.

Poster #9

CFTR interactions in neurons, and implication in synaptic transmission

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Protein-protein interactions differ among cell types and cellular localization of these interactions can further define protein function. Interactions between cystic fibrosis transmembrane conductance regulator (CFTR) and SNARE protein Syntaxin-1A (STX1A) have been confirmed in epithelia (Naren et al., 2000). Our lab has established a role for CFTR regulation of cytosolic Cl- in neurons and demonstrated CFTR (Krishnan et al., 2017) and STX1A (McMains et al., 2011) expression in retinal amacrine cells (ACs). Here we ask whether there are physical interactions between neuronal CFTR and STX1A. Co-IP was achieved using CFTR antibodies in adult chick (Gallus gallus) brain protein homogenates to form an immunocomplex with CFTR. Once eluted, Co-IP products were blotted and probed for STX1A and SNARE protein SNAP-25. To further test for in vitro interactions between CFTR and STX1A, a binding assay used recombinant whole CFTR protein to supplement protein homogenates in Co-IP. Immunoblots of the CFTR supplemented sample show increases of 2.3-fold in STX1A and 3.7-fold in SNAP25 probe signal, indicating that increasing CFTR concentration increases the level of CFTR-STX1A interactions. Given the increase of SNAP25 in the Co-IP we expanded the CFTR interactors search using Co-IP products in mass spectrometry analysis. Resulting peptides were scored using

Sequest and excluded if present in bead-only controls. Protein function groups were assigned using UniProtKB and visualized using Stringdb. Neuronal protein function groups include the synaptic vesicle cycle and endocytosis. To rule out the possibility that CFTR and STX1A binding only occurs in vitro, colocalization was examined via immunocytochemistry in cultured ACs. Results (mean ± SEM, n =33) show Pearson's correlation coefficient of 0.69 ± 0.02 and Manders' M1 of 0.091 ± 0.01 and M2 of 0.91 ± 0.02 in AC processes indicating overlap in protein expression. Because STX1A functions at the neuronal synapse, we tested if CFTR inhibition effects synaptic function with whole cell voltage clamp recordings of spontaneous postsynaptic quantal currents (SPCs) from EE18-21 ACs with ≥3 presynaptic ACs. CFTR inhibition (CFTRinh172, 10 µM) increases the frequency of events/60s (mean± SEM, n =5) as compared to control [CFTRinh172, 99.6 ± 25.9, p =.003) control, 68.2 ± 20.6 and wash 81 ± 24.1 (p =.02)], suggesting CFTR somehow limits spontaneous vesicle fusion. These data demonstrate interactions between CFTR and STX1A in ACs, while presenting a neuronal CFTR interactome suggesting additional roles in synaptic function. Furthermore, elevation of SPCs frequency upon CFTR inhibition suggesting a presynaptic role for CFTR.

Poster #10

Effect of Chronic Stress and sleep deprivation on long -term memory

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Purpose: Chronic stress and sleep deprivation (SD) are recognized contributors to memory impairments. However, the specific mechanisms underlying these memory impairments remain unclear. Previous work in our laboratory uncovered that the temporoammonic (TA) pathway neurons in the entorhinal cortex exhibit delta oscillations during sleep, that are driven by hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels and are crucial for memory consolidation. While the entorhinal cortex is known to be susceptible to chronic stress, the specific effects of chronic stress and SD on entorhinal cortical delta oscillations and their consequences for memory consolidation remain unexplored. The purpose of this study is to examine the effect of chronic stress and SD on memory consolidation mediated by the TA pathway. **Methods:** Wild-type C57BL/6 mice were subjected daily to the chronic variable stress (CVS) paradigm, in which a combination of two to three out of seven stressors are presented unpredictably, followed by SD for 30 days. Subsequently, a battery of behavioral tasks assessed their memory performance. Corticosterone levels, pre- and post-stressor exposure, were systematically monitored via fecal samples over the stress exposure period, and anxiety levels were evaluated with the open field task. Following the behavioral battery, mouse brains were collected for immunohistochemical and western blot analyses to examine the impact of CVS and

SD on HCN channels. Additionally, mice, injected with AAVs carrying genes for GCaMP6f and TdTomato (AAV9-CaMIIα-GCaMP6f and AAV9-CaMIIα-tdTomato-WPRE) and implanted with an optical probe targeting the TA pathway terminals onto hippocampal CA1 were subjected to CVS and SD to investigate its effect on entorhinal cortical delta oscillations using fiber photometry. Results: Mice that received CVS and SD displayed impaired long-term spatial memory, evident from the equal time spent in the target quadrant compared to non-target quadrants in the Morris water maze task. However, these mice exhibited intact spatial working memory in the spontaneous alternation task. **Conclusion:** Mice subjected to prolonged periods of CVS followed by SD exhibit compromised long-term spatial memory while retaining intact working memory. This indicates a reparative role of sleep in ameliorating the detrimental impacts of chronic stress on long-term memory storage. The interference with this compensatory mechanism, particularly over protracted durations, leads to discernible long-term memory impairment.

Poster #11

Recurrent ethanol treatment does not produce a cumulative effect on plasma leptin levels in rats.

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Purpose: Hypoleptinemia is a potent orexigenic signal acting on the CNS. Chronic ethanol (EtOH) consumption is associated with weight gain in humans, and acute ethanol treatment leads to reductions in leptin concentrations in both fasted humans and rats. The objective of this study was to determine whether short-term recurrent ethanol treatment has a cumulative effect on plasma leptin levels in rats, and whether treatment in the fed or fasted state influences the leptin lowering effect of EtOH. We hypothesized that recurrent EtOH treatment would have a cumulative leptin-lowering effect, and that this effect would be more pronounced in the fed state when leptin levels are highest. **Methods:** Two separate groups of male Sprague Dawley rats were exposed to either oral or intravenous (IV) treatment with EtOH on three consecutive days (2g/kg via oral gavage or 0.067 g/kg/min IV for 30 min; n=7/group). Each rat served as its own control, receiving saline treatment either 7 d prior to or 7 d following exposure to EtOH. The oral group was fasted 12-14 h (overnight) prior to treatment, while the IV group was not fasted. Plasma leptin and EtOH levels were measured each day at baseline and 3 h following EtOH treatment. A two-way repeated measures ANOVA was used to test for differences in plasma leptin and EtOH levels due to treatment (saline vs. EtOH) or day (cumulative effect of treatment) in the oral and IV treated groups independently. **Results:** Baseline leptin levels in the oral treatment (fasted) group were 3.4 + 0.3 and 3.9 + 0.2 ng/mL under saline and EtOH treated

conditions, respectively. There was a significant main effect of treatment but not of day in the oral EtOH group (p=0.04 and p=0.38, respectively). Average daily change in leptin levels 3 h post treatment in saline and EtOH treated rats were $-0.18 + 0.05$ and $-0.72 + .1$ ng/mL, respectively. Baseline leptin levels in the IV (fed) group were $7.8 + 0.3$ and $6.7 + 0.1$ ng/mL, in saline and EtOH treated rats respectively. There was no significant main effect of treatment or day in the IV group (p=0.17 and p=0.41, respectively). Average daily changes in leptin levels 3 h following treatment in saline and EtOH treated rats were $-1.7 + 0.2$ and $-1.3 + 0.3$ ng/mL, respectively. **Conclusions:** Although we were able to replicate previous work indicating reduced leptin levels following acute EtOH treatment in fasted rats, our results do not support a cumulative leptin-lowering effect of recurrent EtOH treatment. Furthermore, IV EtOH treatment in the fed state did not have any impact on leptin levels. This suggests that the leptinlowering effects of EtOH may either require the fasted state or ingestion and exposure of the GI system to EtOH.

