Comprehensive Neuroscience Center

2021 Online Retreat

Zoom link (only to be used by each registered attendee; please do not share)

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CNC Online Retreat
Friday May 14, 2021

8:00 – 8:30am Welcome and State of the Center – Dr. Adrienne Lahti, CNC Director
"What can the CNC do for you?"

Session I: Substance Use Disorders Pillar

8:30 – 8:35am Session introduction, Pillar leaders: Drs. Jeremy Day & Aurelio Galli
8:35 – 8:47am **Sam Mabry** (GBS Neuroscience, Galli lab), *Microbial regulation of psychostimulant abuse*
8:47 – 9:00am **Jennifer Tuscher, PhD** (Neurobiology, Day lab), *Single-nucleus RNA-sequencing reveals cell-type specific transcriptional responses to cocaine and dopamine*

Session I feedback link: https://uab.co1.qualtrics.com/jfe/form/SV_72Fhuhzul8sGNiS

Session II: Circadian Rhythm and Sleep Pillar

9:00 – 9:05am Session introduction, Pillar leaders: Drs. Amy Amara, Karen Gamble, Patricia Patrician, & Courtney Peterson
9:05 – 9:17am **Lacy Goode** (GBS Neuroscience, Gamble lab), *Diurnal variation of inhibitory synaptic transmission in hippocampal CA1*
9:17 – 9:30am **Adeel Memon, MD** (Neuroengineering, McMahon and Amara labs), *Effects of exercise on frontal delta oscillation during slow-wave sleep*

Session II feedback link: https://uab.co1.qualtrics.com/jfe/form/SV_9G3DrzS6bndGH42

Session III: Epilepsy and Related Disorders Pillar

9:30 – 9:35am Session introduction, Pillar leaders: Drs. Farah Lubin & Larry Ver Hoef
9:35 – 9:47am **Ayushe Sharma** (Behavioral Neuroscience, Szaflarski lab), *Everyone has a fire inside, but some have one in their brains*
9:47 – 10:00am **Anandh Ramaniharan, PhD** (Neurology, Ver Hoef lab), *Next generation quantification of hippocampal dentation*

Session III feedback link: https://uab.co1.qualtrics.com/jfe/form/SV_8cyXNLIhfZRIp8y

10:00 – 10:10am **BREAK**

Session IV: Glial Biology and Pathology Pillar

10:10 – 10:15am Session introduction, Pillar leaders: Drs. Michelle Gray & Anita Hjelmeland
10:15 – 10:27am **Deepayan Kar** (Vision Science, Dr. Curcio lab) *Connectomics of the human retina: Morphology and abundance of two distinct Müller glia types identified in the adult fovea*
10:27 – 10:39am **Ken Matoba, PhD** (Psychiatry & Behavioral Neurobiology, Kano lab) *Thalamic microglia activation, cognitive decline, and aging*

Session IV feedback link: https://uab.co1.qualtrics.com/jfe/form/SV_ehcP2vSLd2pyfUW

Session V: Mental Health and Disorders Pillar

10:40 – 10:45am Session introduction, Pillar leaders: Drs. Yogesh Dwivedi & Nina Kraguljac

10:45 – 10:57am **Lindsay Stager** (Medical/Clinical Psychology, Fobian lab) *Sleep as a novel moderator between BMI and working memory*

10:57 – 11:10am **Kongpyung Kim, PhD** (Psychiatry Behavioral Neurobiology, Niwa lab) *A novel cortico- cortical pathway underlying social isolation-induced social behavioral deficits in the postpartum period*

Session V feedback link: https://uab.co1.qualtrics.com/jfe/form/SV_cRVyKVIxe8Gv8lE

Session VI: Neuroimaging Pillar

11:10 – 11:15am Session introduction, Pillar leaders: Drs. Junghee Lee & Kristina Visscher

11:15 – 11:27am **Sara Sims** (Medical/Clinical Psychology, Visscher lab), *Functional network segregation is associated with executive functioning in the healthy oldest old: findings from the McKnight Brain Aging Registry*

11:27 – 11:40am **Juliann Purcell** (Medical/Clinical Psychology, Knight/Mrug labs), *Stress-elicited neural activity in young adults varies with childhood sexual abuse*

2020 CNC Pilot Awardees

11:40 – 12:05pm **Dr. Andrew Hardaway** (Psychiatry & Behavioral Neurobiology, SOM), *Process of illumination: real-time dopamine signaling measurement using a genetically-encoded biosensor*

12:05 – 1:05pm **LUNCH BREAK and Pillar breakout rooms**

1:05 – 1:25pm Dr. Ashley Harms (Neurology, SOM), *The role of T cells in alpha-synuclein models of Parkinson disease*

Session VI and CNC Pilot awardees feedback link:
https://uab.co1.qualtrics.com/jfe/form/SV_b3Cvmw9I4RDduh8