Poster #12

"Assessing the Therapeutic Potential of Ketamine in Alzheimer's Disease in a mouse model"

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Alzheimer's disease (AD) is a leading cause of dementia, defined by a decline in cognitive ability and decreased independence in daily tasks. AD is accompanied by degeneration of both neurons and glial cells and is accompanied by amyloid plaque formation and alterations to cholinergic systems in the brain. Furthermore, several risk factors, including age, genetic predisposition, brain injury, vascular difficulties, infections, and environmental effects, all contribute to disease development. Currently, only two medication classes are approved for treating AD: cholinesterase enzyme inhibitors and N-methyl D-aspartate (NMDA) receptor antagonists. However, these drugs only control AD symptoms, without curing or preventing disease progression. Interestingly though, ketamine may have potential neuroprotective effects on neurons, glial cells, and astrocytes, which could provide therapeutic benefits and delay the onset of symptoms in patients. Here, we investigated the potential neuroprotective benefits of ketamine administration in a mouse model of Alzheimer's disease. Following drug administration, animals were assessed behaviorally on the novel object recognition, Y maze, and forced swim tests. Animals were assessed longitudinally for several months following ketamine administration and then sacrificed to assess alterations to brain neuropathology.

Effects of Temporoammonic Pathway Hyperpolarization on Delta Oscillations and Memory Consolidation

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Purpose: Delta oscillations in the temporoammonic (TA) pathway of the entorhinal cortex via hyperpolarization-activated cyclic-nucleotide-gated (HCN) channels, mediate memory consolidation during sleep. We have previously shown that the blockade of the HCN channels leads to memory impairment, however, the effect of membrane hyperpolarization on delta oscillation and memory consolidation is unknown. Since HCN channels are activated by membrane hyperpolarization, we hypothesize that chemogenetic membrane hyperpolarization of the TA pathway will increase delta oscillation and thereby lead to enhanced memory consolidation. **Methods:** To test this hypothesis, we conducted input-specific in vivo neuronal activity recordings from the TA pathway in C57/BL6 mice while inducing membrane hyperpolarization in these neurons. To record from the TA pathway neurons, we injected a viral cocktail that expresses calcium indicator Gcamp6f and TdTomato under the glutamatergic CaMKII promoter in EC layer 3. Since the TA pathway have long projections from EC layer 3 to hippocampal CA1, we implanted optical probes in Gcamp6f expressing axon terminals of CA1 region. To modulate the TA pathway neurons, we injected a virus that expresses hM4Di, which is a chemogenetic receptor that is selectively activated by deschloroclozapine (DCZ), under the glutamatergic CaMKII promoter. The recordings were performed for five consecutive days with three habituation sessions, one day with saline injection, one day with DCZ injection, and one day of wash-out. After 14 days of delay, these mice are subjected to spatial memory consolidation tasks of delayed non-match to sample and Morris water maze. The DCZ injection would be delivered immediately after the training session, which is followed by a testing session 24 hours after to assess the memory performance. **Results:** In vivo, neuronal activity recordings showed a significant increase in the delta oscillations after the DCZ treatment in comparison to the saline treatment. The spatial memory consolidation tasks are expected to reflect the changes in memory consolidation due to the enhanced delta oscillations in the TA pathway. **Conclusion:** Our findings suggest that hyperpolarization of TA pathway neurons leads to increased delta oscillations. The findings of the spatial memory consolidation tasks would further illuminate the behavioral correlate of enhancing delta oscillations in the TA pathway.

Feature or Memory: Influences on Visual Search in Varying Levels of Clutter

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The **purpose** of this study was to investigate the use of visual properties (featurebased-search) versus memory (memory-based-search) in visual search. **Methods:** 148 individuals participated in the study. The data was collected using Eyelink 1000 Plus eye tracker and Experiment Builder software. For Experiment 1, visual search performance for a target in low, medium, and high clutter charts that either repeated or did not repeat across three blocks were the mean measures. For Experiment 2, visual search performance for a target in low and medium clutter charts that either repeated or did not repeat across five blocks were the mean measures. We used within-subject mixed analysis of variance and follow-up standard t-tests to assess significance. **Results:** The results of Experiment 1 showed that search was faster for repeated than non-repeated high clutter charts, but not for low or medium clutter charts. In Experiment 2, search was not faster for repeated charts, supporting feature-based-search. **Conclusions:** Feature-based-search is supported for easy search (low and medium clutter) and memory-based search for difficult search (high clutter).

Regulation of oxytocin neurons by oxytocin receptor expressing neurons in the perinuclear zone of the hypothalamus

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The neuropeptide hormone oxytocin induces contraction of the uterus and mammary gland during parturition and milk ejection, respectively. Oxytocin is synthesized by oxytocin neurons in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus. Oxytocin is released from axon terminals of oxytocin neurons in the posterior pituitary into the general circulation. Oxytocin neurons display synchronized burst of high frequency action