1:25 – 2:00pm Award announcements and closing remarks

ABSTRACTS

Microbial Regulation of Psychostimulant Abuse

Mabry SJ, Cao X, Carter AM, Elam A, Patel S, Zhu Y, Wu H, Galli A

Overshadowed by the opioid epidemic, the resurgence of amphetamines (AMPHs) and its derivatives (e.g. methamphetamine) in the United States has gone largely unnoticed. AMPHs are highly effective psychostimulants commonly used for the treatment of neuropsychiatric disorders such as attention deficit hyperactivity disorder. AMPHs lead to an increase in extracellular dopamine (DA) levels through a reversal of the DA transporter (DAT) function, which causes non-vesicular DA release (DA efflux). Recent evidence suggest a potential role for imbalance in the gut microbiome (dysbiosis) in the pathogenesis of substance use disorders. Microbial products such as short-chain fatty acids (SCFAs) are suspected to play a role in this process. In particular, the SCFA butyrate is known to cross the blood brain barrier and have effects on both neurons and glial cells. *Fusobacterium nucleatum* (*F. nucleatum*) secretes butyrate. *F. nucleatum* is an anaerobic filamentous gram-negative bacterial species from the Fusobacterium genus. Importantly, AMPH abuse increases *F. nucleatum* growth in both rodents and humans, pointing to a possible role of *F. nucleatum* in AMPH actions. We demonstrate that, in gnotobiotic *Drosophila*, colonizing of the intestinal tract with *F. nucleatum* leads to an enhanced (DA) efflux in response to AMPH, as measured by both amperometry and locomotor behavior. Furthermore, butyrate, which is an HDAC inhibitor, parallels this effect in gnotobiotic flies. Trichostatin A (TSA), another inhibitor of HDAC, as well as genetic knock down of HDAC1 via RNAi, both promote the same enhanced DA efflux and locomotion as observed in flies cultured with *F. nucleatum*. The observed behavioral effects are specific to HDAC1, as RNAi knockdown of all other HDAC isoforms have no effect on AMPH responses. We hypothesize that *F. nucleatum*-driven HDAC inhibition increases acetylation of the DAT promotor therefore augmenting DAT expression. This ultimately leads to an increase in DA efflux in response to AMPH.

Single-nucleus RNA-sequencing reveals cell-type specific transcriptional responses to cocaine and dopamine

Jennifer J. Tuscher, Robert A. Phillips III, Corey G. Duke, Morgan E. Zipperly, Lara Ianov, & Jeremy J. Day

Substance use disorders remain a global health crisis, with overdose rates of psychostimulants continuing to rise in many developed countries. A shared feature of drugs of abuse is their ability to elevate dopamine levels in brain regions that govern reward learning and response, such as the nucleus accumbens (NAc). Although molecular changes in response to cocaine have been studied in this brain region for decades, much remains unclear about which transcriptional changes initiated by drug experience promote the long-lasting synaptic and behavioral adaptations that underlie the addicted state. This is in part due to the cellular heterogeneity of the NAc, which contains multiple neuronal and non-neuronal cell types. Moreover, multiple neurotransmitter systems converge on the NAc, each of which can exert transcriptional control in response to drugs of abuse. In order to dissect cocaine and dopamine-induced transcriptional changes, we first performed single-nucleus RNA-sequencing on 15,631 nuclei from male and female rats after acute cocaine exposure to generate a molecular atlas of the NAc. This approach revealed 16 transcriptionally distinct cell subtypes in the NAc, and identified population-specific responses to cocaine. We next utilized a well-characterized striatal neuron culture system to further define dopamine-induced transcriptional responses. We identified an overlapping core set of immediate early genes that are upregulated following cocaine experience *in vivo* and dopamine receptor activation *in vitro*. These findings provide new insights into how cellular diversity contributes to transcriptional responses to cocaine, and suggest the importance of population-specific gene targets for therapeutic intervention in substance use disorders.

Diurnal variation of inhibitory synaptic transmission in area CA1 of the hippocampus

Lacy K. Goode, Allison Fusilier, Karen Gamble. Department of Psychiatry and Behavioral Neurobiology

The hippocampus is heavily involved in learning and memory. Although there is a large body of evidence indicating that the processes of learning and storing memories are regulated by time of day, there is little known regarding the impacts of time of day on hippocampal neuronal physiology. The inhibitory interneurons of area CA1 provide GABAergic inhibition onto the principal pyramidal cells and thus play a key role in regulating hippocampal output and function. To determine whether this GABAergic inhibition varies across time of day, spontaneous inhibitory post-synaptic currents (sIPSCs) were recorded from CA1 pyramidal cells using whole-cell voltage clamp during the day and night. sIPSC event amplitude and inter-event interval were both greater during the day, indicating overall greater inhibition during the day compared to night. Next, to investigate time of day variation of interneuron physiology, the spontaneous action potential firing rate of parvalbumin-expressing (PV) interneurons was examined during the day and night. Action potential firing rate was higher during the day compared to night, in line with previous findings of increased day-time inhibition. To determine whether the circadian molecular clock, a transcriptional/translational feedback loop of core clock genes, is necessary for the observed day-night differences, we generated a transgenic mouse model in which *bmal1*, a core clock gene, is knocked out of PV interneurons. Preliminary sIPSC recordings from CA1 pyramidal cells show that the increased day-time inhibition is reduced with this molecular clock knock out in this inhibitory population. Future studies aim to further characterize the impact of time of day and the circadian molecular clock on both intrinsic and synaptic physiology of different neuronal populations in the hippocampus. Given that many neurological disorders impacting the hippocampus also display circadian variation (e.g., Alzheimer's disease and epilepsy), understanding how hippocampal physiology is impacted by time of day can provide insight into the development of therapeutics targeting circadian disruption and inform the appropriate timing of existing treatments.

Effects of exercise on frontal delta oscillation during slow-wave sleep.

Adeel A. Memon, MD, Kimberly H. Wood, PhD, Allen Joop, MS, Raima Memon, MD, Jennifer Pilkington, Corina Catiul, MD, Marcas Bamman, PhD, Svjetlana Miocinovic, MD, PhD, Amy W. Amara, MD, PhD

Objective: This novel study tests the hypothesis that 16 weeks of high-intensity exercise rehabilitation combining resistance training plus body-weight interval training, compared with a sleep hygiene control, will improve the slow-wave sleep activity (SWA) during non-rapid eye movement stage 3 (N3) sleep in patients with Parkinson's disease (PD).

Background: SWA (<4 Hz) during N3 has been linked with age-related neural plasticity and PD cognition (1). Physical exercise has become the standard of care as a non-pharmacological intervention for improving motor symptoms of PD (2) and we have previously shown that exercise increases N3 in PD (3). However, it remains to be determined if exercise enhances SWA during N3 sleep.

Methods: We conducted a quantitative post hoc analysis evaluating absolute delta spectral power on 55 patients with PD. Patients were randomized to exercise (supervised three times a week for 16 weeks; n=27) or sleep hygiene, no exercise control (in-person discussion and monthly phone calls; n=28). Participants underwent polysomnography (PSG) at baseline and post-intervention. PSG included EEG, from which we analyzed delta frequency (1-4 Hz) spectral power in frontal leads (F3 or F4) in artifact-free 30-second epochs using the fast Fourier transformation (Matlab pwelch function).

Results: Baseline demographics showed no significant group differences in age, disease duration, levodopa-equivalent dose (LED), or dopamine agonist LED. Individual group level descriptive statistics showed mean+/-SD frontal absolute delta power during N3 in exercise group 81.8+/-61.2 (pre-intervention) and 102.9+/-62.9 (post-intervention). In sleep hygiene group it was 73.0 +/- 47.4 (pre-intervention) and 58.2 +/- 49.3 (post-intervention). Overall, the exercise group showed significant improvement in sex-adjusted absolute N3 delta power compared with the sleep hygiene group (group x time interaction: $F = 4.07$, $P=0.0493$).

Conclusions: High-intensity exercise rehabilitation increases absolute N3 delta power in PD. Because SWA is important for cognition in PD, our findings demonstrate an essential step in identifying exercise as an effective non-pharmacological treatment. Future research should evaluate the beneficial effects of exercise on other quantitative objective sleep measures to elucidate mechanisms underlying the beneficial effects of exercise on sleep in PD.

Everyone has a Fire Inside, but Some Have One in Their Brains.
Ayushe A. Sharma, Jerzy P. Szaflarski

There is an association between epilepsy, seizure intractability, and neuroinflammation (NI). Chronic neuroinflammation is a key pathological component of epileptogenesis, i.e., the structural, functional, and molecular changes caused by chronic NI gradually transform a normal neural network into one that is hyperexcitable. Methods for imaging inflammation are being developed, but primarily focus on positron emission tomography (PET). There are less invasive approaches for imaging neuroinflammation using magnetic resonance imaging. One of them is volumetric magnetic resonance spectroscopic imaging and thermometry (MRSI-t). MRSI-t data allow mapping brain temperature and visualizing brain temperature elevations that are a proxy for focal inflammation. MRSI-t is easy to implement, reproducible, and inexpensive when compared to PET. In this presentation, I will discuss the stability of MRSI-t signals in the healthy human brain and the application of MRSI-t to investigating temporal lobe epilepsy. I will also discuss MRSI-t's potential for tracking treatment response, as demonstrated by preliminary data from our study of pre to on-cannabidiol brain temperature changes.