potential preceding each milk ejection, resulting a bolus release of oxytocin necessary for contraction of the mammary gland during milk ejection. Oxytocin is also released from the soma and dendrites of oxytocin neurons. The somato-dendritic release of oxytocin increases during milk ejection and facilitates synchronous bursting activity of oxytocin neurons. It is believed that the effect of oxytocin on oxytocin neurons is mediated by the oxytocin receptor (OXTR) expressed on oxytocin neurons themselves. However, our study on OXTR reporter (OXTR-Venus) mice did not find OXTR-Venus on oxytocin neurons. Instead, OXTR-Venus was found in non-oxytocin neurons in the perinuclear zone (PNZ) area immediately dorsal to the SON. These OXTR-Venus neurons had processes projecting to oxytocin neurons in the SON. The objective of our research is to elucidate the regulatory mechanism of OXTR neurons in the PNZ on the activity of oxytocin neurons in the SON during lactation. To examine the type of neurotransmitter from the OXTR neurons, we created double reporter mice that express glutamic acid decarboxylase2 (GAD2)-mCherry and OXTR-Venus. Most of the OXTR-Venus neurons in the PNZ also expressed GAD2-mCherry. The total number of OXTR-Venus x GAD2-mCherry neurons was significantly higher in lactating females than in virgin females. These findings suggest that OXTR neurons in the PNZ are GABAergic and increase in number during lactation. Brain slice whole-cell patch clamp recordings on oxytocin neurons were conducted to examine if oxytocin induces GABA inputs to oxytocin neurons. Significantly higher frequency of GABA post synaptic currents burst was observed in lactating females than in virgin females. Bath application of selective OXTR agonist (TGOT) caused an increase in frequency of intraburst post synaptic currents in oxytocin neurons in lactating females, but not in virgin females. These findings suggest that the somato-dendritic release of oxytocin stimulates GABAergic inputs from OXTR neurons in the PNZ to oxytocin neurons in the SON during lactation.

Poster #16

Reward-oriented spatial learning outcomes in acute stress is sex-linked

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Stress disrupts brain homeostasis by altering neural activity, and synaptic substrates that underlie cognitive and adaptive processes. Acute and chronic stress paradigms have been implicated in memory loss, alteration of stress-linked neural circuits, and spine dysgenesis in the cognitive centers. Previous studies have shown sex-linked differences in neural circuits associated with adaptive stress response. The **purpose** of the current study was to ascertain the correlation between physical stress and learning propensity. This was aimed at examining sex-linked stress sensitivity, specifically, behavioral changes, and alterations in brain markers that are pertinent to

stress signaling or synaptic plasticity. **Methods:** A total of 20 adult C57B6 mice (10 male, 10 female) were subjected to physical stress daily and reward-oriented task learning accuracy was tested on the same day (after a washout period). At the end of a 6-day period, they were subjected to Elevated Plus Maze (EPM) and Open Field Test (OFT) which were recorded and analyzed using EthoVision. Statistical analysis was done using OriginPro. **Results:** Female mice subjected to physical stress showed a decline in task learning propensity compared with males exposed to similar conditions. In a conditioned place preference test (reward) combined with a spatial task (T-Maze), stressed female mice recorded significantly lower learning outcomes when compared with control. Conversely, stressed male mice show robust learning outcomes and were comparable with the controls. In support of this outcome, stressed male mice completed the trials of a learning task in a shorter duration when compared with the control or stressed female mice. Further analysis of anxiogenic behavioral outcomes – in EPM tests – at the end of learning sessions demonstrate aberrant frequency of open-closed arm transitions for stressed female mice. However, exploratory behavior in an OFT was comparable for stressed males and females. **Conclusions:** Taken together, our results show that physical stress decreased daily spatial learning outcomes in female mice, compared to males. Keywords: acute stress, CPP, spatial learning, sex, circuits.

Poster #17

Unraveling the potential circuitry of BNST, CeA, and DRN triad on the neural regulation of positive and aversive stimuli

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Neural circuits containing projections from the dorsal raphe nucleus (DRN), bed nucleus of the stria terminalis (BNST), and central amygdala (CeA) govern psychosocial conditions and anxiogenic behaviors. How these circuits contribute to the expression of anxiogenic behaviors that are primarily driven by aversive stimuli has been tested with great certainty. However, the role of this (triad) circuit in the expression of behaviors that discriminate between positive and negatively valenced stimuli is still poorly understood. The **purpose** of this study was to investigate the encoding mechanism of this to positive and negatively valenced stimuli **Methods:** Here, we deployed high-throughput in vivo neural recording techniques in head-fixed anesthetized mice. High channel count probes were positioned in the DRN, CeA, and BNST for concurrent recording of neural spikes when odorants (neutral, aversive, and rewarding) were presented. A total of 14 C57BL/6 adult mice (males = 7; females = 7) were used to assess the encoding mechanism of the DRN-CeA-BNST triad and ascertain sex-linked differences relative

to the valence of the odorants. Multi-unit and single-unit analyses were performed for putative neurons sampled in the DRN, CeA, and BNST. The response pattern of putative units within the triad were compared for stimuli-specific events and sex-linked differences. **Results:** Putative units in the DRN, CeA, or BNST showed a net increase in FR when a positive or negatively valenced stimulus was presented. However, putative units within the DRN or BNST components of the triad discriminated between valences by showing significantly higher thresholds of FR increase when an aversive stimulus was presented. Interestingly, there was a significant sex difference in the fidelity of encoding. As such, ensembles sampled in females showed higher levels of sensitivity in comparison to male ensembles. **Conclusions:** In conclusion, the results demonstrate sex-linked sensitivity of the triad to both positive and negative valenced stimuli. Furthermore, the encoding mechanism discriminates between valences by altering the magnitude of FR change.

Poster #18

Emotional stress decreases endocannabinoid signaling in cerebellar cortex

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We have recently shown that a decrease in endocannabinoid signaling in the cerebellum is essential for fear memory formation. Since emotional stress can modify subsequent fear memory, the **purpose** of this study is to test whether predator odor stress could affect endocannabinoid signaling in the cerebellar cortex. **Methods:** Male C57BL/6 mice were exposed to fox urine for 5 minutes and the cerebellum was isolated three hours later. Since endocannabinoid (eCB) signaling reduces neurotransmitter release, we tested the effect of an endocannabinoid receptor (CB1R) antagonist on spontaneous GABA release, marked by miniature IPSCs (mIPSCs) recorded in stellate cells. **Results:** Bath application of a CB1 receptor antagonist NESS0327 enhances the frequency of mIPSCs in naive mice, indicating the presence of tonic eCB. However, NESS0327 failed to modify mIPSC frequency in mice that were exposed to predator odor, suggesting that predator odor stress decreases tonic endocannabinoid signaling in the cerebellar cortex. The reduction in eCB signaling could be due to a loss of endocannabinoid receptor signaling. To test this, we applied a CB1R agonist, WIN55212-2 and found out that WIN55212-2 reduced the frequency of mIPSCs in molecular layer interneurons from stressed

mice by around 30%, comparable to that in naïve animals. Consequently, fox urine exposure was not able to change the CB1R signaling, and may thus alter eCB levels. 2-Arachidonoyl Glycerol (2AG), cerebellum's main eCB in the cerebellum, is produced by diacylglycerol lipase (DAGL) and degraded by monoacylglycerol lipase (MAGL). We quantified MAGL activity and noted that predator odor stress did not alter the activity of MAGL compared to naive mice. We next tested whether stress reduced DAGL levels in cerebellar cortex using western blotting. We demonstrate that fox urine exposure reduced the DAGL expression by around 40% compared to naive mice. **Conclusion:** Our results propose that predator odor stress reduces endocannabinoid signaling in cerebellar cortex by decreasing 2-AG production via DAGL. (Supported NIH R01 NS106915, VA I01 BX003893-01A1).