Next generation quantification of hippocampal dentation

Anandh Kilpattu Ramaniharan[1] and Lawrence Ver Hoef[1,2]
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[2]*Department of Neurology, Birmingham VA Medical Center, Alabama 35233.*

Hippocampal dentation (HD) is a feature of human hippocampal morphology that refers to surface convolutions seen in the CA1/subiculum region (Figure 1) of the inferior aspect of the hippocampus. The degree of HD is highly heterogenous, ranging from quite bumpy to smooth in the hippocampi of healthy individuals. We have previously quantified HD based on a *subjective* visual rating system and reported that HD is positively correlated with memory performance. Recently, we have developed an *objective* method based on high resolution hippocampal segmentations to quantify HD by transforming a strip of a 3D surface mesh that captures the prominence of dentation into a dimensionally reduced 2D plot with the characteristic undulations of HD. Then, the area under the curve of the 2D plot is measured, yielding a quantity that reflects to degree of HD. We found that the AUC values were significantly correlated with subjective visual assessment of HD but did not significantly correlate with memory performance in initial analysis. The main limitation of this approach is that the segmentation under-estimates the depth of prominent dentes on the 3D surface rendering and does not closely match the complexity of the contour that visible on 2D images (Figure 1). Consequently, the AUC values don't fully capture the visually salient prominence of dentation in many cases (Figure 1(D)). We hypothesize that performing AUC analysis on a surface representing the middle of CA1/subiculum layer (the "midlayer") would capture HD more accurately than on the inferior surface of a volumetric segmentation of the whole hippocampus (Figure 2). To overcome this shortcoming, we generate a midlayer surface by finding the set of points half-way between the inferior surface of the SRLM (strata radiatum, lacunosum, and moleculare) and the inferior surface of the CA1/subiculum that is used for AUC analysis.

To demonstrate this method, a bumpy (prominently dentated) hippocampus was considered and SRLM was segmented manually in all the three planes (Figure 2(B)). The midlayer was obtained by finding the midpoint of the shortest line connecting each point of SRLM to the CA1/subiculum (Figure 2(D & F)) using a MATLAB script. This generates a point cloud dataset that can be converted into a midlayer surface mesh, upon which our AUC method was applied.

As seen in Figure 2(D), the topologic complexity of the surface contour due to HD is represented on the midlayer compared to the inferior hippocampal surface. Comparison of the surfaces of the inferior hippocampus and midlayer show that the dentation was found to be more prominent on the midlayer than observed on the CA1/subiculum region (Figure 2(G-H)) from the same hippocampus. Consequently, the modified AUC value obtained from the midlayer ($AUC_{midlayer}$=24.98) was greater than inferior surface ($AUC_{inf.\ surface}$=21.95).

We found that our newly developed next generation quantification of HD method using midlayer more completely captures the morphologic complexity of HD compared to our previous approach. This method will be more sensitive to capturing extremes of dentation, which may allow for more powerful correlations with memory performance or assessment of morphologic changes in disease states.

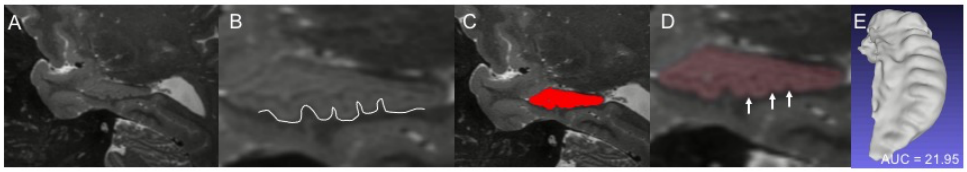

Figure 1. Illustration of segmentation under-estimating the depth of prominent dentes on the 3D surface rendering. (A) High resolution T2 MRI data showing hippocampus in the sagittal plane, (B) zoomed in view of (A) showing dentation highlighted by curved line (white color), (C) segmentation result of whole hippocampus on high resolution T2 MRI data, (D) zoomed in view of (C) showing under-estimation of segmentation highlighted by white arrows, (E) 3D surface rendering from high resolution T2 MRI data showing hippocampal dentation.

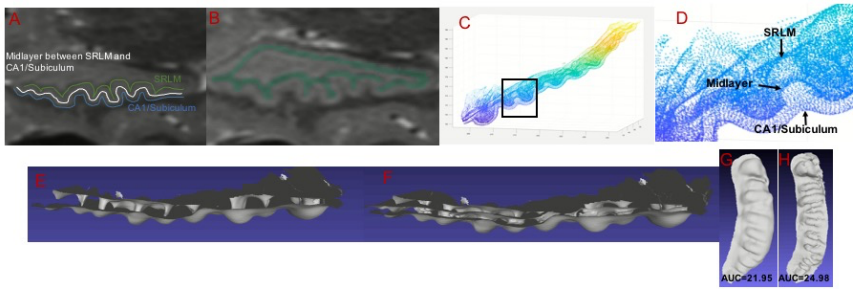

Figure 2. Demonstration of our method to quantify dentation on the midlayer between SRLM and inferior surface of the CA1/subiculum. (A) Identification of SRLM, inferior surface of the CA1/subiculum and Midlayer on high resolution T2 MRI data shown by green, blue and white curved lines, (B) manual segmentation of SRLM on high resolution T2 MRI data, (C) display of SRLM, inferior surface of the CA1/subiculum and midlayer as point cloud data with black box highlighting it, (D) zoomed in view of SRLM, inferior surface of the CA1/subiculum and midlayer shown by black arrows, (E) surface mesh of SRLM and inferior surface of the CA1/subiculum without midlayer, (F) surface mesh of SRLM, midlayer and inferior surface of the CA1/subiculum, (G) inferior surface of the CA1/subiculum showing dentation and its AUC value and (H) surface of midlayer showing prominent dentation than inferior surface of the CA1/subiculum and its AUC value.