Poster #19

Maresin-1 turns Astrocytes and Microglial cells into anti-inflammatory effectors

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Parkinson's disease (PD) is a neurodegenerative disorder that affects the dopaminergic neurons in the Substantia Nigra (SN). Astrocytes, the largest and most abundant type of supporting cells in the central nervous system, participate in the detection and communication of stress signals from neurons to microglial cells. For this purpose, astrocytes change their phenotype, in some cases transforming themselves into reactive types with the subsequent release of cytokines and chemokines with the activation of NFkB/p65 transcription factor. These phenotypes direct the defensive neuroprotective efforts to modulate neuroinflammation. Our overall hypothesis is that DHA derivative, Maresin 1, induces the second step in the activation of Astrocytes and Microglia that make the transition from chronic to resolving reactivity when cytokines of abnormal α-synuclein structures are present. The **purpose** of the present work is to test "in vivo" the conversion of astrocytes and microglia in a 6- hydroxydopamine (6-HODA) toxicity rat model. **Methods:** Dopaminergic neuronal death was induced in transgenic rats expressing green-fluorescent protein under the tyrosine hydroxylase receptor, by stereotactic injection of 6HODA. 5μg of Maresin-1 was intranasally administered. Nuclear NFkB/p65 and β-catenin were assessed by immunohistochemistry and analyzed using Imaris software. **Results:** microglia were more abundant in the site of injection. Dopaminergic neurons were preserved by the intranasal administration of Maresin 1 showing no differences in neuronal numbers between the side of the injection and the contralateral control. β-catenin and NF-κB were decreased in SN of the animals treated with Maresin 1 in comparison with the ones treated with Saline. Phagocytosis of α-synuclein fibrils by astrocytes show that cytokines decreased their ability of clearance, however Maresin 1 augmented this process around 5 times. **Conclusions:** Altogether these data shows that "in vivo" Maresin 1 induces a change in Microglia and Astrocytes that favors the benign

phenotypes of both cells. These processes may be involved in the rescue of the dopaminergic neurons observed in the treated animals.

Poster #20

Dopaminergic Neurons Regulate Aging and Reproduction in Drosophila

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Dopamine neurons in the brain modulate cognitive functions and the physiology of peripheral tissues. Previous research has demonstrated that dopamine neurons regulate longevity and health span in flies. When microtubule dynamics were promoted in specific dopamine neurons in flies, a 50 percent extension of the lifespan was observed. The long-lived flies displayed an unusually extended reproductive span, a phenomenon reminiscent of the positive correlation between the reproductive span and lifespan of women. Although the correlation implies fundamental mechanisms for fertility regulation and health, the underlying biology is largely unknown. For example, it is not known how aging of the ovary proceeds from other tissues, what links fertility to longevity, whether reproductive status plays a primary role in determining overall health and aging, and how reciprocal interactions between the brain and the reproductive organs impact these processes. The co-extension of fertility and lifespan induced by dopamine neurons, as revealed by our previous studies in flies, provides a new animal model for dissecting reproduction-driven extensions of both health and lifespans and for unraveling the molecular and cellular mechanisms governing the complex interactions among the brain, fertility, health, and longevity. With this unique model, the neuronal and molecular basis of this complex system is beginning to be understood. Innervation of the subesophageal zone by dopamine neurons appears to be critical for lifespan extension. The subesophageal zone is the brain region that integrates sensory input and translates it into motor and neuroendocrine actions. More importantly, this region has also been shown to coordinate reproductive behaviors in female flies. Connecting neurons in the subesophageal zone innervate and regulate the corpora cardiaca, an endocrine gland. Production of adipokinetic hormone (AKH) in the corpora cardiaca, a functional analog of vertebrate glucagon, is upregulated in the dopamine neuron-inducing long-lived flies. The AKH receptor is expressed in the brain, fat bodies, and ovary and regulates energy homeostasis in flies. Upregulation of AKH production suggests that AKH signaling is a potential mediator of the fertility and lifespan extension that is dependent on dopamine neurons. Collectively, these results suggest that a brain-gonad axis engages specific dopaminergic circuits

and hormonal pathways that modulate reproduction and longevity. Future studies that dissect the dopaminergic circuits in the brain will help further understanding of the source of sensory inputs and the nature of information output. Analysis of ovary and other peripheral tissues will unravel the cellular responses and the executors of lifespan extension induced by dopamine neurons.

Poster #21

Identifying the Cognitive and Neural Mechanisms of Spatial Reasoning

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Spatial reasoning skills are important in science, technology, engineering, and mathematics disciplines. These skills can be improved with training. Better understanding the cognitive processes that are most impacted by training can help refine training protocols to optimize their effectiveness and generalizability. The **purpose** of this work is to determine the cognitive processes involved in mental rotation that are most sensitive to training and individual differences. **Methods:** In a completed and an ongoing study, participants complete a mental rotation task where they determine if two objects are rotated versions of the same object or mirror objects. Accuracy, response time, brain activity, and eye movements are recorded. In the completed study, functional magnetic resonance imaging data was collected pre- and post-training on the mental rotation task. In the ongoing study, electroencephalogram data is being recorded across a large cross-sectional sample and in a training experiment. **Results:** In the completed study, and consistent with previous work, accuracy decreased, and response time increases as the angle of disparity between the two objects increased. Furthermore, the number of saccades between objects decreased and saccade amplitude increased after training. Right motor cortex and right lateral occipital cortex activity were impacted by the type of training. **Conclusions:** The data suggest that training leads to encoding more complete representations of the objects and better mental manipulations of these representations. The ongoing study will look to confirm and extend these findings with electroencephalogram data in crosssectional and longitudinal training studies. Together these studies will help to reveal the cognitive mechanisms involved in mental rotation that are sensitive to variations in performance.