Connectomics of the human retina: Morphology and abundance of two distinct Müller glia types identified in the adult fovea

Deepayan Kar MS[1], Ramya Singireddy MD[1], Ursula Bertram [2], Yeon Jim Kim [2], Richard Schalek PhD[3], Dongfeng Cao PhD[1], Kenneth R. Sloan PhD[1], Andreas Pollreisz MD[4], Dennis M. Dacey PhD[2]*, Christine A. Curcio PhD[1]*

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Müller glial cells of the human retina provide vital structural and functional support to foveal cone photoreceptors responsible for high spatial acuity and color vision. Insight into the neural-glial relationships of retina has been challenged by the elaborate morphology of classic Müller glia, i.e., large cells spanning the retina from internal to external limiting membranes. Using serial-section electron microscopic reconstructions of a rapidly preserved 28-year-old donor retina, we tested a hypothesis of two morphologically distinct populations of foveal Müller cells (Syrbe, 2018). In the foveal center we identified a novel class of 'inner' Müller glia. Like classic 'outer' cells, 'inner' Müller glia have cell bodies in the inner nuclear layer, are packed with intermediate filaments, and fill in among neurons. Unlike classic glia, 'inner' Müller glia do not reach the external limiting membrane but instead terminate at the outer plexiform layer, preferentially ensheathing cone pedicles and the cone-driven 'private-line' circuit of midget bipolar and ganglion cells. In the foveal center inner Müller glia outnumber cones by 1.8-fold (221,448 vs 123,026 cells mm^2). Cell body counts show that inner Müller glia outnumber classic glia by 1.7-fold (41,872 vs 24,631 mm^2). Müller glia account for 80% and 95% of the volume of retinal layers known to harbor macular xanthophyll pigment (Snodderly 1984, Li 2020). These findings suggest that Müller glia are highly specialized to support unique neural circuitry of human foveal vision and further suggest glial contributions to foveal tractional disorders and age-related macular degeneration, a leading cause of vision loss worldwide.

Ken Matoba, Shinichi Kano

Thalamic microglia activation, cognitive decline, and aging

Microglia are resident immune cells and maintain homeostasis in the central nervous system. Although recent studies have revealed the functional heterogeneity in microglia, little is known about the impact of regional heterogeneity in microglia on cognitive function. Cognitive decline after brain injuries is associated with microglia accumulation in the thalamus both in human patients and rodent models. However, it is unclear whether and how thalamic microglia influence cognitive decline. In this research, we found that local depletion of microglia in the thalamus, but not in the hippocampus, attenuated cognitive decline after brain injury. Microglia activation in the thalamus after brain injury damaged neurons, and impaired neuronal activities in the thalamus and its connected areas, such as the hippocampus, the medial prefrontal cortex, and the perirhinal cortex. Chemogenetic activation of the thalamic neurons attenuated cognitive decline. Local activation of thalamic microglia by intracranial LPS injection caused a similar cognitive decline in non-brain injury mice. In aging mice, thalamic microglia showed a more detrimental phenotype and worsened cognitive decline. Thus, our findings revealed the critical role of thalamic microglia activation in cognitive decline, which synergizes with aging.

Title: Sleep as a Novel Moderator in the Relationship Between BMI and Working Memory

Authors: Lindsay M. Stager, MA and Aaron D. Fobian, PhD

Background
Obesity is a growing problem in the U.S. with many negative implications for health and well-being. Past literature highlights impaired cognitive performance in individuals with overweight/obesity as compared to same age peers with normal weight. This relationship has been observed in regard to cognitive flexibility, inhibitory control, working memory, and many other aspects of cognitive function and may also influence eating behavior. While the directionality of this relationship is unknown, the influence of several related factors needs to be assessed. For example, poor sleep is associated with both elevated BMI and impaired cognitive function. Therefore, sleep may be an important moderator in the relationship between weight status and cognitive function. Thus, this study explored the role of sleep in the relationship between weight and working memory.

Methods
Data came from Waves IV and V of the National Longitudinal Study of Adolescent to Adult Health. 673 participants (46.4% male; 67.3% white; M_{age}=39.06 years, SD_{age}=1.78) provided data regarding weight, sleep, and working memory as well as relevant demographic variables at both Waves IV and V. Sleep was assessed through individual self-report while BMI was evaluated using objective measures of height and weight. Working memory was measured using Digit Span Backward.

A regression model assessed the moderating effects of sleep duration at Wave V on the relationship between Wave V BMI and working memory while controlling for Wave IV sleep duration, gender, income, and age.