Cell Type Specific Signatures Of Social-Stress Escalated Alcohol Consumption In The Paraventricilar Thalamus

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Social stress is pervasive in humans, and its severity is associated with various neuropsychiatric conditions, including addiction. Social stress can lead to escalated alcohol consumption and increased risk of relapse to alcohol seeking in humans and animals. The biological underpinnings of this are not clear and must be elucidated to facilitate identification of therapeutic targets and inform therapeutic strategies. Using a system for activity-dependent genetic tagging and a mouse model for social defeat stress (SDS)-induced escalation of alcohol consumption, we examined the overlap between neurons activated by SDS and those activated by alcohol consumption in the same subjects. Using bigenic Fos-2A-Cre:Ai14 mice, we found that repeated SDS increased alcohol consumption in both male and female mice and led to robust neural activation in several brain regions compared to unstressed controls. Of these, the paraventricular thalamus (PVT) was particularly intriguing as it was also strongly activated by both SDS and alcohol exposure and there was a high degree of overlap (88%) between stress (expressing tdTomato) and alcohol activated (expressing cFos) cells. Chemogenetic inhibition of SDS-activated cells in the PVT attenuated stress-escalated alcohol consumption in both sexes. Single nuclei RNA sequencing (snRNASeq) of the PVT from male bigenic mice exposed to both stress and alcohol revealed five transcriptionally distinct neuronal subtypes within the PVT, PVT1-5. Of these, the highest number of stress and alcohol activated cells were found in PVT2. Differential gene expression (DEG) analysis revealed that majority of the DEGs were localized to cells activated by both stress and alcohol. Pathway and upstream regulatory element analysis of DEGs revealed that genes belonging to the transforming growth factor beta family were overrepresented suggesting a role for this pathway in stress and alcohol induced neuroadaptations within the PVT2 cell type. Future studies will examine the consequences of perturbing this pathway on social stress-escalated alcohol consumption. Funding: AA030652-01 and LSUHSC startup funds

Untargeted Lipidomics Reveals Elovanoid-Mediated Suppression of Oxidized Phospholipids in Ischemic Stroke Model

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Oxidative damage to protein, DNA, and lipids are all involved in the pathogenesis of neurodegenerative diseases. Cellular membrane lipids containing polyunsaturated fatty acids are susceptible to attack, lipid peroxidation, by enhanced reactive oxygen species (ROS). Elovanoids (ELVs) are bioactive lipid mediators derived from omega-3 very long chain polyunsaturated fatty acids (VLC-PUFAs) and have shown neuroprotective signaling. **Purpose:** The goal of this study was to test if ELVs could counteract lipid peroxidation in rat brains, generated by ischemia-reperfusion injuries, by measuring oxidized phospholipid profiles using untargeted lipidomics. **Methods:** Male Sprague-Dawley rats were exposed to 2 hours of middle cerebral artery occlusion (MCAo). ELV-N34 was administered intranasally at 1, 24, and 48 hours after reperfusion. Rats were sacrificed on day 3, and brains were removed and sectioned. Folch extraction was used to isolate lipids. Untargeted lipidomics were performed on a Waters™ Xevo G2-XS QToF (quadrupole time-of-flight) system with MSe mode. MS/MS spectra of oxidized phospholipids were processed and searched against a spectral library in MS-DIAL (v5.1). **Results:** After MS spectra was processed, approximately 2000 features were identified and matched to references in the spectral library. Of nearly 100 oxidized phospholipids, OxPE (oxidized phosphatidylethanolamine) was the highest, followed by OxFA (oxidized fatty acid), and OxPC (oxidized phosphatidycholine). Higher levels of OxPLs were found in the cortex compared to subcortex. After treatment with ELV-N34, cortex showed significant decrease in OxPE, and subcortex showed slight decrease in OxPC. **Conclusions:** ELV-N34 elicits downregulation of OxPL formation concomitant with neuroprotection when uncompensated oxidative stress evolves. This could be resultant from ELV induced changes in TXNRD1, a redox homeostasis regulating protein.

Inhibition of Lipid Peroxidation by Elovanoid Precursor: A Comprehensive Untargeted Lipidomic Approach

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Purpose: Amyloid-beta peptide accumulates as in senile plaques in Alzheimer's disease brain. Same conditions can be observed in patients with Age-related macular degeneration (AMD). In addition, increased lipid peroxidation and insufficient levels of antioxidants will lead to uncompensated oxidative stress (UOS) environment in both cases. Oxidized phospholipids (OxPLs) species can cause detrimental perturbations to membranes of photoreceptor cells (PRC) and to the retinal pigment epithelial cell (RPEC) altering their structure and function. Elovanoids (ELVs), are a distinctive class of lipid mediators essential for maintaining the integrity of photoreceptor cells. They are oxygenated derivatives of very long-chain polyunsaturated fatty acids (VLC-PUFAs) C32:6 n3 and C34:6 n3. Due to high metabolic demands, RPE cells are under constant oxidative stress. Here, we present a study on ELV biosynthesis and the enhanced cell survival under uncompensated oxidative stress conditions in RPEC. We have identified OxPL species in RPEC under UOS conditions via untargeted lipidomic approach using liquid chromatography-tandem mass spectrometry (LC-MS/MS). **Methods:** RPEC were exposed to UOS, +/- ELV-N34 precursor (FA 34:6). Extracted lipids were analyzed by LC-MS/MS. Automatic data-processing, including peak assignments and deconvolution of MS/MS data were carried out using MS-DIAL software. Final data were matched with a reference library of known oxidized lipid compounds. **Results:** Under UOS conditions, high levels of OxPLs, were observed, with the majority being oxidized phosphatidylethanolamine followed by oxidized phosphatidylcholine. Oxidized lipid profiles of RPEC treated with ELV-N34 precursor showed decreased levels compared to UOS samples. **Conclusion:** Our data demonstrate the protective role of ELV – N34 precursor in preventing oxidation of phospholipid species. Therefore, ELV would likely to involve in regulatory functions of lipid peroxidation that may include targeting ferroptosis.

ELV-N34 or RvD6-isomer counteracts damaging astrocyte phenotypes protecting the brain from Omicron BA.5-mediated long COVID

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Neurodegenerative diseases induce astrocyte phenotypes that trigger inflammation and cell damage. This cell induction also takes place in post-acute neurological syndrome from SARS-CoV-2 infection. The **purpose** of this study is to determine the effects of the molecules secreted by human nasal epithelial cells infected with SARS-CoV-2 Omicron BA.5 variant on human astrocytes and whether elovanoid 34 (ELV34) and resolvin D6 (RvD6) can counteract this activity. **Methods:** Human nasal epithelial cells from 50- year-old healthy donors were infected with Omicron BA.5 for one hour. The cells were treated with 500nM ELV-34, RVD6 or vehicle before and after the infection. The exudate (conditioned media) was used to induce human astrocytes in culture. Two of the identified factors that changed the phenotype of the astrocytes, were used to treat intranasally male and female mice, to mimic the virus nasal infection. **Results:** we found that the secretome from Omicron BA.5 infected human nasal epithelial or human lung cells induced the activation of human astrocytes to a reactive pro-inflammatory phenotype as defined by nuclear translocation of NF-kB/p65. Remarkably, the secretome from these cells incubated with Elovanoid (ELV)- N34 or Resolvin D6 (RvD6)-isomer (500nM) did not trigger the formation of reactive astrocytes. One of the factors involved is CXCL1, secreted by Omicron BA.5-infected nasal epithelial cells. So, when CXCL1 was administered intranasally to mice along with Interferon type I, the infiltration of fluorescein indicated a permeabilization of the neurovascular unit. **Conclusions:** Astrocytes are close to this barrier and contribute to restricting the access of damaging molecules to the brain parenchyma. Together, these results point to a specific way of entry of chemokines and cytokines as part of the secretome from infected cells that may play a role in long COVID brain sequelae.

Neuroinflammation and Neurodegeneration in Adipor1-/- and Mfrprd6 Mice Linked to Fatty Acid Elongases 2 and 4 Downregulation

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Purpose: Docosahexaenoic acid (DHA), an omega-3 fatty acid abundantly present in the central nervous system and the retina, plays a pivotal role in preserving vision by maintaining the integrity of photoreceptor discs' morphology. Notably, its multifaceted contributions include antioxidative, anti-inflammatory, and anti-apoptotic properties through the generation of lipid mediators. Our investigation focused on mutant Adipor1 and Mfrp mice, revealing a selective reduction in DHA and very long-chain polyunsaturated fatty acids (VLC-PUFAs; ≥ 28 carbons), primarily formed by elongases ELOVL2 and ELOVL4 (Elongation of Very Long-chain fatty acids). These mutant mice displayed compromised retinal function and a progressive loss of photoreceptor cells. **Methods:** To decipher the underlying mechanism driving inflammation in these models of retinal degeneration, we harvested retinas and RPE-eyecups from Adipor1$-/-$, Mfrprd6 , and C57BL/6J (wild-type; WT) male and female mice. Utilizing capillary Jess (Protein Simple) Western blot, we assessed the protein expressions of Elovl2 and Elovl4. Additionally, we conducted the FAM-FLICA Caspase-1 Assay on eye sections to ascertain caspase-1 activation and employed immunohistochemistry with Iba-1 antibody to investigate microglia invasion in the mutant mice. **Results:** Elovl2 and Elovl4 proteins were notably reduced in the mutant mice, indicating a potential link to the observed retinal abnormalities. Further analysis using FAM-FLICA demonstrated a significant increase in caspase 1 activity by 47% and 189% in Adipor1$-/-$ and Mfrprd6 mice, respectively. Immunostaining revealed a higher number of Iba-1 positive cells in the retinas of both mutant groups, indicative of increased microglia invasion. **Conclusions:** These results suggest that Adipor1$-/-$ and Mfrprd6 mice are susceptible to uncontrolled neuroinflammation, leading to a cascade of events including microglia invasion and caspase 1-dependent retina damage. This implies a pyroptotic immune response and highlights the potential targeting of the inflammasome pathway as a therapeutic strategy for addressing retinal degeneration in these mutant models.

Cell heterogeneity in limbal/corneal cells relevant to nerve regeneration defined using Single and Spatial Cell transcriptomics

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We use the cornea as a model to study interplay of cell-type specific transcriptomic regulation, critical for nerve regeneration in the central and peripheral nervous system. The **purpose** of this study was to use single-RNA-sequencing (snRNASeq) and spatial transcriptomics interrogate cell populations and gene expression in central cornea/limbus. **Methods:** Nuclei isolated from cornea/limbus of 3-month, male C57BL/6 wild-type (WT) mice (N=6) were processed by 10xGenomics pipeline, Cellranger. Central corneas were damaged with 2mm trephine, epithelium and anterior stroma removed with corneal rust ring remover (Algerbrush II). Two days post-injury, corneas were excised, formalin-fixed paraffin-embedded, and 5μm sections prepared for Visium CytAssist mediated probe hybridization, library construction, sequencing, data analysis using Spaceranger, data visualization and cell cluster annotation using Loupe Browser. Cell populations were distinguished by t-distributed stochastic neighbor embedding (t-SNE). RNAscope® assay was used to validate two genes, ALDH3A1 and SPARC. **Results:** Unbiased cell clustering recovered 25039 corneal and 24183 limbal single nuclei, dimensionality reduction detected specific clusters: 8 (cornea), 5 (limbus); 5 (WT normal cornea) and 1 (damaged cornea) based on unique molecular signatures. Corneal clusters included transient amplifying and epithelial cells: corneal, basal, superficial, wing, stromal keratocytes, lymphocytes, and dendritic cells. Limbal clusters included basal and wing, epithelial, limbal progenitor, limbal stem cells and lymphatic endothelium. **Conclusions:** Transcription profiles differ in central cornea and ocular surface epithelium with varying expression profiles. Gene expression of ALDH3A1 and SPARC decreased in central cornea after injury. snRNASeq identifies unique cell clusters spatially in cornea/limbus activated by injury that enable delineation of gene expression critical for repair validated using RNAscope® assay. The direct impact of these gene clusters on nerve regeneration is under study.

Analysis of Elovanoids Mechanism of Protection in Ischemic Stroke Using a Single-cell Multiome Approach

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Ischemic stroke results in severe loss of neurological functions, and a large proportion of survivors display the onset of cognitive impairments. Administration of a novel class of very long-chain polyunsaturated fatty acids (VLC-PUFAs) derivatives termed elovanoids (ELV34) or its VLC-PUFA precursor (FA34) are protective against both in vitro and in vivo models of uncompensated oxidative stress and ischemic stress. We found that ELV34 or FA34 delivery attenuates sensorimotor deficits after ischemic stroke. Furthermore, we uncovered that ELV and its precursors protect against ischemic damage by altering the phenotype of glial cells and modulating the expression of pro/anti-inflammatory and neuroprotective genes. The **purpose** of this study was to investigate the mechanisms of protection by ELV34 and FA34 after experimental ischemic stroke. **Methods:** Adult Sprague-Dawley rats underwent 2 hours of middle cerebral artery occlusion (MCAo) via intraluminal suture. Rats received vehicle, ELV34, or FA34 delivered intranasally 1 hour, 1 day, and 2 days after 2 hours of MCAo. Brains were harvested on day 3 from the ipsilesional cortex (penumbra region) and subcortex. Nuclei were isolated and processed according to 10X Genomics Single Cell Multiome protocol. **Results:** ELV34 or FA34 treatment reduced neurological deficits after MCAo. Joint RNA + ATAC single-cell analysis revealed an increase in microglia and leukocyte abundance as well as a loss of neuronal populations after MCAo. ELV34 or FA34 reduced the loss of neuronal populations and restored the pool of homeostatic microglia after stroke. Furthermore, differential gene expression analysis revealed that ELV or its precursor regulated pathways related to phagocytic clearance, inflammatory signaling, and cellular trafficking to promote neuroregeneration in microglia, astrocytes, neurons, and other neural cells. **Conclusions:** ELV/precursors may exert their bioactivity by modulating conversion to neuroprotective cell phenotypes in neurodegenerative diseases such as stroke.