Results
The overall interaction model was significant (Adj. R^2=.30, $F(7,642)=8.76$, $p<.01$). BMI interacted with sleep such that elevated BMI significantly predicted lower working memory but only for individuals who reported sleeping ≤5 hours each night ($t(642)=-2.75$; $p<.01$). For individuals who slept >5 hours each night, there was no significant relationship between weight and working memory.

Discussion
The above results underscore the role of sleep in the relationship between weight status and cognitive function, highlighting a unique mechanism through which to combat obesity. Future weight management interventions may consider sleep as a pathway through which to improve cognitive function and subsequently produce healthier eating behaviors. As traditional interventions targeting energy balance often fail to produce long-term changes in adiposity, identification of such additional modifiable mechanisms is critical.

A novel cortico-cortical pathway underlying social isolation-induced social behavioral deficits in the postpartum period.

Kongpyung Kim and Minae Niwa
Department of Psychiatry and Behavioral Neurobiology, UAB

Background: Early life stress, such as psychosocial stress during adolescence, increases the risk for postpartum mood disorders. Nonetheless, the biological mechanisms by which adolescent psychosocial stress influences postpartum behaviors later in life have not been well characterized. Previously, we have established a novel mouse model in which mild adolescent isolation stress results in social behavioral deficit at one week postpartum. Furthermore, our *in vivo* microdialysis study revealed that our novel mouse model showed an aberrant reduction of extracellular glutamate levels in the prelimbic cortex (PrL). Human imaging studies have linked functional changes in the projections from the anterior insula (AI) to the dorsal anterior cingulate cortex [dACC, homologous to the PrL in rodents] to postpartum behavioral changes. Based on our *in vivo* microdialysis data and on human imaging studies conducted by other groups, we examined whether adolescent social isolation, in conjunction with the stressful events of pregnancy/delivery, leads to deficits in postpartum behaviors related to social cognition via functional alternations of the glutamatergic pathway from the AI to the PrL (AI-PrL pathway).

Methods: To perform optogenetics for neuronal manipulation, adeno-associated viruses (AAV) 5-Syn-FLEX-ChrimsonR or AAV5-EF1a-DIO-eNpHR3.0 viruses were injected to the AI of virgin vesicular glutamate transporter 1 (Vglut1)-Cre female mice at 5 weeks of age. To conduct *in vivo* calcium imaging with a mini-epifluorescence microscope for activity readouts, we injected AAV expressing the calcium indicator GCaMP6f in a conditional manner (AAV1-Syn.Flex-GCaMP6f) and implanted a gradient refractive index lens above the PrL at the same time. This strategy enabled us to manipulate the glutamatergic projections from the AI to the PrL and monitor calcium dynamic of glutamatergic neurons in the PrL at the same time. After surgery, animals were exposed to mild social isolation during late adolescence (from 5 to 8 weeks of age), which alone caused no endocrine or behavioral changes. Each mouse was then mated with a C57BL/6J male and gave birth to pups. Three-chamber social interaction tests (SIT) were performed at one week postpartum. During SIT, calcium image recording with or without optical manipulation of the AI-PrL pathway was conducted. Single-cell neural signals were extracted with regions of interest (ROI) detection using principal and independent component analysis, and analyzed with receiver operating characteristic (ROC) analysis to quantify each neuron's response during social interaction events.

Results: Calcium imaging of glutamatergic neurons in the PrL during SIT was used to identify the subsets of neurons that are excited or suppressed during interactions with a familiar or novel mouse. We found that the inhibition of sniffing behaviors to a novel mouse in stressed dams was accompanied by the decreased fraction of excited glutamatergic neurons and the increased fraction of suppressed glutamatergic neurons during interactions with a novel mouse. Optical activation of the AI-PrL pathway in stressed dams increased the time they spent sniffing a novel mouse by normalizing the disturbance in the excited and suppressed glutamatergic neurons during interactions with a novel mouse. In contrast, optical inhibition of the pathway in unstressed dams led to behavioral deficits in social novelty recognition. Under the condition of neural silencing, the fraction of excited glutamatergic neurons was decreased while the fraction of suppressed glutamatergic neurons was increased in the PrL during interactions with novel mice. The fractions of excited or suppressed glutamatergic neurons in the PrL during interactions with a familiar mouse were not affected by social isolation nor optical manipulation of the pathway.

Conclusion: Our present study demonstrated that adolescent social isolation, in conjunction with the stressful events of pregnancy/delivery, induces hypofunction of the AI-PrL pathway and leads to subsequent social behavioral deficit in the postpartum period. These data provide the opportunity to understand the causal role of the AI-PrL pathway, a novel cortico-cortical circuit, in postpartum social novelty recognition. Our novel mouse model may be a promising model to study the pathological mechanism underlying postpartum behavioral deficits and to explore novel therapeutic strategies for it. We continue to examine how pre-partum adverse life events affect hormonal systems, neural function, and behaviors in the developmental trajectory from adolescence to the postpartum period, and work to dissect the mechanisms, from molecules to circuits and behavior.