A multiomic analysis reveals robust neuroprotection conferred by Elovanoid 34:6 and precursor Free Fatty Acid 34:6 following experimental traumatic brain injury

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One-third of the approximately 70 million people suffering from traumatic brain injury (TBI) have an increased risk for developing chronic cognitive impairments. We studied neuroprotection by Elovanoid-34:6 (ELV-N34) and its precursor free-fatty-acid-34:6 (FFA34:6) following TBI in male Sprague-Dawley rats using fluid percussion injury (FPI) or controlled cortical impact (CCI) models. At 1 and 24 hours post-surgery, rats were intranasally administered saline, ELV-N34, or FFA34:6 (only in the CCI model). Rats underwent composite neurological testing to assess sensorimotor integration. On day 14, FPI animals were sacrificed, and MRI and diffuse tensor imaging (DTI) were performed to assess lesion size and white matter connectivity. On day 3, CCI animals were used for multi-omic analysis using 10x Chromium, Illumina Sequencing, and Seurat v4.0.1. Total neurological scores for animals administered ELV-N34 and FFA34:6 were lower than controls, and scores for FFA34:6 treated rats were lower than those of ELV34:6 treated rats ($p < 0.05$). MRI and DTI showed smaller lesions and preserved white matter connectivity in the ELV34:6 group. Single cell analysis with ELV-N34 treatment revealed downregulation of Spp1, Fos, and Gfap genes and upregulation of Trem2 and Pld5 genes. FFA34:6 treatment revealed downregulation of inflammatory genes Spp1, Ccl2, and Vim. We demonstrated that ELV-N34 and FFA34:6 convey behavioral, structural, and genetic neuroprotective bioactivity in experimental TBI.

Spatially resolved transcriptomics uncover differential gene expression mechanisms in age-related macular degeneration

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We study AMD because it accumulates debris beneath the retinal pigment epithelium (RPE), forming so-called "Drusen" analogous to senile plaques of Alzheimer's, including the accumulation of amyloid-beta peptide. We found a decrease in components of the pathway leading to the formation of the pro-homeostatic mediators, the elovanoids (ELVs), specifically in the rod photoreceptors of retinas from donors with age-related macular degeneration (AMD). Retinas were formalin-fixed paraffin-embedded (FFPE), and 5µm microtome sectioning, H&E staining, 10X Genomics Visium CytAssist, and Illumina Sequencing were followed by analysis with Spaceranger and Seurat bioinformatics. By mapping the transcriptome of the human retina, we found gene expression differences in the normal retinas compared to the AMD retinas, both in the rod and cone areas. Transferrin (TF), APOE, and ABCA4 genes were decreased in AMD. Our data has revealed gene clusters and transcriptomic signatures in regulatory pathways of cell survival in rods and cones in AMD.

Elovanoids are Neural Resiliency Epigenomic Regulators Targeting Histone Modifications, DNA Methylation, Tau Phosphorylation, Telomere Integrity, Senescence Programming, and Dendrite Integrity

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Cellular identity, developmental reorganization, genomic structure modulation, and susceptibility to neurodegenerative diseases involve epigenomic regulation engaging multiple signaling interplay. The **purpose** of this study is to demonstrate that elovanoids (ELVs), lipid mediators derived from very-long-chain polyunsaturated fatty acids (VLC-PUFAs, n-3, C >28), and their precursors in human neurons/astrocytes in culture overcome the damage triggered by oligomeric amyloid-B (OAβ), erastin (ferroptosis-dependent cell death), or other insults like uncompensated oxidative stress (UOS), NMDA mediated cellular excitotoxicity, or oxygen-glucose deprivation (OGD), that target epigenomic signaling. **Methods:** Primary human neuronal-glial (HNG) cells

cultured for 21 days and then stressed with oligomeric amyloid beta OAβ (10μM) or erastin (10μM) to induce ferroptosis, 30 min later, lipid mediators added (200 nM) and incubated for 24 hours. Genomic DNA is extracted for measurement of different parameters to determine the relative methylation states of samples treated with vehicle (Control), OAβ/Erastin, and ELVs or Neuroprotectin D1 (NPD1). DNA methylation (5-mC), 5-mC hydroxylase (TET), DNA methyltransferase, and DNA demethylase activity/inhibition, and histone modifications at lysine 9 of histone H3 (H3-K9) measured using sandwich ELISA. RNA extracted, and transcripts analyzed by qPCR for telomerase integrity (TERT transcription) and telomere length. **Results:** We uncover that ELVs protect dendrites, counteract damage targeting histones H3K9 and H3K27 methylation and acetylation. ELVs restore tau hyperphosphorylation (pThr181, pThr217, pThr231, and pSer202/pThr205 (AT8)), and counteract senescence associated secretory phenotype (SASP), and senescence gene programming (p16INK4a, p27KIP, p21CIP1, and p53). ELVS also restores DNA methylation (DNAm) modifying enzymes: TET (DNA hydroxymethylase), DNA methyltransferase, DNA demethylase, and DNA methylation (5mC) phenotype. Moreover, ELVs revert OAβ-triggered telomere length (TL) attrition as well as upregulation of telomerase reverse transcriptase (TERT) expression fostering dendrite protection and neuronal survival. **Conclusions:** Our results indicate that ELVs modulate epigenomic resiliency by pleiotropic interrelated signaling and may act as molecular guardians and neural resiliency epigenomic regulators.

Poster #32

The Influence of Native Language on Motion Event Encoding: An ERP Study

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The **purpose** of this study was to investigate the extent to which English native language influences visual attention to, and implicit processing of, motion events manipulating path and manner. Linguistic relativity is the idea that native language influences cognition and perception. According to linguistic relativity, speakers of manner-on-verb languages (e.g., English) and path-on-verb languages (e.g., Spanish) differentially attend to motion events based on their manner and path, respectively. However, little research has addressed how linguistic differences related to path and manner influence perception. **Methods:** 34 monolingual English speakers and 35 Spanish-English bilinguals viewed motion events followed by sentences describing the preceding video presented one word at a time, while their EEG was measured with a 64

electrode Brainvision cap. Trials were either congruent (manner and path of video matched sentence), manner incongruent (manner of video did not match manner of sentence), path incongruent (path of video did not match path of sentence), or completely incongruent (neither manner nor path of the video matched sentence). Participants' task was to press a button indicating whether or not each sentence was congruent to the preceding video. **Results:** We found a main effect of group that was driven by better overall performance in accurately categorizing motion events for monolinguals than bilinguals. There was also a main effect of condition driven by all participants being significantly less accurate when identifying path and manner incongruencies than congruent events. We identified significant clusters of activation at an alpha of 0.05 across groups during processing of path and manner independently. Comparing manner congruency across groups in the N400 time window (350-550 msec) revealed a significant interaction over left-central electrodes. This interaction was driven by a larger N400 effect between congruent and incongruent trials for bilingual compared to monolingual adults. These findings suggest bilinguals demonstrated greater surprisal on trials involving manner incongruencies compared to monolinguals. Comparing path congruency across groups in the N400 time window (350-550 msec) revealed a significant main effect of group at widespread left-central electrodes driven by a larger N400 effect between congruent and incongruent trials for monolingual compared to bilingual adults, suggesting path incongruencies were more semantically taxing for monolinguals than bilinguals. **Conclusions:** Taken together, our findings indicate native language influences both explicit and implicit perception of motion events.