Functional Network Segregation is associated with executive functioning in the Healthy Oldest Old: Findings from the McKnight Brain Aging Registry

Sims SA[6], Visscher KM[6], Stewart, P[6], Raichlen DA[1], Bharadwaj PK[2], Franchetti MK[2], Rezaei RF[11,12], Merritt S[9], Jessup CJ[2], Porges ES[11,12], Geldmacher D[7], Hishaw GA[4], Alperin N[10], Trouard TP[5], Wadley VG[8], Levin BE[9], Woods AJ[11,12], Rundek T[9], Cohen RA[11,12], Alexander GE[2,3]

School of Anthropology[1] and Departments of Psychology[2], Psychiatry[3], Neurology[4], and Biomedical Engineering[5], University of Arizona and Evelyn F. McKnight Brain Institute, Tucson, AZ; Departments of Neurobiology[6] and Neurology[7] and Division of Gerontology, Geriatrics, and Palliative Care[8], University of Alabama at Birmingham School of Medicine and Evelyn F. McKnight Brain Institute, Birmingham, AL; Departments of Neurology[9] and Radiology and Biomedical Engineering[10], University of Miami Miller School of Medicine and Evelyn F. McKnight Brain Institute, Miami, FL; Department of Clinical and Health Psychology[11], College of Public Health and Health Professions and Center for Cognitive Aging and Memory[12], University of Florida and Evelyn F. and William L. McKnight Brain Institute, Gainesville, FL.

Measuring relationships among brain regions using functional connectivity metrics has been a successful biomarker of disease and has been shown to relate to cognitive function. The majority of work has been performed in younger adult populations and older populations with mean age under 85. Little work has described functional connections in the oldest-old.
There are two main benefits of characterizing functional connectivity in healthy oldest-old populations: it allows us to characterize what a healthy oldest old brain should look like by identifying typical distributions of functional connectivity metrics and because these participants have relatively large variability on cognitive metrics, we can examine how variability in cognition relates to functional connections.

Data were acquired as part of the McKnight Brain Aging Registry, across the four McKnight Brain Research Foundation sites. For this analysis, 125 community-dwelling, cognitively unimpaired older adults, ages 85-99 were included who had undergone structural and BOLD resting state MRI scans. Cortical surfaces were rendered for each participant and BOLD scans were preprocessed using Ciftify algorithms. Functional connectivity network segregation was measured within three well-characterized networks: Default Mode Network, Cingulo-Opercular Network, and Fronto-Parietal Network. Brain network functioning is an important avenue for aging and cognitive research since network infrastructure, including network integration and segregation, is likely to have a large impact on cognition.

We found that this cohort of healthy oldest old participants showed strong, reproducible connectivity networks for the three networks we tested. Further, level of connectivity segregation within the Default Mode Network, Cingulo-Opercular Network, and Fronto-Parietal Network was positively associated with executive functioning. This work shows feasibility for examining connectivity in the healthy oldest old and helps set the stage for understanding how individual variability in connectivity relate to cognitive performance in this oldest-old cohort.

Stress-elicited neural activity in young adults varies with childhood sexual abuse

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Abstract

Childhood adversity is linked to poor psychological health outcomes that persist into adulthood, including internalizing (e.g., anxiety and depression) and externalizing (e.g., physical aggression and defiance) problems (Anda et al., 2006; Chen et al., 2010; Gilbert et al., 2009; Irish et al., 2010). Sexual abuse, in particular, is linked to increased risk of suicide attempts, borderline personality disorder, and eating disorders (Archer et al., 2017; Brewerton, 2007; Yates et al., 2008). Prior neuroimaging work indicates that experiences of childhood abuse disrupt the function of the prefrontal cortex, hippocampus, and amygdala (Elsey et al., 2015; McLaughlin et al., 2015). These structures comprise a neural circuit that supports emotion expression and regulation processes. Dysfunction of this circuit has been linked to aggression, anxiety, depression, and posttraumatic stress disorder (Burrus, 2013; Elsey et al., 2015; Harnett et al., 2018). Prior neuroimaging research has often combined physical and sexual abuse into a single variable (Cisler et al., 2015; Elsey et al., 2015; Lanius et al., 2005). However, behavioral investigations reveal differences in the outcomes of physical and sexual abuse (e.g., increased risk of eating disorders following sexual abuse, but not physical abuse). A better understanding of the neural outcomes of each type of abuse is necessary to determine mechanisms by which they lead to future psychopathology. Therefore, the present study investigated the relationship childhood sexual abuse has with stress-elicited brain activity in young adulthood.

Participants were recruited from a large, longitudinal study of youth in Birmingham, AL. Participants (N=300, M_{age}=20.03; 50% female, 67% African American, 33% White) completed questions pertaining to physical and sexual abuse from the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). Questions were answered on a scale from 0 (never experienced) to 2 (often experienced) and summed. Participants also completed a neuroimaging session, during which they engaged in a variation of the Montreal Imaging Stress Task (MIST), a psychosocial stress task consisting of two conditions: Control and Stress. A linear mixed effects model was run in AFNI to determine the relationship between sexual abuse and stress-elicited brain function. Race and sex were included as covariates.