Poster #33

Identification of Possible Early Gene Markers of Alzheimer's Disease By 2-Month APP Knock-In Mouse Model in Defined Cell Clusters

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Alzheimer's Disease (AD) occurrence is expected to triple by the year 2060. Due to a lack of the understanding of causative mechanisms we are devoid of effective therapies. We have explored the hippocampus and cortex of the 2-month-old APPNL-G-F (APPKI) using 10x Genomics Chromium Single Cell Multiome Assay for Transposase Accessible Chromatin (ATAC) + Gene Expression (GEX) to define at the transcriptome level, cell specific alterations in immune, lipid, metabolic and neurodevelopment related gene clusters. Additionally, we have assessed DNA-methylation to uncover related CpG islands and gene promoters. The APPKI is an AD model with three additive/synergistic mutations that show typical Amyloid-

β (Aβ) pathology and neuroinflammation. The hippocampus and cortex of the right hemisphere were flash-frozen in liquid nitrogen. Nuclei isolation was done by the Chromium Nuclei isolation kit and data generation following 10x Single Cell Muiltiome workflow and analysis performed using R-based packages: Seurat and Signac. We found a) Inflammatory gene expression changes in C1qa/b/c, Cox6c, Cox7c, and Cox8a; b) Chromatin accessibility modifications in DNA corresponding with Nr3c1, Jund, Spib, Meox1, and Lhx5; c) Prominent methylation in regions correlated with Necdin: and d) epigenomic landscape, senescence gene programming, autophagy, extracellular matrix and inflammaging changing. Overall, the APP KI model allowed us to identify cell specific early dysfunctional gene clusters.

Poster #34

Enhanced Neurobehavioral Rehabilitation and Increased Homeostatic Gene Expression Following Experimental Ischemic Stroke with Combined NPD1 and RvD1 Therapy

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Stroke ranks as the second leading global cause of death with many survivors experiencing severe cognitive impairments. Current treatments, such as tissue plasminogen activator (tPA) and thrombectomy, lack efficacy for the majority of stroke patients. This study investigates potential mechanisms and efficacy of combined Neuroprotectin D1 (NPD1) and Resolvin D1 (RvD1) therapy in ischemic stroke. We utilized an ischemic stroke model to explore experimental neuroprotective strategies that could influence long-term outcomes, including the onset of dementia. Adult Sprague-Dawley rats underwent transient middle cerebral artery occlusion (MCAo) via a poly-L-lysine coated intraluminal suture inserted into the common carotid artery. NPD1 (222 mg/kg) + RvD1 (222 mg/kg) was administered intravenously through the femoral vein one hour after two-hour MCAo. Neurobehavioral assessments encompassed visual, tactile, proprioceptive, and postural reflexes, as well as beam balance and rotarod tests. Pro- and anti-inflammatory gene expression were analyzed using RNA in-situ hybridization. NPD1 + RvD1 exhibited protective effects on composite neurologic scores for up to four weeks post-MCAo and demonstrated enhanced performance in rotarod and beam balance tests during the initial two weeks. Notable upregulation of Lcn2, Amigo2, and Thbs1 gene expression, associated with neuroprotective astrocyte and microglia phenotypes, was observed with NPD1 + RvD1. Moreover, NPD1 + RvD1 induced the activation of genes involved in anti-inflammatory responses, promotion of angiogenesis, and maintenance of neuroglial cell homeostasis. These results suggest that NPD1 + RvD1 may operate through complementary signaling pathways to mitigate post-stroke adverse effects.

From Stem cell to GABAergic Vs Dopaminergic differentiation

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Neurodegenerative diseases, including dementia, Parkinson's, and Alzheimer's, impose a significant healthcare burden due to the lack of effective treatments. Understanding their molecular pathology is crucial for formulating potential therapies. Stem cells, with their capacity to differentiate into specific cell types, hold promise for generating neurons and glial cells. Embryonic stem cells (ESCs) can differentiate into various neuronal types, including GABAergic neurons crucial for maintaining brain excitatory-inhibitory balance. However, clinical use of GABAergic-induced neurons faces challenges such as bypassing the blood-brain barrier without eliciting allogeneic responses. Though Neural Stem Cell (NSC) transplantation shows promise, it carries risks such as tumor formation due to heterogeneous neuronal populations. Encapsulated mouse ESCs treated with all-trans-retinoid acid (RA) efficiently generated GABAergic neurons, yet the underlying molecular mechanisms remain poorly understood. To address this gap, we conducted transcriptome analysis comparing encapsulated ESCs to standard 3D cell culture (embryoid bodies) after RA treatment for two or four days. Our findings reveal differential gene expression profiles between encapsulated cells and embryoid bodies, particularly after four days of RA treatment. Genes associated with excitatory pyramidal neurons, like Nxf7, showed differential expression at four days in embryoid bodies compared to encapsulated cells. Conversely, genes involved in inhibitory neuron development, such as Slit1 and Tnip1, were upregulated in encapsulated cells after four days of RA treatment. This study enhances our understanding of ESC differentiation into specific neuronal subtypes, informing potential therapeutic interventions for neurodegenerative diseases. Further research could lead to targeted approaches for generating homogeneous neuronal populations and improving treatment efficacy.

Impact of Sex and Diet on Gut Microbiota and Cognitive Function in Sprague-Dawley

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The objective of this research project is to identify baseline sex-dependent differences in gut microbial diversity and composition as well as how they influence sex differences seen in the cognitive function of Sprague-Dawley rats. The central hypothesis for this project is that there are sex differences in both gut microbiota and cognitive performance. The first aim of this project is to determine the extent to which sex hormones impact gut microbial diversity and cognitive behavior in female and male rats. In addition, this project aims to elucidate how short-term diet intervention of either the Mediterranean diet or Western diet may further influence the aforementioned sex differences. Through these observations, the project sheds light on the sex-specific mechanisms of the gut-brain axis, providing greater understanding for the sex-biases seen in mild cognitive impairment, Alzheimer's disease, and other related dementias while also investigating the potential for diet modulation as an intervention for cognitive decline.