Results of the linear mixed effects model revealed that stress-elicited brain activation in the dorsolateral prefrontal cortex (PFC), ventromedial PFC, hippocampus, and parahippocampal gyrus varied negatively with sexual abuse. In all regions, higher levels of sexual abuse were associated with lower differential stress-elicited brain activity. There were no regions where physical abuse was associated with stress-elicited brain activity.

Results of the current investigation suggest that childhood sexual abuse has a lasting impact on neural reactivity to stress that persists into young adulthood. Specifically, neural stress reactivity in the dorsolateral PFC, ventromedial PFC, hippocampus, and parahippocampal gyrus was diminished in individuals reporting childhood sexual abuse. Alterations in the activity of this neural circuitry has been linked to depression, anxiety, and posttraumatic stress disorder (Burrus, 2013; Elsey et al., 2015; Harnett et al., 2018). Given the role these regions play in emotion expression and regulation processes, changes in stress elicited PFC and hippocampal activity may represent a neural mechanism by which childhood sexual abuse leads to future psychopathology.

Process of Illumination: Real-time Dopamine Signaling Measurement using a Genetically-Encoded Biosensor".

J. Andrew Hardaway

Dopamine is a critical neuromodulator of neuronal physiology and neural circuit function, the dysregulation of which underlies a number of brain disorders like Parkinson's disease, addiction, attention-deficit hyperactivity disorder, bipolar disorder, and schizophrenia. Although techniques for the measurement of dopamine in the brain have existed for many years, the inability to detect dopamine within distinct genetically and spatially discrete neural circuits has limited the assignment of dopamine's exact function. In this oral presentation, I will outline my lab's efforts in using the genetically encoded dopamine biosensor, dLight, to measure dopamine signaling in real time during behavior, following pharmacological perturbations, and in combination with optogenetic manipulations.

Ashley Harms 2020 CNC Pilot Awardee

The role of T cells in alpha-synuclein models of Parkinson disease

α-synuclein (α-syn), a key pathological component of Parkinson disease (PD), has been implicated in the activation of the innate and adaptive immune system. This immune activation includes microgliosis, increased inflammatory cytokines, and the infiltration of T cells into the central nervous system (CNS). More recently, peripherally circulating CD4 and CD8 T cells derived from individuals with PD have been shown to produce Th1/Th2 cytokines in response to α-syn, suggesting there may be a chronic memory T cell response present in PD. To better understand the potential effects of these α-syn associated T cell responses we utilized an α-syn overexpression mouse model, T cell deficient mice, and a combination of immunohistochemistry and flow cytometry. In this study, we found that α-syn overexpression in the midbrain of mice leads to the upregulation of the major histocompatibility complex II (MHCII) protein on CNS myeloid cells as well as the infiltration of IFNγ producing CD4 and CD8 T cells into the CNS. Interestingly, genetic deletion of TCRβ or CD4, as well as the use of the immunosuppressive drug fingolimod, were able to reduce the CNS myeloid MHCII response to α-syn. Furthermore, we observed that CD4 deficient mice were protected from the dopaminergic cell loss observed due to α-syn overexpression. These results suggest that T cell responses associated with α-syn pathology may be damaging to key areas of the CNS in PD and that targeting these T cell responses could be an avenue for disease modifying treatments.

CNC shared instruments

1. Molecular Biology

- BioRad "Gene-Gun" for biolistic transfection and fluorescence labeling of adherent cells and tissue slices

2. Optogenetics

- Blue and yellow LEDs with bare fiber optic to use with in vitro slices
- Blue and yellow LEDs with fiber optic launch for cannulas and commutator for in vivo behaving rodents

3. Microscopy

- Stereology microscope (Shelby 962): Zeiss AxioImager with *StereoInvestigator* software, motorized stage, CCD camera
- In vivo fiber-optic confocal (Shelby 1075C1): Leica FCM1000, 488nm excitation; 505-700nm emission (e.g. GCaMP, dLight); 11 frames/second; resolution: 3.3µm; 300µm diameter probe with 300µm field-of-view; 1.5mm diameter probe with 600x500µm field-of-view; head-fixed mice
- In vivo "miniscope" imaging and surgery suite (Shelby 1031E1): iNSCOPIX nVoke, blue light excitation; green emission (e.g. GCaMP, dLight); video rate; head-mounted for freely moving mice

4. Image analysis workstations

- *StereoInvestigator* software for off-line analysis of stereology data (Shelby 1062)
- *NeuroLucida* software for dendritic trees and spines, astrocyte branching (Shelby 1062)
- *Imaris* software for dendritic spines, co-localization, and time-lapse particle tracking (Shelby 1062)

5. Rodent EEG

- Rat and mouse EEG, long-term and short-term, simultaneous in several rodents; funded by CNC, HSF, CIRC, and Neurobiology (RSB-430C)